REVIEW ARTICLE

DRUG THERAPY

Inhaled Nitric Oxide Therapy in Adults

Mark J.D. Griffiths, M.R.C.P., Ph.D., and Timothy W. Evans, M.D., Ph.D.

BACKGROUND AND HISTORICAL PERSPECTIVE

Nitric oxide was largely regarded as a toxic pollutant until 1987, when its biologic similarities to endothelium-derived relaxing factor were demonstrated.[1] Subsequently, nitric oxide and endothelium-derived relaxing factor were considered a single entity, modulating vascular tone through the stimulated formation of cyclic guanosine 3′,5′-monophosphate (Fig. 1).[2] Endogenous nitric oxide is formed from the semiessential amino acid L-arginine by one of three (neural, inducible, and endothelial) isoforms of nitric oxide synthase. The physiologic role of endogenous nitric oxide was first shown when an infusion of an inhibitor of all forms of nitric oxide synthase in healthy volunteers led to systemic and pulmonary pressor responses.[3] However, the role of nitric oxide in maintaining low pulmonary vascular resistance in healthy persons has since been challenged.[4] Inhaled nitric oxide had a negligible effect on pulmonary blood flow in healthy humans,[5] but when healthy persons were breathing 12 percent oxygen, it reversed the pulmonary hypertension that was induced without affecting systemic hemodynamics.[6] In 1991, inhaled nitric oxide was shown to be a selective pulmonary vasodilator in patients with pulmonary hypertension,[7] as well as in animals with pulmonary hypertension induced by drugs or hypoxia.[8] Two years later, inhaled nitric oxide emerged as a potential therapy for the acute respiratory distress syndrome (ARDS), because it decreased pulmonary vascular resistance without affecting systemic blood pressure and improved oxygenation by redistributing pulmonary blood flow toward ventilated lung units in patients with this condition.[9]

Despite such promise, the potential therapeutic role of inhaled nitric oxide in adults remains uncertain; licensed indications are restricted to pediatric practice. Furthermore, recent changes in the marketing of inhaled nitric oxide have dramatically increased its cost, which has inevitably led to a need to justify continuing its administration to adults. This review will consider the biologic actions of inhaled nitric oxide, discuss clinical indications for its administration in adults, and assess possible future developments.

CHEMICAL REACTIONS OF INHALED NITRIC OXIDE

Nitric oxide is a gas that is colorless and odorless at room temperature and is relatively insoluble in water. It is poorly reactive with most biologic molecules, but because it has an unpaired electron, it can react very rapidly with other free radicals, certain amino acids, and transition metal ions.[10] In biologic solutions, nitric oxide is stabilized by forming complexes with — for example — thiols, nitrite, and proteins that contain transition metals.[11]

Atmospheric concentrations of nitric oxide typically range between 10 and 500 parts per billion but may reach 1.5 parts per million (ppm) in heavy traffic[12] and 1000 ppm in tobacco smoke.[13] When inhaled with high concentrations of oxygen,

From the Adult Intensive Care Unit and Intensive Care Services, Royal Brompton Hospital, and Imperial College London — both in London. Address reprint requests to Dr. Evans at the Unit of Critical Care, Imperial College London, Royal Brompton Hospital, Sydney St., London SW3 6NP, United Kingdom, or at t.evans@rbh.nthames.nhs.uk.

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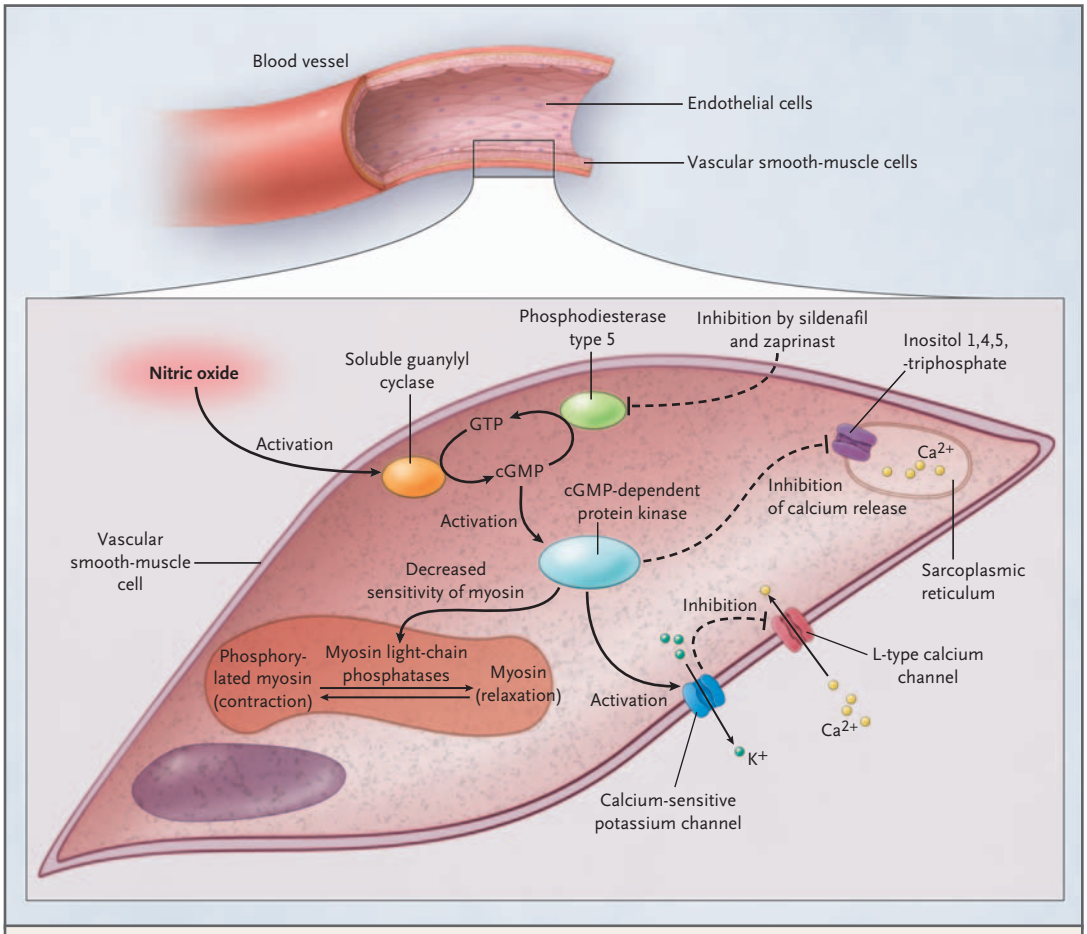

Figure 1. Regulation of the Relaxation of Vascular Smooth Muscle by Nitric Oxide.

Nitric oxide activates soluble guanylyl cyclase, leading to the activation of cyclic guanosine 3′, 5′-monophosphate (cGMP)–dependent protein kinase (cGKI). In turn, cGKI decreases the sensitivity of myosin to calcium-induced contraction and lowers the intracellular calcium concentration by activating calcium-sensitive potassium channels and inhibiting the release of calcium from the sarcoplasmic reticulum. cGMP is degraded by phosphodiesterase type 5, which is inhibited by sildenafil and zaprinast. GTP denotes guanosine triphosphate.

gaseous nitric oxide slowly forms nitrogen dioxide.[14] Once dissolved in airway-lining fluid, nitric oxide may react with reactive oxygen species such as superoxide to form reactive nitrogen species such as peroxynitrite, a powerful oxidant that can decompose further to yield nitrogen dioxide and hydroxyl radicals (Fig. 2).[15] Therefore, nitric oxide is potentially cytotoxic, and covalent nitration of tyrosine in proteins by reactive nitrogen species has been used as a marker of oxidative stress.[16]

Nitric oxide is rapidly inactivated by hemoglobin in blood, by haptoglobin–hemoglobin complexes in plasma, and by a reaction with heme ferrous iron and ferric iron that forms nitrosylhemoglobin.[17] Nitric oxide forms methemoglobin and nitrate on reaction with oxyhemoglobin, which predominates in the pulmonary circulation. Most of the methemoglobin is reduced to ferrous hemoglobin by NADH–cytochrome *b5* reductase in erythrocytes. In healthy subjects who have inhaled nitric oxide (80 ppm) for one hour, plasma nitrate concentrations may be four times as high as baseline levels.[18] Almost 70 percent of inhaled nitric oxide is excreted as nitrate in the urine within 48 hours.[19]

More than 100 proteins, including hemoglobin[20] and albumin,[21] contain reduced sulfur (thiol)

groups that react reversibly with nitric oxide to form *S*-nitrosothiols; these compounds are vasodilators that inhibit platelet aggregation.[22] *S*-nitrosothiols may also "store" nitric oxide within the circulation. For example, *S*-nitrosohemoglobin in red cells has been postulated to regulate microvascular flow and oxygen delivery.[23]

PHYSIOLOGIC EFFECTS OF INHALED NITRIC OXIDE ON THE CARDIOVASCULAR SYSTEM

Inhaled nitric oxide relaxes pulmonary vessels, thereby decreasing pulmonary vascular resistance, pulmonary arterial pressure, and right ventricular afterload (Table 1).[6-8] The selectivity of nitric oxide for the pulmonary circulation is the result of rapid hemoglobin-mediated inactivation of nitric oxide.[29] In the presence of biventricular cardiac failure, inhaled nitric oxide may sufficiently increase pulmonary blood flow and, hence, left atrial end-diastolic pressure to precipitate pulmonary edema.[30]

Early studies in patients with ARDS compared the effect of inhaled nitric oxide with another vasodilator (epoprostenol, or prostacyclin or prostaglandin I_2) administered intravenously.[9] The intravenously administered vasodilator worsened oxygenation owing to antagonism of hypoxic pulmonary vasoconstriction. In contrast, the advantage of inhaled nitric oxide was that only the vasculature associated with ventilated lung units was within reach of an inhaled gas diffusing across the alveolar-capillary membrane. Selective dilatation of these vessels would improve ventilation–perfusion matching (Fig. 3).

Circulating modulators of vascular tone, such as the potent vasoconstrictor endothelin-1 and endogenous nitric oxide, influence the effect of inhaled nitric oxide. Decreased responsiveness is associated with the induction of nitric oxide synthase by endotoxin both in patients with ARDS associated with septic shock[31] and in animal models (Fig. 3E).[32] Conversely, the positive effect of inhaled nitric oxide on gas exchange depends on the extent to which pulmonary vasoconstriction and ventilation–perfusion mismatching are contributing to impaired oxygenation. For example, in a study of mountaineers who were either susceptible or not susceptible to high-altitude pulmonary edema, inhaled nitric oxide decreased the pulmonary arterial pressure of susceptible subjects, but improved oxygenation only in the subjects with the greatest degree of hypoxemia (those who had pulmonary edema) by increasing the blood flow to the areas of lung that were relatively unaffected.[33]

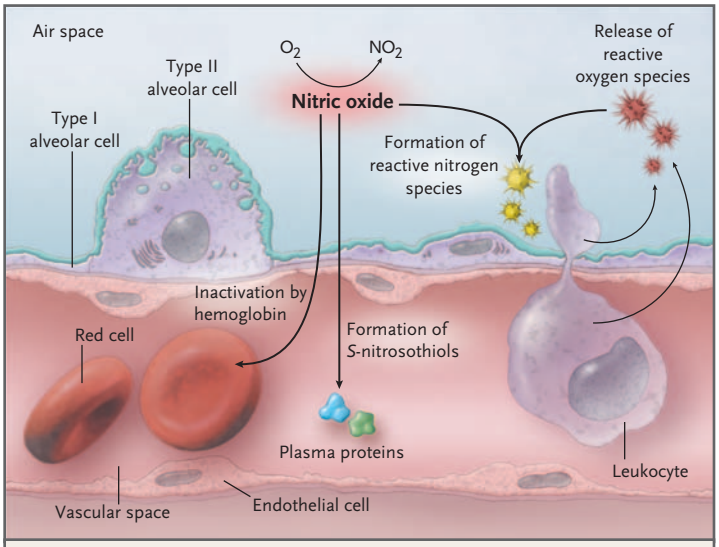

Figure 2. Biochemical Fates of Inhaled Nitric Oxide at the Alveolar-Capillary Membrane.

Small amounts of nitrogen dioxide (NO_2) may be formed if inhaled nitric oxide mixes with high concentrations of oxygen (O_2) in the air space. Depending on the milieu of the lung parenchyma, nitric oxide may react with reactive oxygen species (derived from activated leukocytes or ischemia–reperfusion injury) to form reactive nitrogen species such as peroxynitrite. In the vascular space, dissolved nitric oxide is scavenged by oxyhemoglobin (forming methemoglobin and nitrate) and to a lesser extent, plasma proteins (e.g., forming nitrosothiols, which are stable intravascular sources of nitric oxide activity).

The effects of inhaled nitric oxide also depend on vascular selectivity. For example, disproportionate arterial, as opposed to venous, dilatation would increase the pulmonary-capillary pressure and exacerbate pulmonary edema. Although many studies have not shown evidence of selectivity, others have demonstrated that 40 ppm of nitric oxide induced venodilatation with decreased pulmonary-capillary pressure[34] and reduced the risk of pulmonary edema in patients with acute lung injury.[35] Apart from changing the pulmonary-capillary pressure, nitric oxide may influence the development of edema through pulmonary vascular recruitment or by decreasing inflammation and helping maintain the integrity of the alveolar-capillary membrane. Such specific effects are difficult to identify with certainty in vivo. Because the effects of nitric oxide probably vary in different settings, apparently contradictory clinical and experimental observations have been produced.

Table 1. Comparison of Ideal Treatment Goals with Those Achieved by Inhaled Nitric Oxide in Adults with the Acute Respiratory Distress Syndrome (ARDS).

Ideal Treatment Goals	Physiological Effects of Inhaled Nitric Oxide
Improved oxygenation	20% Improvement in approximately 60% of patients for only 1 to 2 days in clinical trials, with no associated survival benefit[24,25]; may significantly improve oxygenation in very severe cases and buy time for the institution of other means of support
Decreased pulmonary vascular resistance	Selective pulmonary vasodilator of uncertain benefit in acute lung injury or ARDS characterized by mild pulmonary hypertension[26]; may have a supportive role in patients with acute right-sided heart failure, particularly in association with increased pulmonary vascular resistance and hypoxemia
Decreased pulmonary edema	May be influenced by effects on hemodynamics, inflammation, infection, and the alveolar-capillary membrane
Reduction or prevention of inflammation	Conflicting evidence of its antiinflammatory efficacy at multiple molecular and clinical levels
Cytoprotection	May contribute to the formation of cytotoxic reactive nitrogen species and reactive oxygen species, especially when administered with high concentrations of oxygen; conversely, may prevent the generation of reactive oxygen species by free iron and scavenge hydroxyl radicals[27]
Protection against infection	Direct antimicrobial effects,[28] but associated with an increased incidence of ventilator-associated pneumonia in one study[25]

Most clinical studies have provided support for the view that inhaled nitric oxide has no effect on the systemic circulation. In contrast, experimental studies have demonstrated a reduction in systemic vascular resistance[36] and restoration of mesenteric perfusion after the inhibition of nitric oxide synthase.[37] Similarly, the inhalation of nitric oxide (80 ppm) by healthy volunteers abolished the vasopressor effect of the inhibition of nitric oxide synthase in the circulation of the forearm, an effect associated with increased arterial concentrations of nitrite and *S*-nitrosylhemoglobin, but not of *S*-nitrosothiols or *S*-nitrosohemoglobin.[18] The concept of a plasma-based repository for nitric oxide activity that may be supplemented by inhaled nitric oxide has become widely accepted; probable contributors include nitrites,[38] iron nitrosyl and *N*-nitrosamine complexes,[39] and nitrated lipids.[40]

When inhaled nitric oxide is used therapeutically, its rapid withdrawal may induce rebound pulmonary hypertension and hypoxemia.[9,41] The inhalation of nitric oxide by healthy animals decreases endothelial nitric oxide synthase activity and increases plasma concentrations of endothelin-1,[42] which inactivates endothelial nitric oxide synthase by nitration.[43] In practice, rebound phenomena may be avoided by withdrawing inhaled nitric oxide gradually. Despite these concerns, in large clinical studies of patients with ARDS, the abrupt discontinuation of inhaled nitric oxide has not caused a deterioration in oxygenation.[24,25]

DIRECT CYTOTOXICITY AND EFFECTS ON INFLAMMATION

Inhaled nitric oxide may modulate the acute neutrophilic inflammation of the lung parenchyma and dysfunction of the alveolar-capillary membrane that characterizes ARDS at several levels. The protective effects of nitric oxide may derive from specific effects on neutrophil function — for example, by attenuation of the respiratory burst and neutrophil-derived oxidative stress.[44] Inhaled nitric oxide has decreased the accumulation of neutrophils in the pulmonary vasculature and air space in animal models of acute lung injury,[45] consistent with its known effects on the adhesion and deformability of neutrophils in vitro.[46] Furthermore, similar effects of inhaled nitric oxide outside the lung have been observed in rodent models of severe sepsis.[47] In a model in which cecal ligation and puncture were used to induce sepsis, mice lacking inducible nitric oxide synthase had fewer neutrophils sequestered in the pulmonary vasculature than normal mice, but they had greater neutrophil migration into the air spaces.[48] Subsequent experiments have confirmed that nitric oxide derived from neutrophils acts as

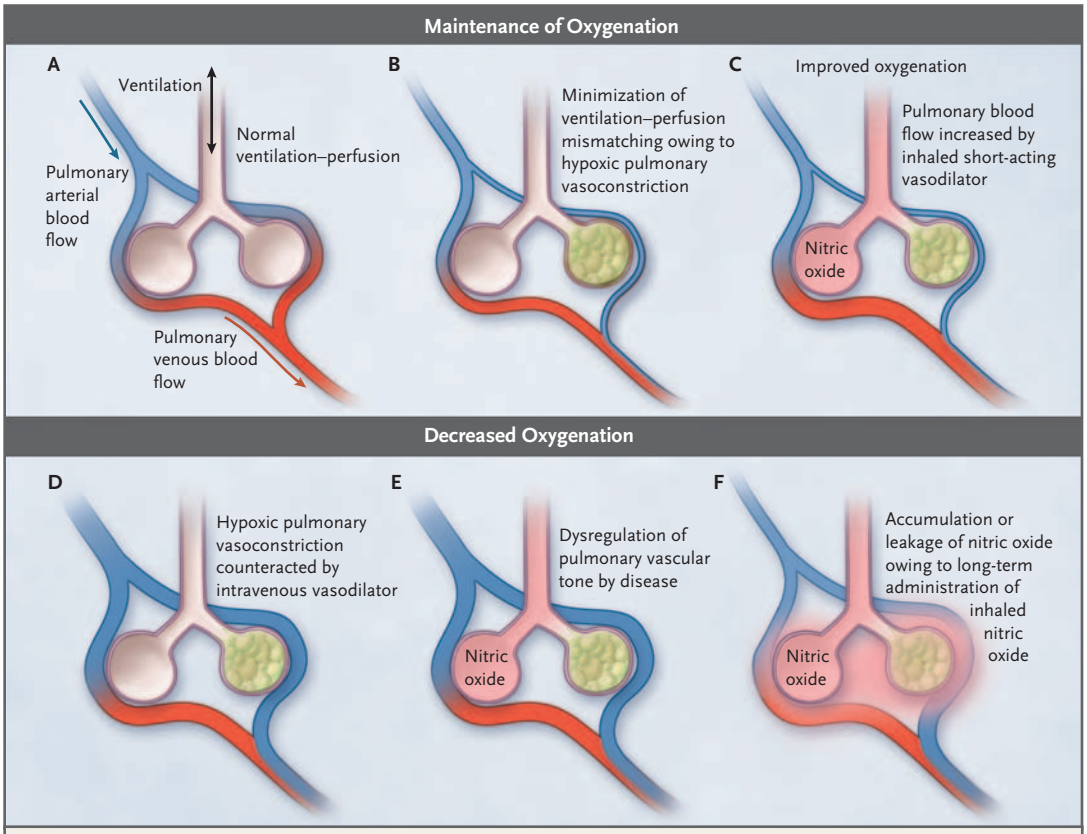

Figure 3. Mechanism of Action and Inaction of Inhaled Nitric Oxide.

Panel A shows normal ventilation–perfusion. Hypoxic pulmonary vasoconstriction (Panel B) minimizes ventilation–perfusion mismatching in the presence of abnormal ventilation. Inhaled vasodilators with a short half-life improve oxygenation by increasing blood flow to ventilated lung units (Panel C). If a vasodilator is administered intravenously (Panel D) or if diseases are associated with dysregulated pulmonary vascular tone, such as sepsis and acute lung injury (Panel E), hypoxic pulmonary vasoconstriction is counteracted, leading to worsening oxygenation. Long-term administration of inhaled nitric oxide, with the accumulation of nitric oxide or leakage between lung units associated with collateral ventilation, as may occur in chronic obstructive pulmonary disease (Panel F), may negate the beneficial effects of inhaled nitric oxide on oxygenation.

an autocrine modulating factor in infiltration of neutrophils into the lungs during sepsis.

The toxic potential of nitric oxide is well known; endogenously produced nitric oxide contributes to the control and killing of multiple pathogens[28] and malignant cells.[49] Studies involving inhibitors of nitric oxide synthase[50] and mice lacking inducible nitric oxide synthase[51] have suggested that nitric oxide–derived reactive nitrogen species contribute to epithelial damage after a variety of insults. The results of interactions between nitric oxide and reactive oxygen species are unpredictable and probably depend on the relative local concentrations of the participants in these reactions.[52] Increased concentrations of oxidative products of nitric oxide were found in the airway-lining fluid of patients with ARDS,[53] and these may be further increased by inhalation of nitric oxide.[54] In rodents, inhalation of nitric oxide (20 ppm) did not increase protein nitration unless hyperoxia was superimposed.[55] Taken together, these observations suggest an important role for oxidative damage and reactive nitrogen species in these pulmonary diseases, but the role of exogenous nitric oxide in modulating these processes is uncertain.

OTHER EFFECTS

Endogenous nitric oxide inhibits the adhesion of platelets to endothelial cells and subsequent aggregation.[2] In experimental microsphere-induced pulmonary embolism, inhaled nitric oxide attenuated increases in pulmonary arterial pressure and platelet aggregation.[56] However, in animals, healthy volunteers, and patients with pulmonary diseases, the effects of inhalation of nitric oxide on the

duration of bleeding and other indexes of platelet function are variable.[52]

Surfactant dysfunction contributes substantially to the pathophysiological characteristics of lung injury. Reactive nitrogen species react with and impair the functions of the surfactant proteins; it has been shown that the surfactant from animals receiving inhaled high-dose nitric oxide (80 to 100 ppm) had a reduced capacity to lower surface tension.[57] Conversely, inhaled nitric oxide increased the production of surfactant proteins in four-week-old lambs.[58] The relevance of these observations to adult humans treated with inhaled nitric oxide is uncertain.

Inhaled nitric oxide has a dose-dependent bronchodilator effect on drug-induced bronchoconstriction in animal models[59] and causes mild bronchodilation in patients with asthma.[60] An interesting finding is that the nitric oxide–derived *S*-nitrosothiols, which act as bronchodilators, were present at lower concentrations in the fluid lining the airways of patients with severe asthma than of healthy subjects, suggesting that this mechanism may contribute to bronchospasm.[61]

ADMINISTRATION OF INHALED NITRIC OXIDE TO ADULTS

Route, Monitoring, and Safety

Nitric oxide is most commonly administered to patients receiving mechanical ventilation, although it may also be given through a face mask or nasal cannulae. Limiting the mixing of nitric oxide and high concentrations of inspired oxygen reduces the risk of adverse effects resulting from the formation of nitrogen dioxide (Fig. 2). This is minimized further by introducing the mixture of nitric oxide and nitrogen into the inspiratory limb of the ventilator tubing as near to the patient as possible[62] and synchronizing injection of the mixture with inspiration.[63]

Although a massive overdose of inhaled nitric oxide (500 to 1000 ppm) is rapidly fatal,[64] studies in animals have provided reassuring data indicating that nitric oxide has minimal pulmonary toxicity when it is inhaled at a concentration of less than 40 ppm for up to six months.[65] Electrochemical analyzers can be used to monitor the concentrations of nitric oxide and nitrogen dioxide in the inspired gas mixture to an accuracy of 1 ppm. More sensitive (chemiluminescence) monitors can detect nitric oxide and its oxidative derivatives in parts per billion.

Up to 40 ppm of inhaled nitric oxide administered clinically should not cause methemoglobinemia in adults in the absence of methemoglobin reductase deficiency.[66] However, guidelines in the United Kingdom recommend measurement of methemoglobin concentrations within six hours after the initiation of nitric oxide therapy and after each increase in the dose.[62] The Control of Substances Hazardous to Health Regulations suggest that environmental concentrations of nitric oxide and nitrogen dioxide should not exceed a time-weighted average of 25 ppm and 2 ppm, respectively, over an eight-hour period.[67] Clearly, it is unlikely that such levels would accumulate from therapeutic administration of nitric oxide in a well-ventilated room (10 to 12 air changes per hour). Consequently, the use of environmental monitoring and equipment to adsorb nitric oxide (nitric oxide scavenging) in the clinical setting is rarely necessary.[62]

Dose–Response Relationship

Early clinical experience with the use of inhaled nitric oxide to treat patients with respiratory failure indicated that higher doses were required to treat pulmonary hypertension than to improve oxygenation. When nitric oxide is administered, only a minority of patients have no response when a response is defined as a 20 percent increase in oxygenation.[68] Although this threshold is widely accepted, its biologic relevance has not been validated across a range of respiratory failure; for example, a 10 percentage point improvement in hemoglobin saturation in a patient with hypoxemia who is breathing 100 percent oxygen may be clinically very important. No radiologic or physiological variables predict a response to inhaled nitric oxide in patients with acute lung injury or ARDS, and the response varies over the clinical course.[69,70]

In the treatment of pulmonary hypertension, a 30 percent decrease in pulmonary vascular resistance during the inhalation of nitric oxide (10 ppm for 10 minutes) has been used to identify an association with vascular responsiveness to agents that can be helpful in the long term[71]; indeed, a positive response to nitric oxide was associated with a favorable response to calcium-channel blockers in a small cohort of patients with primary pulmonary hypertension.[72]

Numerous small studies involving patients with acute respiratory failure have examined the dose–response relationship of inhaled nitric oxide

and oxygenation, demonstrating marked variation in any one patient and between patients, as well as some evidence of a plateau in effect when the dose was between 1 and 10 ppm. The time-dependent variation in the dose–response relationship of inhaled nitric oxide in patients with severe ARDS has been explored with the use of a prospective, randomized protocol in which patients received either inhaled nitric oxide (10 ppm) or a placebo.[73] Dose–response relationships (nitric oxide, 0 to 100 ppm) were constructed in the two groups on days 0, 2, and 4 of the study. Two important observations emerged: first, the dose–response curves for changes in oxygenation and mean pulmonary pressure were shifted to the left only in patients who inhaled nitric oxide (10 ppm) continuously. Second, "supramaximal" doses of nitric oxide were associated with worsening oxygenation. These observations imply that the optimal dose of inhaled nitric oxide must be determined by titration against the therapeutic target in each patient at least every two days, and probably more frequently.

CLINICAL INDICATIONS FOR ADMINISTERING INHALED NITRIC OXIDE TO ADULTS

Acute Lung Injury and the Acute Respiratory Distress Syndrome

In adults with acute lung injury, inhaled nitric oxide is used more often to improve oxygenation than to decrease pulmonary vascular resistance. Two small (a total of 70 patients), single-center studies[74,75] and four multicenter, randomized, placebo-controlled trials[24,25,76,77] have failed to determine the therapeutic role of inhaled nitric oxide in patients with acute respiratory failure.[78] A French multicenter study that recruited 203 patients reported no decrease in the duration of mechanical ventilation or the mortality rate among patients treated with inhaled nitric oxide as compared with those taking a nitrogen placebo, but that study has been published only in abstract form.[76] A phase 2 American study that was not statistically powered to demonstrate a benefit in mortality rate reported that doses of 1.25 to 40 ppm of inhaled nitric oxide were well tolerated (Table 2).[24] The percentage of patients having a response (defined by a 20 percent increase in the arterial partial pressure of oxygen) to the various doses was similar: approximately 60 percent of patients in both studies.

A European multicenter study that planned to enroll 600 subjects enrolled 268 patients with early acute lung injury and then changed the protocol after 140 patients had been recruited.[77] Ultimately, three groups of patients were analyzed: those who had less than a 20 percent increase in arterial partial pressure of oxygen in response to inhaled nitric oxide, patients with a response who were treated conventionally, and patients with a response who were treated with the lowest effective dose of inhaled nitric oxide. The mortality rates in the three groups were similar at 30 days. Another American multicenter study performed between 1996 and 1999 compared the effects of continuously inhaled nitric oxide (5 ppm) with those of a placebo in patients with ARDS that was not associated with severe sepsis or multiorgan failure.[25] Despite the lower dose, the increase in oxygenation (specifically in the partial pressure of arterial oxygen) lasted only for the first day of therapy, a finding similar to that in the first American study. Nitric oxide had no significant effect on any outcome measure (Table 2).

Two important questions are raised by these studies. First, why are the effects of inhaled nitric oxide so short-lived? Increasing sensitivity to nitric oxide during its inhalation may diminish its beneficial effects and increase toxicity.[73] Alternatively, constant inhalation may lead to equilibration of the vasodilator effect between ventilated and nonventilated areas (Fig. 3E). Such effects might be mitigated by performing daily dose–response assessments or by including regular nitric oxide–free periods in the regimen, depending on whether rebound phenomena occur. Clearly, any continued benefit may depend on the use of other therapeutic approaches such as maintaining alveolar recruitment. Second, if the clinical benefits are real, why do they not translate into improved outcome? Because ARDS is a heterogeneous condition with multiple causes requiring different interventions that independently affect the outcome, very large numbers of patients would be required for a study to demonstrate benefit. Furthermore, many large studies evaluating modes of ventilation[80,81] and prone positioning[82] in patients with ARDS have shown no correlation between improved oxygenation and the outcome. This result is partly explained by the observation that only a minority of patients with ARDS die from respiratory failure; the majority die from multiorgan failure.[83]

Table 2. Results of Multicenter Clinical Studies of the Use of Inhaled Nitric Oxide in Patients with Acute Respiratory Failure.

Study	Year	Duration of Intervention	Patients*	Intervention		Primary Outcome	Secondary Outcomes
				Control	Inhaled Nitric Oxide		
		days					
Dellinger et al.[24]	1998	28	Patients with ARDS, enrolled within 72 hr after diagnosis†; patients with severe sepsis, nonpulmonary organ failure, or both, excluded	Nitrogen in 57 patients	1.25 ppm in 22 patients 5 ppm in 34 patients 20 ppm in 29 patients 40 ppm in 27 patients 80 ppm in 8 patients‡	Duration of mechanical ventilation	Oxygenation§; pulmonary arterial pressure§; response; 28-day survival
Lundin et al.[77]	1999	30	Patients with acute lung injury with a PaO_2:FiO_2 <165 mm Hg who had been receiving mechanical ventilation 18–96 hr¶	Conventional therapy with no placebo in 93 patients	2, 10, or 40 ppm (lowest effective dose; mean ±SD, 9±8 ppm for 9±6 days) in 87 patients	Reversal of acute lung injury	30-day and 90-day survival; dependency on intensive care; duration of hospitalization and acute lung injury; organ failure‖
Taylor et al.[25]	2004	28	ARDS and a PaO_2:FiO_2 <250 mm Hg†; patients with severe sepsis, non-pulmonary organ failure, or both excluded	Nitrogen in 193 patients	5 ppm in 192 patients	Survival without need for mechanical ventilation during the first 28 days	Oxygenation and positive end-expiratory pressure§; 28-day survival; survival after successful two-hour trial of unassisted ventilation; survival after oxygenation criteria met for extubation

* PaO_2:FiO_2 denotes the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen.
† The definition of the American–European Consensus Conference on the Acute Respiratory Distress Syndrome (ARDS) was used.[79]
‡ The 80-ppm dose was stopped, owing to consensus that the dose was likely to be higher than the peak of the dose–response curve.
§ There were significant differences in this outcome between the control group and the group receiving inhaled nitric oxide.
¶ Of 268 patients with a response to nitric oxide, 180 underwent randomization.
‖ The group receiving inhaled nitric oxide had an increased incidence of acute renal failure (as defined by a serum creatinine concentration of more than 3.5 mg per deciliter or the need for renal replacement therapy) ($P<0.03$).

Targeting Pulmonary Vascular Resistance

The inhalation of nitric oxide by patients with acute lung injury, which is characterized by mild pulmonary hypertension,[26] has been associated with a small, short-lived decrease in pulmonary arterial pressure.[24,25] This observation has encouraged the use of inhaled nitric oxide as a supportive treatment for acute right ventricular dysfunction complicating cardiac surgery,[84-86] although there are no adequate trial data to support this practice. Inhaled nitric oxide has also been associated with marked hemodynamic improvement in patients with acute massive pulmonary embolism,[87] suggesting that in these patients, reversible pulmonary vasoconstriction contributes to right ventricular dysfunction. The expression of endothelial nitric oxide synthase is decreased in the pulmonary arteries of patients with chronic primary and secondary pulmonary hypertension,[88] suggesting a possible therapeutic role for agents that enhance vasodilatation mediated by nitric oxide. Inhaled nitric oxide improves hemodynamic variables and exercise tolerance in patients with chronic pulmonary hypertension of various causes.[89]

Pulmonary hypertension is present in 40 percent of patients with severe chronic obstructive pulmonary disease, and despite the usually mild degree of pulmonary hypertension present in patients at rest, its presence independently predicts an adverse outcome.[90] Long-term oxygen therapy improves survival rates, but it has little hemodynamic effect. In contrast, inhaled nitric oxide alleviates pulmonary hypertension in patients with severe chronic obstructive pulmonary disease but exacerbates hypoxemia at rest.[91] During exercise, inhaled nitric oxide alleviates pulmonary hypertension without inducing hypoxemia,[92] possibly by increasing relative ventilation and therefore increasing the delivery of nitric oxide to lung units that fill relatively quickly during inspiration, which leads to improved ventilation–perfusion matching. A similar mechanism is thought to confer an advantage for so-called pulsed therapy (long-term administration of oxygen therapy and inhaled nitric oxide as a bolus after the start of inspiration) over continuously inhaled nitric oxide.[93] Thus, pulsed therapy for three months in patients with pulmonary hypertension related to chronic obstructive pulmonary disease markedly decreased pulmonary arterial pressure and improved cardiac output without impairing oxygenation, as compared with oxygen therapy alone.[94] However, the expense of administering nitric oxide and the risks of rebound phenomena have precluded its routine use in these circumstances.

Lung Transplantation

Lung injury associated with ischemia and reperfusion and oxidative stress is an important cause of morbidity and mortality after lung transplantation. Endogenous nitric oxide activity is decreased after lung transplantation, despite the increased expression of endothelial nitric oxide synthase.[95] Inhaled nitric oxide has been used effectively to provide support for patients with acute lung injury after lung transplantation,[96] and small studies have suggested a prophylactic role.[97-99] However, a randomized, placebo-controlled trial of inhaled nitric oxide administered to 84 transplant recipients, starting 10 minutes after reperfusion and continuing for a minimum of 6 hours, demonstrated no benefit in terms of oxygenation, the time to extubation, or the 30-day mortality rate.[100]

Sickle Cell Disease

Sickle cell disease results in widespread chronic inflammation and recurrent ischemia–reperfusion injury in organs such as the lungs and is caused by microvascular occlusion by stiff erythrocytes containing polymerized deoxyhemoglobin S. The effects of this condition on the intravascular availability of endothelium-derived nitric oxide are complex.[101] The use of high-dose inhaled nitric oxide (80 ppm for 1.5 hours) in patients with sickle cell disease markedly reduced the scavenging potential of hemoglobin within the circulation (because of the weak interaction of nitric oxide with methemoglobin), producing a measurable decrease in arterial plasma nitric oxide consumption.[102] However, to date, only isolated case reports have described the use of inhaled nitric oxide in patients with acute chest syndrome,[103] and the results of a randomized, controlled trial are awaited.

ALTERNATIVES AND ADJUNCTS TO INHALED NITRIC OXIDE

Other Inhaled Vasodilators

Multiple nitric oxide donors have been administered by inhalation in models of acute pulmonary hypertension[104] and in patients after cardiac surgery.[105] This treatment results in various degrees of selective pulmonary vasodilatation. In newborn

lambs, aerosolized sodium nitrite caused potent, selective, nitric oxide–dependent pulmonary vasodilatation through its reaction with deoxyhemoglobin at a low pH, suggesting that nitrite may be a cheap and stable alternative to inhaled nitric oxide.[106]

Epoprostenol, the most extensively studied alternative to inhaled nitric oxide, is also an endothelium-derived vasodilator with antithrombotic effects. Inhaled epoprostenol has an effect on hemodynamics and oxygenation similar to that of nitric oxide in patients with ARDS,[107,108] sepsis,[109] or severe heart failure.[110] Epoprostenol has a longer half-life (three to six minutes), causing recirculation and thereby a greater pulmonary and systemic hypotensive effect, but causes less improvement in oxygenation.[108] Inhaled nitric oxide and nebulized prostacyclin have been observed to have additive effects — for example, after lung transplantation[111] — as predicted with drugs acting through different signaling pathways (Fig. 1). The response rates of patients with ARDS to both agents are similar,[112] but whether a failure to respond to one agent predicts a lack of response to the other is unclear.

Nebulized epoprostenol has been studied less frequently than inhaled nitric oxide, but at therapeutic doses (10 to 50 ng per kilogram per minute), the rates of predicted side effects, such as systemic hypotension and bleeding after surgery, have not been clinically important.[113] Iloprost, a long-acting prostacyclin analogue (half-life, 20 to 30 minutes), improves the exercise tolerance of patients with severe pulmonary hypertension when administered by intermittent rather than by continuous nebulization.[114] Inhaled prostaglandin E_1 (6 to 15 ng per kilogram of body weight per minute) has effects similar to those of inhaled nitric oxide (2 to 10 ppm) in patients with ARDS.[115]

Adjunctive Therapies That Increase the Effectiveness of Inhaled Nitric Oxide

The secondary messengers of nitric oxide and prostacyclin, cyclic guanosine 3′,5′-monophosphate and cyclic AMP, are inactivated predominantly by phosphodiesterase type 5 and type 3, respectively (Fig. 1). Orally administered sildenafil, an inhibitor of phosphodiesterase type 5, is a selective pulmonary vasodilator, partially because phosphodiesterase type 5 is highly expressed in the lung. Sildenafil has augmented pulmonary vasodilatation induced by inhaled nitric oxide,[116] although a second inhibitor of phosphodiesterase type 5, zaprinast, predictably worsened oxygenation through the attenuation of hypoxic pulmonary vasoconstriction in an ovine model of acute lung injury.[117] Such agents may therefore be most useful when pulmonary hypertension rather than respiratory failure is the chief concern.

Almitrine, an agonist at peripheral arterial chemoreceptors, is a selective pulmonary vasoconstrictor that specifically enhances hypoxic pulmonary vasoconstriction. The addition of almitrine to low-dose inhaled nitric oxide improves oxygenation in patients with ARDS,[118] but concern about the effects of long-term infusion has hampered the wider investigation of this combination.

In patients with acute respiratory failure, the effect of nitric oxide depends on the degree of recruitment of injured lung units by — for example — positive end-expiratory pressure, prone positioning, or ventilatory maneuvers designed to inflate collapsed lung, which may explain how the response to nitric oxide varies over short periods. Partial liquid ventilation with perfluorocarbons facilitates the delivery of dissolved gases to alveoli by enhancing recruitment of the injured lung units. Inhaled nitric oxide has enhanced the effects of partial liquid ventilation on gas exchange in animal models,[119] demonstrating the potential benefit of combining therapeutic strategies in patients with ARDS.

CONCLUSIONS AND FUTURE DIRECTIONS

Inhaled nitric oxide is a selective pulmonary vasodilator that improves ventilation–perfusion matching at low doses in patients with acute respiratory failure, potentially improving oxygenation and lowering pulmonary vascular resistance. Large clinical trials have indicated that physiologic benefits are short-lived in adults with acute lung injury or ARDS, and no associated improvement in mortality rates has been demonstrated. However, clinical trials involving patients with acute lung injury or ARDS have been statistically underpowered to show a decrease in mortality rates and have not considered recent insights into the effect of continuous inhalation on the dose–response relationship of this agent. In patients with acute respiratory failure, the potential toxicity or protective effects of inhaled nitric oxide,

particularly any effects on cell survival and inflammation, are poorly understood.

On the basis of the evidence, inhaled nitric oxide is not an effective therapeutic intervention in patients with acute lung injury or ARDS, and its routine use to achieve this end is inappropriate. However, inhaled nitric oxide may be useful as a short-term adjunct to cardiorespiratory support in patients with acute hypoxemia, life-threatening pulmonary hypertension, or both.

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