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Since the recognition of nitric oxide (NO) as a key endothelial-derived vasodilator molecule in 1987, the field of NO research has expanded to encompass many areas of biomedical research. It is now well established that NO is an important signaling molecule throughout the body. The therapeutic potential of inhaled NO as a selective pulmonary vasodilator was suggested in a lamb model of pulmonary hypertension and in patients with pulmonary hypertension in 1991.[1,2] Because NO is scavenged by hemoglobin (Hb) on diffusing into the blood and is thereby rapidly inactivated, the vasodilatory effect of inhaled NO is limited largely to the lung. This is in contrast to intravenously infused vasodilators that can cause systemic vasodilation and severe systemic arterial hypotension.

Recent data indicate that inhaled NO can be applied in various diseases. For example, studies suggest that inhaled NO is a safe and effective agent to determine the vasodilatory capacity of the pulmonary vascular bed. This article summarizes the pharmacology and physiology of inhaled NO and reviews the current uses of inhaled NO for the treatment, evaluation, and prevention of cardiovascular and respiratory diseases.

Pharmacology and Physiology of Inhaled NO

Chemistry of NO Gas

NO is a colorless, odorless gas that is only slightly soluble in water.[3] NO and its oxidative byproducts (eg, NO_2 and N_2O_4) are produced by the partial oxidation of atmospheric nitrogen in internal combustion engines, in the burning cinder cones of cigarettes, and in lightning storms. Medical-grade NO gas is produced under carefully controlled conditions, diluted with pure nitrogen, and stored in the absence of oxygen. The recent article by Williams[4] provides a review of the chemistry of NO.

Therapeutic Versus Endogenous NO Concentrations in the Airway

Although early studies of inhaled NO in the treatment of pulmonary hypertension used concentrations of 5 to 80 ppm, it has since been realized that concentrations >20 ppm provide little additional hemodynamic benefit in most patients. In some adults with acute respiratory failure, the effective concentrations of inhaled NO required to improve oxygenation can be as low as 10 ppb.[5,6] Of note, NO has been detected in exhaled human breath. The majority of exhaled NO in normal humans appears to be derived from nasal bacterial flora (25 to 64 ppb), with lower concentrations measured in the mouth, trachea, and distal airway (1 to 6 ppb).[5,7]

Mechanism of Action

After inhalation, NO diffuses rapidly across the alveolar-capillary membrane into the subjacent smooth muscle of pulmonary vessels to activate soluble guanylate cyclase (Figure 1). This enzyme mediates many of the biological effects of NO and is responsible for the conversion of GTP to cGMP. Increased intracellular concentrations of cGMP relax smooth muscle via several mechanisms. The physiological actions of cGMP are limited to its area of synthesis by its hydrolysis to GMP by cyclic nucleotide phosphodiesterases (PDE) or by its export from the cell. Of the 11 reported PDE isozymes, PDE5 is considered to be the most active cGMP-hydrolyzing PDE in smooth muscle (for review, see the work by Rybalkin et al[8]). PDE5 has a high affinity for cGMP and is selectively inhibited by compounds such as zaprinast, sildenafil, and verdenafil.

In addition to its pulmonary vasodilating effects, inhaled NO has several other effects in the lung. For instance, inhaled NO has been shown to cause bronchodilation[9,10] and to possess antiinflammatory[11] and antiproliferative[12] effects.

Enhancement of Ventilation-Perfusion Matching by NO Inhalation

The intrapulmonary distribution of ventilation and blood flow [ventilation-perfusion ($\dot{V}/\dot{Q}$) distribution] is a major determinant of the efficiency of transpulmonary oxygenation and determines the partial pressure of oxygen in systemic arterial blood (Pa_{O_2}). In the normal lung, a low oxygen tension constricts the vascular bed in hypoxic regions and redistributes blood flow

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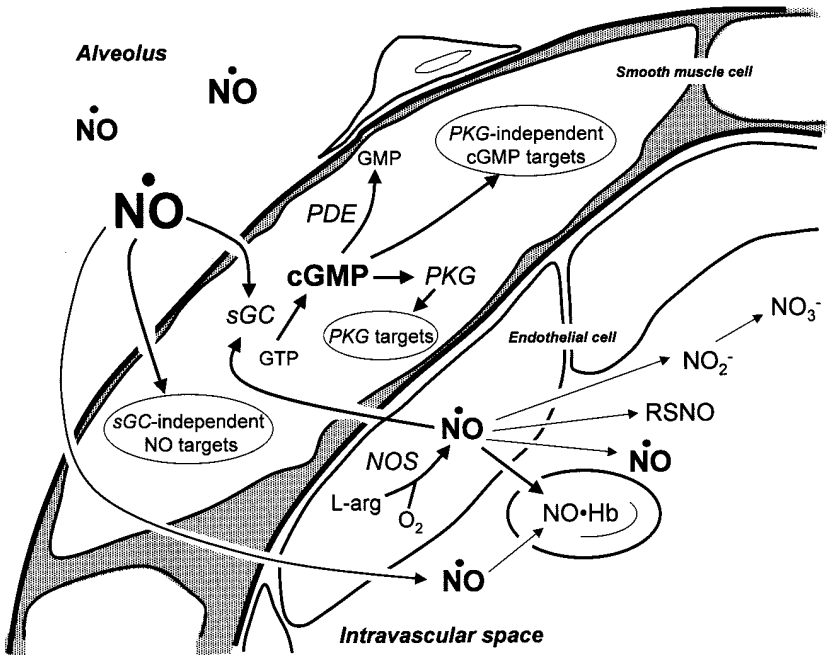

Figure 1. NO signaling pathway in the lung. PKG indicates cGMP-dependent protein kinases; NOS, NO synthase; L-arg, L-arginine; sGC, soluble guanylate cyclases; and RSNO, S-nitrosothiol.

toward lung regions with better ventilation and a higher intraalveolar partial pressure of oxygen. Inhaled NO enhances this mechanism by increasing blood flow to well-ventilated lung areas that, in some diseases, have an elevated vasomotor tone. This vasodilatory effect of inhaled NO is in marked contrast to intravenously administered vasodilators. Such intravenous agents produce diffuse dilation of the pulmonary vasculature, including areas of nonventilated lung, thereby increasing intrapulmonary shunting and reducing the Pa_{O_2} (Figure 2). The beneficial effects of inhaled NO to reduce intrapulmonary shunting and oxygenation have been demonstrated in patients with acute respiratory distress syndrome.[13,14]

Metabolic Fate of Inhaled NO

After inhalation, NO diffuses into the bloodstream and rapidly reacts with oxyhemoglobin to form methemoglobin (metHb) and nitrate and with deoxyhemoglobin to form iron-nitrosyl-Hb. Of note, recent reports describe a possible role for intravascular NO-derived molecules in conserving and stabilizing NO bioactivity that may contribute to the regulation of regional blood flow and oxygen delivery.[15,16] Almost 70% of inhaled NO is excreted within 48 hours as nitrate in the urine.[17] Blood levels of nitrate have been reported to increase ≈4-fold during breathing of 80 ppm NO.[15]

Clinical Applications of Inhaled NO

Pulmonary Hypertension of the Newborn

Pulmonary hypertension in the newborn may be idiopathic or associated with premature closure of the ductus arteriosus, pneumonia, meconium aspiration, prematurity, or lung hypoplasia.[18] In many infants with pulmonary hypertension, right-to-left shunting of venous blood across the patent ductus arteriosus and foramen ovale produces severe systemic hypoxemia. In other patients, closure of these vascular conduits causes right-side heart failure and systemic hypotension. Although treatment with

dilators ameliorates pulmonary hypertension in some infants, in many it does not. Extracorporeal membrane oxygenation (ECMO) therapy is lifesaving for some infants with pulmonary hypertension; however, it is costly, invasive, and associated with important morbidities.

In ventilated newborn animals with acute pulmonary hypertension, inhaled NO rapidly increases lung blood flow without causing systemic hypotension.[19,20] Similar observations of selective pulmonary vasodilation induced by inhaled NO have been made in ventilated newborn animals with pulmonary hypertension caused by sepsis, lung hypoplasia, or inflammation.[21–24] In severely hypoxemic babies with pulmonary hypertension, inhaled NO rapidly increases arterial oxygen tension without causing systemic hypotension.[25,26] Randomized controlled studies demonstrated that NO inhalation safely improves arterial oxygen levels and decreases

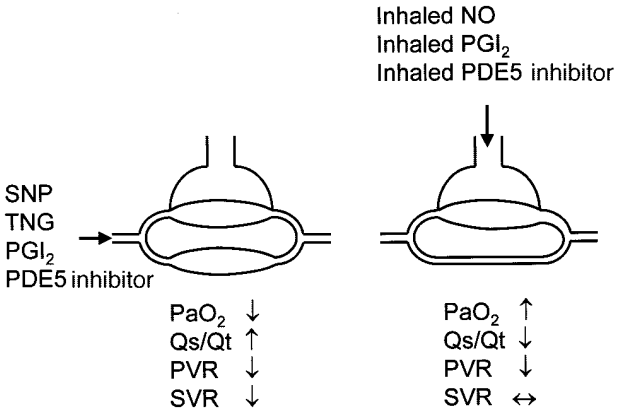

Figure 2. Differing pathophysiological effects of inhaled pulmonary vasodilators and intravenous vasodilators. SNP indicates sodium nitroprusside; TNG, nitroglycerine; PGI_2, prostaglandin I_2; Qs/Qt, right-to-left shunt fraction; and SVR, systemic vascular

the need for ECMO therapy.[27,28] On the basis of these data, the US Food and Drug Administration approved the use of inhaled NO for the treatment of newborns with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

Preventing Chronic Lung Disease in the Newborn

Although advanced ventilator and medical therapies such as high-frequency ventilation and exogenous surfactant decrease the airway injury associated with the respiratory care of premature infants, the incidence of chronic lung disease remains high and causes important morbidity. Experimental data indicate that NO decreases vascular cell proliferation and that chronic NO inhalation may decrease the pulmonary vascular disease observed in the newborn lung.[12,29] Recently, a randomized, placebo-controlled clinical study in a single center demonstrated that 7 days of NO inhalation prevents chronic lung disease in premature infants.[30]

Safety and Cost-Effectiveness of Inhaled NO in the Newborn

Large clinical trials have demonstrated that NO inhalation is safe in the hypoxemic term newborn. Inhaled NO has not been associated with clinically evident bleeding in babies with pulmonary disease. In premature babies, studies suggest that inhaled NO does not increase the incidence of intraventricular hemorrhages.[30–33]

Several studies indicate that NO inhalation is a cost-effective therapy for treating newborns with hypoxic respiratory failure in part because it decreases the need for ECMO.[34,35]

Diagnostic Use of Inhaled NO

Pulmonary Vasoreactivity Testing in the Cardiac Catheterization Laboratory

Demonstration of a positive response to vasodilating agents in patients with pulmonary hypertension correlates with a favorable long-term clinical outcome.[36] Although a number of vasodilators, including intravenous prostacyclin and calcium channel blockers, have been used for diagnostic testing during cardiac catheterization, systemic administration of these agents can produce severe hypotension, increased intrapulmonary right-to-left shunting, and death.[37,38] In contrast, recent studies indicate that inhaled NO safely and effectively assesses the capacity for pulmonary vasodilation in pediatric[39] and adult patients[40,41] with pulmonary hypertension without causing systemic hypotension and predicts responsiveness to medical vasodilator therapy.[42] For example, a >20% decrease in pulmonary artery pressure or pulmonary vascular resistance (PVR) to inhaled NO accurately predicts a subsequent response to oral vasodilators such as nifedipine.[38,43] According to a survey in 2000, 94% of pediatric cardiologists consider inhaled NO to be useful in testing pulmonary vasoreactivity in the cardiac catheterization laboratory.[44]

Treatment of Perioperative Pulmonary Hypertension With Inhaled NO

Congenital Heart Disease

Postoperative pulmonary hypertensive crises are an important cause of morbidity and mortality after surgery for congenital heart disease[45] and may be precipitated by diminished NO [illegible] has been reported to ameliorate the postoperative pulmonary hypertension of congenital heart disease[47] and to decrease the need for postoperative ECMO.[48] In a randomized double-blind study, Miller and colleagues[49] examined the effects of the prophylactic use of inhaled NO in high-risk infants undergoing congenital heart surgery. They reported that compared with placebo, infants who after surgery inhaled 10 ppm NO continuously until just before extubation had fewer pulmonary hypertensive crises and shorter times to eligibility for extubation.

Cardiac Transplantation

Pulmonary hypertension in the cardiac transplant recipient is a major cause of right-side heart failure and early death. Goals in the management of acute right ventricular (RV) failure include preservation of coronary perfusion through maintenance of systemic blood pressure and reducing RV afterload by decreasing the PVR.[50] Inhaled NO has been shown in a small group of patients to selectively reduce PVR and to enhance RV stroke work after cardiac transplantation.[51]

Insertion of Left Ventricular Assist Device

RV dysfunction occurs in 20% to 50% of patients after insertion of a left ventricular assist device (LVAD).[52] The ability of the RV to pump sufficient quantities of blood to the LVAD is critically related to the intrinsic contractility of the RV and the RV afterload, which is influenced by the PVR. The PVR is usually elevated in patients with long-standing congestive heart failure and can be further increased in the early postoperative period by the effects of cardiopulmonary bypass. A trial of inhaled NO is recommended before implantation of an RV assist device is considered because this invasive procedure may be avoided if there is a salutary response to inhaled NO.[53] In a randomized, double-blinded trial, Argenziano and coworkers[54] demonstrated the hemodynamic benefits of inhaled NO (decreased pulmonary artery pressure and increased LVAD flow) in LVAD recipients with pulmonary hypertension.

Inhaled NO to Treat Ischemia-Reperfusion Injury

Ischemia-reperfusion injury is one of the major causes of early graft failure after lung transplantation. Inhaled NO has been shown to attenuate ischemia-reperfusion injury in the lung and other organs in preclinical[55] and in clinical studies.[56,57] However, a recent randomized, placebo-controlled study demonstrated that inhaling 20 ppm NO beginning 10 minutes after reperfusion does not affect the physiological or clinical outcome of patients after lung transplantation.[58]

Inhaled NO and Acute Respiratory Distress Syndrome

In early clinical studies of patients with severe acute respiratory distress syndrome, inhaled NO has been shown to produce selective pulmonary vasodilation,[13] to decrease pulmonary capillary pressure[59] and pulmonary transvascular albumin flux,[60] and to improve oxygenation.[13] However, subsequent clinical trials reported disappointing outcome results. Inhaled NO therapy did not affect the duration of ventilatory support or mortality in 2 single-center pilot trials[61,62] and in 3 multicenter randomized trials.[63–65] Because most patients dying from acute respiratory distress syndrome [illegible]

beneficial effects of a lung-selective therapy such as inhaled NO will alter the overall survival rate.

Chronic Obstructive Pulmonary Disease

Severe chronic obstructive pulmonary disease (COPD) is frequently complicated by pulmonary hypertension and hypoxemia. Systemic hypoxemia in COPD is caused primarily by $\dot{V}/\dot{Q}$ mismatching and not by intrapulmonary right-to-left shunting (as in acute respiratory distress syndrome). A recent randomized controlled trial demonstrated that the combined use of supplemental oxygen and inhaled NO for a period of 3 months via a portable inspiratory pulsing device caused a greater improvement of pulmonary hemodynamics than supplemental oxygen alone and did not worsen the oxygenation of COPD patients.[66]

Toxicity and Side Effects of Inhaled NO

Inhalation of low levels of NO appears to be safe. The major clinical toxicity is due to the formation of NO_2 and methemoglobinemia. A review of the toxicology of inhaled NO has recently been published.[67]

Nitrogen Dioxide and Methemoglobinemia

Formation of NO_2 during NO breathing is dependent on the NO concentration, inspiratory oxygen concentration (Fio_2), and residence time of these gases.[68] Increased airway reactivity has been reported in humans after exposures to as low as 1.5 ppm NO_2.[69] At higher inhaled NO_2 doses, pulmonary edema is the major toxicological effect[70] and can result in death.[71] In a simulation using a model lung and commercially available ventilators, production of NO_2 during NO inhalation at 20 ppm appears to be minimal ($<$0.7 ppm) even with an Fio_2 of 95%.[72]

Inhaled NO can combine with Hb to form nitrosylhemoglobin, which is rapidly oxidized to metHb. The rates of uptake and release of NO from ferrous (Fe^{2+}) Hb are 10^5- to 10^6-fold greater than those of oxygen. Tissue hypoxia can be produced at excessive circulating metHb concentrations.[67] The enzyme metHb reductase rapidly converts metHb to Hb in the red blood cell.

Blood metHb concentrations and inspired NO_2 concentrations are frequently monitored during clinical administration of inhaled NO. Significant methemoglobinemia or NO_2 formation is uncommon in patients breathing NO at doses $\leq$80 ppm (see review by Steudel et al[73]).

Rebound Pulmonary Hypertension

Sudden discontinuation of inhaled NO can cause severe rebound pulmonary hypertension, an increase in intrapulmonary right-to-left shunting, and a decreased Pao_2.[13] It has been suggested that downregulation of endogenous NO synthesis and/or elevated endothelin-1 levels by inhaled NO is responsible in part for this rebound phenomenon.[74,75] Although the precise underlying mechanisms remain to be elucidated, to avoid rebound pulmonary hypertension, a slow, stepwise reduction of the inhaled NO concentration is recommended.

Increased LV Filling Pressure

Inhaled NO has been demonstrated to be a selective pulmonary vasodilator in heart failure patients, although breathing NO [illegible] pressure in patients with severe LV dysfunction.[37,76] Investigators learned that the elevation in LV filling pressure that occurs with NO breathing is due to the augmentation of filling into a relatively noncompliant LV and is not caused by a negative inotropic effect.[77,78] Nonetheless, it is important to be aware of the possibility that inhaled NO can produce pulmonary vasodilation and may overwhelm a failing LV, thereby producing pulmonary edema.[79]

Delivery and Monitoring of NO

NO can be safely inhaled when delivered by face mask, by nasal cannula, or via an endotracheal tube. An ideal inhaled NO delivery device requires delivery synchronized with respiration and minimal production of NO_2 and should be simple to use with full monitoring capacity (high and low alarms and precise monitoring of NO, NO_2, and O_2).[80] This can be achieved with several commercially available systems. Although NO and NO_2 are more accurately measured by chemiluminescence devices, electrochemical detectors have proved adequate for measuring inhaled NO and NO_2 levels and are integrated components of several clinical delivery systems.

Future Directions

Randomized clinical trials will unquestionably lead to a more precise definition of the role of inhaled NO in treating various clinical situations in which the physiological benefits of inhaled NO have been suggested by preclinical studies and uncontrolled clinical trials. Multicenter, randomized clinical trials are needed in several areas, including the diagnostic use of inhaled NO and treatment of postoperative pulmonary hypertension after adult cardiac surgery.[51]

Although most patients breathe NO for a relatively short period of time (hours to days), long-term use of inhaled NO has been reported in a limited number of ambulatory patients with pulmonary hypertension,[81,82] pulmonary fibrosis,[83] and COPD.[66] In this regard, pharmacologically extending the brief half-life of NO in the lung is an attractive strategy. Inhibitors of PDE5 such as zaprinast and sildenafil potentiate and/or prolong the pulmonary vasodilating effects of inhaled NO.[84–86] Of note, sildenafil has been shown to be a selective pulmonary vasodilator in patients with pulmonary hypertension.[86–88] Exploration of the effects of PDE inhibitors alone and in combination with inhaled NO warrants further studies.

In the last several years, data supporting the extrapulmonary effects of inhaled NO have accumulated. For example, inhaled NO appears to modestly inhibit platelet activation in some species[89,90] and to attenuate neutrophil-mediated ischemia-reperfusion injury.[55] Decreased bioavailability of NO may contribute to the pathogenesis of sickle cell disease, and inhaled NO has been suggested to modulate the course of this disease.[91] In this regard, the treatment of vaso-occlusive crises with inhaled NO in patients with sickle cell disease may become a promising therapy. Preliminary results from a randomized, double-blind, placebo-controlled trial demonstrated beneficial effects of inhaled NO in attenuating the intensity and duration of pain in acute vaso-occlusive crises [illegible]

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