CLINICAL CONCEPTS AND COMMENTARY

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Use of Inhaled Nitric Oxide Perioperatively and in Intensive Care Patients

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NITRIC oxide (NO) is an endogenous molecule that has important physiologic functions. In blood vessels, NO produced in the endothelium causes vasodilation by increasing cyclic guanosine 3′,5′-monophosphate (cGMP) in the vascular smooth muscle. The NO-cGMP pathway plays a significant role in the modulation of vascular tone, and, in disease states, a dysfunctional endothelium may result in altered flow or hypertension. The understanding of the endogenous NO-cGMP pathway led to the idea of using exogenous inhaled gaseous NO as a therapeutic vasodilator. It was hypothesized that inhaled NO would act like endothelial NO to cause pulmonary vasodilation. Because NO rapidly binds to hemoglobin, the vasodilation would be limited to the pulmonary circulation.

In 1991, inhaled NO was shown to vasodilate the pulmonary circulation dose-dependently in lambs breathing a hypoxic gas mixture. Also in 1991, Pepke-Zaba *et al.*[1] demonstrated that inhaled NO decreased pulmonary artery pressure and pulmonary vascular resistance (PVR) in patients with primary pulmonary hypertension (fig. 1). The vasodilation occurred within minutes of delivery of inhaled NO and was reversible within minutes of its discontinuation, and there was no systemic vasodilation. These studies triggered an intensive international investigation of the potential therapeutic role of inhaled NO in virtually all diseases associated with pulmonary hypertension.

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Since the acceptance of this manuscript, inhaled nitric oxide has received Food and Drug Administration approval for treatment of term and near-term (older than 34 weeks) neonates with hypoxic respiratory failure associated with pulmonary hypertension.

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Perioperative Uses of Inhaled NO

Inhaled NO causes vasodilation that is proportional to the PVR in the presence of pulmonary vasoconstriction. Inhaled NO has very little effect on PVR if pulmonary vascular tone is not elevated, pulmonary hypertension is secondary to fixed or fibrotic disease, or the pulmonary artery pressure is elevated secondary to increased cardiac output. The influence of inhaled NO-induced pulmonary vasodilation on cardiac function is dependent on the degree of right ventricular (RV) dysfunction; *i.e.*, if RV function is normal in the presence of pulmonary hypertension, there is minimal influence on RV ejection fraction or cardiac output.[2] Conversely, in the presence of RV dysfunction, inhaled NO may increase RV ejection fraction and increase cardiac output. Inhaled NO has an important advantage over intravenous therapy directed at reducing PVR: It does not decrease systemic pressure and thereby jeopardize coronary perfusion pressure to the right ventricle.

Pulmonary hypertension may be present in patients with mitral valve disease or left ventricular failure. In patients undergoing mitral valve surgery or coronary artery bypass grafting, our group demonstrated that inhaled NO (5-40 ppm) selectively decreases PVR by 5-30%.[3] Fullerton *et al.*[4] also demonstrated that inhaled

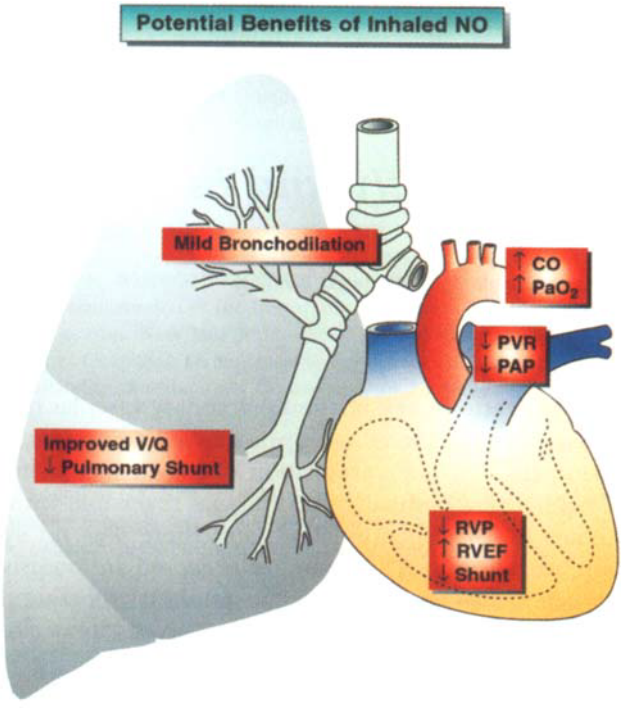

Fig. 1. The potential beneficial effects of inhaled nitric oxide include mild bronchodilation, improved ventilation/perfusion ration (V/Q) matching and decreased pulmonary shunt in the lungs, decreased right ventricular pressure (RVP), decreased intracardiac shunt, increased right ventricular ejection fraction (RVEF), decreased pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), increased cardiac output (CO), and increased arterial oxygen tension (PaO_2).

NO decreased PVR in patients undergoing coronary artery bypass grafting; however, in contrast to our study, they did not find that PVR was altered in patients with mitral valve disease. Although inhaled NO may decrease PVR in cardiac surgical patients, there appears to be minimal influence on cardiac output unless it is limited by RV failure.

Cardiac transplantation surgery may be an ideal indication for inhaled NO. The donor heart has not been exposed previously to the elevated PVR that may be present in the recipient and is therefore at risk for RV failure. In this situation inhaled NO produces pulmonary vasodilation and may improve RV function and increase cardiac output.[5]

The benefit from the decreased RV afterload caused by inhaled NO may be particularly apparent in patients who require a left ventricular assist device because RV failure is one of the most common causes of death. Inhaled NO may decrease the need for RV assist devices or pharmacologic support of the right ventricle and increase systemic blood flow by decreasing resistance through the pulmonary circulation and increasing filling of the left ventricular assist device.[6]

Lung transplantation may be complicated by a reperfusion syndrome manifested by pulmonary edema, pulmonary hypertension, and RV failure. In a study of 243 patients who underwent lung transplantation, severe allograft dysfunction with a low arterial oxygen tension developed in 13%.[7] Although inhaled NO (30–60 ppm) resulted in an improvement in oxygenation and pulmonary artery pressure, there was no effect on the requirement for extracorporeal membrane oxygenation (ECMO), duration of mechanical ventilation, or mortality rate.

Inhaled NO may have an important place in the postoperative management of pediatric congenital heart disease. In patients with pulmonary hypertension resulting from left-to-right cardiac shunts, inhaled NO selectively decreases PVR. More importantly, in patients in whom cardiac output is limited by an elevated PVR, *e.g.*, those undergoing Fontan-type procedures, inhaled NO decreases PVR and increases cardiac output. These acute benefits were confirmed in 1998 in a randomized double-blind study of 40 pediatric patients, but inhaled NO had no discernible influence on morbidity or mortality rates.[8] Numerous case reports have suggested that inhaled NO (2–80 ppm) may save lives and permit weaning of these patients from cardiopulmonary bypass.

In contrast to the effectiveness of inhaled NO for improving RV function, a number of studies have shown that inhaled NO may increase pulmonary artery occlusion pressure and produce pulmonary edema in patients with left ventricular dysfunction.[9] Presumably, inhaled NO increases blood flow to the left ventricle by decreasing PVR, and, if the left ventricle is on the flat or descending portion of the Starling curve, pulmonary edema may occur as a result of the increase in preload.

Inhaled NO may be used for preoperative assessment of the reversibility of pulmonary hypertension in establishing the need for either heart or heart and lung transplantation. In infants with congenital heart disease, evaluation of the pulmonary vasodilatory capacity also may be important in predicting surgical outcome. Traditionally, hyperoxic breathing has been used to dilate the pulmonary vasculature selectively, as have nonselective intravenous vasodilators. Several studies have shown that inhaled NO may be used preoperatively to evaluate these patients without the limitation of systemic vasodilation.

Intensive Care Uses of Inhaled Nitric Oxide

Inhaled NO increases blood flow toward ventilated areas of the lungs by dilating primarily those pulmonary vessels that are ventilated. This reduces intrapulmonary shunting, improves ventilation-perfusion matching, and therefore increases arterial oxygenation (fig. 1). These effects are in contrast to intravenous vasodilators that worsen oxygenation. In 1993, Rossaint *et al.* [10] reported that inhaled NO (18 or 36 ppm) increased oxygenation and decreased PVR in patients with acute respiratory distress syndrome (ARDS), and these benefits persisted for up to 53 days without tolerance. Inert gas analysis revealed that NO improved the ventilation-perfusion inequality and decreased right-to-left shunting.

Several ARDS studies have shown that inhaled NO may increase oxygenation dose-dependently (0.1-40.0 ppm). Approximately 40% of patients do not respond to inhaled NO, and minimal responses are observed in patients with chronic fixed pulmonary disease or sepsis. Typically, patients who respond to inhaled NO show an improvement in oxygenation (arterial oxygen tension) of 5-30%, which may allow the inspired oxygen concentration to be decreased.

Inhaled NO used in combination with other therapies may improve oxygenation further in patients with diffuse ARDS and focal lung lesions. The most important adjuvant is alveolar recruitment by aggressive ventilation techniques to improve NO delivery. Ventilation with the patient in the prone position also has an additive beneficial effect with inhaled NO. Pharmacologic vasoconstriction with almitrine bismesylate or phenylephrine, in combination with NO, increases oxygenation more than either therapy alone. Phosphodiesterase inhibitors also may increase the effects of inhaled NO by decreasing cGMP metabolism.

Despite numerous studies that showed that inhaled NO improves oxygenation, there is no evidence that inhaled NO improves long-term morbidity or mortality rates in ARDS patients. In 1998, a randomized phase II trial showed that inhaled NO (5 ppm) increased oxygenation over the first 24 h in ARDS patients; however, oxygenation in the patients did not differ from that in controls after 24 h, and inhaled NO did not affect morbidity and mortality rates.[11] Michael *et al.*[12] also showed that the improvement in oxygenation in response to inhaled NO was not sustained beyond 24 h. Preliminary data from two European multicenter ARDS studies also showed that outcome was not altered by the use of inhaled NO. These studies did not include severely hypoxemic patients, did not control for different ventilator modes, and did not evaluate whether subsets of ARDS patients respond differently to inhaled NO. It is possible that there may be subsets of patients with severe hypoxemia or RV failure in whom inhaled NO can play an important therapeutic role. Furthermore, differences in mortality rate with inhaled NO may be difficult to demonstrate (and may not be an appropriate end point for evaluation), because relatively few patients with ARDS die of pulmonary disease.

The effects of inhaled NO on oxygenation in patients with chronic obstructive pulmonary disease is unclear. Yoshida *et al.*[13] demonstrated that the combination of NO (2 ppm) and oxygen decreased pulmonary artery pressure and increased oxygenation more than oxygen inhalation alone. In contrast, other reports have observed either no improvement or worsening oxygenation in patients with chronic obstructive pulmonary disease. In such patients or in those with asthma, the bronchodilatory effects of inhaled NO appear to be very weak compared with β-adrenergic agonists.

Pediatric Intensive Care

Persistent pulmonary hypertension of the newborn is characterized by increased PVR, with right-to-left shunting through a patent foramen ovale or patent ductus arteriosus, resulting in hypoxemia. Conventional therapy has included hyperventilation, alkalosis, hyperoxia, inotropic support, intravenous dilators, and ECMO. In 1992, Kinsella[14] and Roberts[15] each reported that inhaled NO improves oxygenation in persistent pulmonary hypertension of the newborn by reducing the right-to-left shunt. In 1997, a multicenter trial determined that inhaled NO doubled systemic oxygenation in 53% of patients.[16] The need for ECMO was significantly lower in the NO group (40%) than in the control group (71%), although overall mortality rate and duration of mechanical ventilation were not altered by inhaled NO.

In a 1997 multicenter trial[17] of 235 infants with hypoxic respiratory failure, the primary outcome, defined as either death by 120 days of age or the initiation of ECMO, was significantly lower in the infants administered inhaled NO (46%) than in the control group (64%). There were no differences in secondary outcomes, which included overall mortality rate, duration of hospital stay, days of respiratory support, air leakage, and bronchopulmonary dysplasia. The decreased need for ECMO in patients with persistent pulmonary hyperten-

sion of the newborn or respiratory failure shows the important therapeutic role for inhaled NO in this patient population.

Sickle cell disease may manifest as acute chest syndrome, characterized by chest pain, pulmonary infiltrate, effusion, or edema. Pulmonary vascular occlusion with ischemia and infarction may play an important role in this syndrome. The successful use of inhaled NO to decrease PVR and increase arterial oxygenation in two children with acute chest syndrome first was reported in 1997.[18] Improved oxygenation is thought to occur because NO increases the oxygen affinity of sickle cell erythrocytes. More extensive studies may lead to the use of inhaled NO as an additional therapy for such patients.

Complications, Monitoring, and Delivery

Inhaled NO increases methemoglobin levels as NO combines with hemoglobin, indicating the need for daily methemoglobin monitoring. Usually the increase in the methemoglobin level is modest, although case reports of high levels (> 5%) have occurred because of inadvertent delivery of high NO concentrations. Methemoglobin levels also may increase in patients with deficiencies of methemoglobin reductase.

Several case reports have documented life-threatening rebound hypoxemia and pulmonary hypertension after withdrawal of inhaled NO.[19] It is possible that rebound pulmonary hypertension results from inhaled NO suppression of the endogenous NO-cGMP pathway, although this is not certain. Because of the variability of rebound pulmonary hypertension, it is important to wean patients from NO levels slowly and to supplement withdrawal by increasing oxygenation or intravenous vasodilators.

There is little evidence to suggest that low concentrations (< 40 ppm) of inhaled NO are toxic even for extended periods. The large, multicenter trials have not reported evidence of toxicity. It is important, however, to consider that NO may result in the formation of other toxic substances. NO is oxidized to nitrogen dioxide (NO_2) in the presence of oxygen, and even low concentrations of NO_2 (2–5 ppm) have been shown to be extremely toxic in rat lungs. Inspired NO_2 levels usually do not exceed 2 ppm with low concentrations of NO; however, it is possible that the NO_2 levels are higher in the alveoli.

Detailed studies of inhaled NO toxicity at the cellular level have been very limited. Animal studies have suggested that potential toxic effects of NO include surfactant inactivation, lung injury, and inflammation. These effects are believed to occur because of the reaction of NO with superoxide, leading to the formation of peroxynitrite and hydroxyl radicals. Other animal studies have suggested that NO is potentially mutagenic and that NO may inhibit enzyme activity *via* stimulation of adenosine diphosphate ribosylation. In addition, NO inactivates or alters the function of a number of iron- and heme-based proteins, including cyclooxygenase, lipoxygenase, and oxidative cytochromes. Inhaled NO also may inhibit platelet function and increase bleeding time, although increased clinical bleeding has not been observed.

Continuous monitoring of inspired NO and NO_2 concentrations is mandatory to protect against inadvertent delivery of toxic doses. Commercial NO systems are available that accurately deliver inspired concentrations between 1 and 80 ppm. NO in nitrogen is administered to the inspiratory limb of the ventilatory circuit in either a pulse or continuous mode to deliver a constant inspired concentration. Inhaled NO usually is delivered during mechanical ventilation, although it may be administered to spontaneously breathing patients *via* a close-fitting mask. Nasal-prong methods also have been described for home administration to patients with pulmonary hypertension.

Conclusion

Inhaled NO is not approved by the Food and Drug Administration and should be considered experimental (see footnote). Inhaled NO may cause selective vasodilation of the pulmonary circulation and increase oxygenation. The apparent beneficial effects of inhaled NO have been shown in various perioperative and intensive care settings. These benefits are particularly apparent in the setting of pulmonary hypertension, RV failure, or hypoxemia. The outcome benefit of inhaled NO has been limited to the decreased need for ECMO in patients with persistent pulmonary hypertension of the newborn and with hypoxic respiratory failure.

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