The promise and reality of nitric oxide in the diagnosis and treatment of lung disease

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ABSTRACT

Endogenously produced nitric oxide plays a major role in lung physiology and pathology. Inhaled nitric oxide given exogenously has been studied extensively as a treatment for many lung diseases, and the results suggest that it may help improve oxygenation in some patients. Several issues need to be addressed, however, before it can be used in routine clinical practice.

Early hopes for nitric oxide have only partly come to fruition

ALTHOUGH THE RESULTS HAVE BEEN mixed, research has shown that inhaled nitric oxide (NO) may benefit select groups of patients: adults with primary pulmonary hypertension and high-altitude pulmonary edema and newborns with persistent pulmonary hypertension.

Inhaled NO has been used investigationally as a treatment for a variety of lung diseases for the past decade. The impetus to study NO began in 1987 when it was identified as the endothelium-derived relaxing factor. At that point, many researchers believed this discovery would lead to innovative and effective treatments for lung disease. These hopes have only partly come to fruition.

NITRIC OXIDE IN THE BODY

Nitric oxide is present in virtually all mammalian organ systems, and it can be detected in the exhaled breath of humans in a concentration of 5 to 10 parts per billion. It plays a key role in virtually all aspects of lung biology.

The diffusible gas is produced by a group of enzymes that are collectively known as nitric oxide synthases (NOS). These enzymes convert the amino acid L-arginine into NO and L-citrulline. Oxygen regulates NOS expression and the enzyme activity.[1]

Nitric oxide is relatively unstable and is rapidly oxidized in solution to the stable metabolic end-products nitrite (NO_2) and nitrate (NO_3). In the human body, NO is inactivated when it binds to hemoglobin; this occurs at a rate 3,000 times that of oxygen.

Three isoforms of NOS, which are the products of individual genes, have been identified, including two constitutive forms: neuronal (nNOS or NOS I) and endothelial (eNOS or NOS III), and an inducible form (iNOS or NOS II). In general, NOS I is continuously expressed by neuronal cells and NOS III is continuously expressed by endothelial cells. NOS II is expressed after cells are exposed to specific cytokines and endotoxin.

The gas is primarily produced in the lungs by cells in the airways (eg, epithelial cells in the lungs, endothelial cells in vessels, and neurons). Once produced, NO is freely diffusible and enters target cells where it activates soluble guanylate cyclase to produce guanosine 3′,5′-cyclic monophosphate, which in turn mediates most of NO's effects. Nitric oxide also diffuses into the airway, where it can be measured in the gas phase.[2]

ROLE OF NITRIC OXIDE IN LUNG PHYSIOLOGY

Vascular effects. NO plays a well-established role in the endothelial-dependent control of vascular tone and in mediating vascu-

*The author discusses therapies that are not yet labeled (FDA-approved) for the use under discussion or products that are still investigational.

lar smooth muscle relaxation in the pulmonary circulation. Nitric oxide is a potent vasodilator in the bronchial circulation and may play an important role in regulating airway blood flow. It also modulates vascular tone through its vasodilatory properties.

Excess amounts of NO may cause the hypotension that is associated with sepsis. Decreased NO levels within the lungs may contribute to the pathological states associated with pulmonary hypertension.

Airway effects. NO promotes bronchodilation by directly relaxing the smooth muscles in the airway. Produced continuously by the overlying airway epithelium, NO can diffuse easily into the bronchial smooth muscle and cause smooth muscle relaxation through the activation of guanylyl cyclase to produce guanosine 3′,5′-cyclic monophosphate. In addition, NO can directly affect bronchial tone because it is the neurotransmitter of the inhibitory nonadrenergic, noncholinergic bronchodilator nerves. Nitric oxide generated by constitutive NOS in these nerves is thought to have a bronchodilatory effect.

NO may also play a critical role in ventilation-perfusion coupling in the lung. This theory is supported by the fact that endogenous NO levels in the lung change rapidly in direct proportion to inspired oxygen.

Nitric oxide is produced in the lungs

HOW NITRIC OXIDE LEVELS CHANGE WITH LUNG PATHOLOGY

Asthma

Patients with asthma have high levels of NO in their exhaled breath and high levels of NOS II enzyme expression in the epithelial cells of their airways. Both exhaled NO and NOS II expression return to normal levels after treatment with corticosteroids.

Although these findings suggest that NO plays a role in asthma pathogenesis, its exact role in airway reactivity remains elusive. Because NO is a bronchodilator, it is possible that the high levels of NO have a beneficial effect on the airway.

On the other hand, NO could be involved in the pathogenesis of asthma by modifying bronchial hyperresponsiveness or the underlying inflammation, or it may be a simple marker of inflammation.

Furthermore, because NO has both inflammatory and anti-inflammatory properties, it can modulate the underlying inflammation in asthma. Thus, the explanation for the elevated levels of NO in asthma has turned out to be more difficult than initially thought.[3]

Primary pulmonary hypertension

Patients with primary pulmonary hypertension have decreased levels of NO in their lungs, which may contribute to the development of pulmonary hypertension. Besides being a potent vasodilator, NO also inhibits proliferation of vascular smooth muscle and alters gene expression of several growth factors (eg, endothelial growth factor and platelet-derived growth factor). An NO deficiency may facilitate the proliferation of vascular cells and remodeling of the pulmonary vasculature.

Recently, we performed fiberoptic bronchoscopy in patients with primary pulmonary hypertension to measure intrabronchial NO and NO biochemical reaction products.[4] We found that NO and the reaction products of NO are reduced in patients with primary pulmonary hypertension compared with healthy individuals. Interestingly, the low levels of NO products correlated directly with the degree of pulmonary arterial hypertension. This evidence indicates that levels of vasodilators are directly related to constriction of the pulmonary vasculature and likely contribute to the pathogenesis of primary pulmonary hypertension.

Other lung diseases

Smokers have low levels of exhaled NO, which is probably because cigarette smoke contains high levels of NO that suppress endogenous production.

NO levels are also low in patients with cystic fibrosis, but the significance of this is not clear.

High NO levels are seen in inflammatory lung diseases such as bronchiectasis.

NO levels are also high in patients with lymphangioleiomyomatosis, which may be related to NOS III expression in the smooth muscles of lymphangioleiomyomatosis lesions.[5]

THERAPEUTIC USES OF INHALED NITRIC OXIDE

Acute respiratory distress syndrome

Observational and retrospective studies first suggested that inhaled NO benefits patients with acute respiratory distress syndrome.[6–8] However, randomized, double-blind studies have produced less-than-exciting results.

In a randomized phase 2 study[9] of 177 patients with acute respiratory distress syndrome, patients received either placebo (nitrogen gas) or inhaled NO at one of five concentrations: 1.25, 5, 20, 40, or 80 ppm. At the end of the 28-day study, the mortality rate, the number of days off mechanical ventilation, and the number of days alive after meeting oxygenation criteria were the same in the placebo and pooled treatment groups. Although oxygenation and pulmonary arterial pressure improved slightly in the patients receiving inhaled NO, the improvements were only temporary.

More recently, in a phase 3 study,[10] 203 patients with this disease were randomized to receive either 10 ppm of NO or placebo (N_2 alone). The results of this 28-day study showed that the inhaled NO did not affect mortality or the duration of mechanical ventilation.

Therefore, inhaled NO is not currently recommended as a routine treatment for acute respiratory distress syndrome.[11] It may, however, be an effective "rescue therapy" for patients with hypoxemia that does not respond to conventional treatment.[11]

Nitric oxide's exact role in airway reactivity is not known

Primary pulmonary hypertension in adults

Exogenous administration of NO by inhalation is probably the most effective and specific therapy for primary pulmonary hypertension. In a study[12] of 8 patients with primary pulmonary hypertension who received NO (80 ppm) upon inspiration via nasal cannulas, researchers measured pulmonary artery pressure and pulmonary vascular resistance at baseline and after 15 minutes of treatment, among other variables. All patients experienced statistically significant reductions in both of these measurements.

However, NO is not a widely used treatment for primary pulmonary hypertension because it is costly and the delivery systems have technical problems that remain unsolved.

Persistent pulmonary hypertension in newborns

Roberts et al[13] theorized that because inhaled NO decreases pulmonary vascular resistance in newborns, it may also decrease severe hypoxemia in infants with persistent pulmonary hypertension. To test their theory, they randomly assigned 58 full-term infants with this condition to receive either a control gas (nitrogen) or NO (80 ppm) mixed with oxygen from a ventilator.

Within 20 minutes of administration, the inhaled NO increased oxygenation by 53% compared with 7% for the control gas. The beneficial effects were sustained in three fourths of the infants who initially responded. Although the number of deaths was the same in each group, only 40% of the inhaled NO group required extracorporeal membrane oxygenation compared with 71% of the control group.

After studying full-term and nearly full-term newborns with hypoxic respiratory failure, the Neonatal Inhaled Nitric Oxide Study Group came to a similar conclusion.[14] They, too, found that inhaled NO (20 ppm) reduced the need for extracorporeal membrane oxygenation but did not affect mortality. Inhaled NO is now used fairly routinely in infants with respiratory distress and hypoxemia.

High-altitude pulmonary edema

Scherrer et al[15] studied the effects of NO in a high-altitude laboratory (altitude 4,550 m) in 18 mountaineers who were prone to high-altitude pulmonary edema and 18 mountaineers who were resistant to this condition. They found that the susceptible subjects had more pronounced pulmonary hypertension and hypoxemia than the resistant subjects. When the NO was inhaled, it attenuated the pulmonary vasoconstriction that was produced by short-term hypoxia and improved arterial oxygenation in the 10 subjects with radiographic evidence of pulmonary edema.

This beneficial effect was likely related to the favorable action of NO on the distribution of blood flow in the lungs. A defect in NO

synthesis may contribute to high-altitude pulmonary edema.

POTENTIAL USE IN ASTHMA PATIENTS

Monitoring exhaled NO

Because both NO and NOS II expression return to normal in patients with asthma after they receive treatment, exhaled NO may be a potentially useful marker of airway inflammation. Monitoring exhaled NO is promising for several reasons. It can be done noninvasively, it can be performed repeatedly, and it can be used in children and patients with severe airflow obstruction for which other techniques are difficult or not possible to perform. Exhaled NO may also be more sensitive than tests that are currently available to detect airway inflammation, which may allow us to further optimize therapy.

Several issues, however, need to be addressed before exhaled NO can be a useful clinical tool in routine asthma monitoring and management. First, we need to have a better understanding of the role of NO in asthma pathogenesis. Second, large population studies are needed to determine the normal range of exhaled NO levels and the effect of systemic diseases, lung diseases other than asthma, and other factors on exhaled NO levels. Third, the methods and equipment for measuring NO need to be standardized and made more portable, less cumbersome and expensive, and easier to maintain and calibrate.

Exhaled nitric oxide may be a useful marker of airway inflammation

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