Inhaled Nitric Oxide for Preterm Neonates

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KEYWORDS

- Preterm infants • Inhaled nitric oxide
- Bronchopulmonary dysplasia • Brain injury
- Pulmonary hypertension

The identification of nitric oxide (NO) as an endothelial-derived vasodilator has led to dramatic advances in the understanding of vascular biology over the past 20 years. Inhaled NO (iNO) was investigated as a pulmonary vasodilator in term neonates with respiratory failure within 4 years of discovery of NO[1,2] iNO is now an approved and established therapy for term and near–term neonates with hypoxic respiratory failure. The introduction of iNO therapy has greatly reduced the need for extracorporeal membrane oxygenation in this group of neonates.[3,4] Hypoxic respiratory failure is also a significant contributor to mortality and morbidity in preterm neonates in the neonatal intensive care unit (NICU). Respiratory failure in preterm neonates, however, has a different cause and clinical course from that occurring in term neonates. The underlying pathologic changes in preterm neonates involve surfactant deficiency, pulmonary immaturity, lung injury with inflammation, oxidant stress, and impaired angiogenesis. Hypoxemia in preterm respiratory failure is often a result of ventilation/perfusion (V/Q) mismatch and intrapulmonary shunting. Pulmonary hypertension can also occur in preterm neonates as a complication of respiratory failure, pulmonary hypoplasia secondary to preterm prolonged rupture of membranes (PPROMs), and oligohydramnios or as a late complication in bronchopulmonary dysplasia (BPD).

Despite improved survival in the era of surfactant therapy and antenatal steroids, BPD and brain injury remain significant adverse outcomes in extremely low birth weight preterm neonates. There is growing interest in the application of iNO as a tool to prevent these adverse outcomes, taking advantage of the beneficial effects of iNO on gas exchange, inflammation, and vascular dysfunction.[5–7] Translational investigations in animal models provided the evidence to consider these beneficial effects as biologically plausible. The history of neonatology is, however, filled with well-intentioned therapies that resulted in significant harm to this vulnerable population. The use of iNO therapy has so far been rightfully limited to controlled clinical trials.

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The purpose of this review is to briefly outline the biology of NO, the role of NO in lung development, the rationale for its use in preterm infants, and the results of recent clinical trials. This review also discusses the role of iNO in the prevention of BPD and brain injury in addition to the unanswered questions from the clinical studies, and identifies areas of future research with this therapy.

BIOLOGY OF NITRIC OXIDE

NO is synthesized as a byproduct of the conversion of L-arginine to L-citrulline by nitric oxide synthase (NOS).[8,9] NO diffuses rapidly across cell membranes; in the case of blood vessels, it reaches the adjacent smooth muscle cells. NO activates soluble guanylate cyclase and increases cyclic guanosine 3′,5′- monophosphate (cGMP) levels in the vascular smooth muscle cell (**Fig. 1**).[10,11] An increase in cGMP levels is associated with decreased cytosolic calcium and relaxation of smooth muscle.[12] iNO can cause selective vasorelaxation of smooth muscle cells by diffusion from the alveoli.[13] NO is rapidly inactivated by combining with hemoglobin in the blood to form nitrosyl hemoglobin and is then oxidized to methemoglobin and inorganic nitrates and nitrites.[14,15]

There are three isoforms of NOS that differ in the site of expression and regulation of their function. Neuronal NOS (NOS-1, nNOS) is constitutively expressed primarily in the airway epithelium in the lung, and its activity is calcium dependent. Inducible NOS (NOS-2) is present in the airway, vascular smooth muscle, and macrophages; its expression is induced by lipopolysaccharide, cytokines, and other mediators of inflammation, and its activity is calcium independent. Endothelial NOS (NOS-3, eNOS) is constitutively expressed in the vascular endothelium and airway epithelial cells, and its activity is calcium dependent.[14] The levels of eNOS and nNOS proteins show developmental increase in late gestation in primates, sheep, and in rodents.[16,17] There is

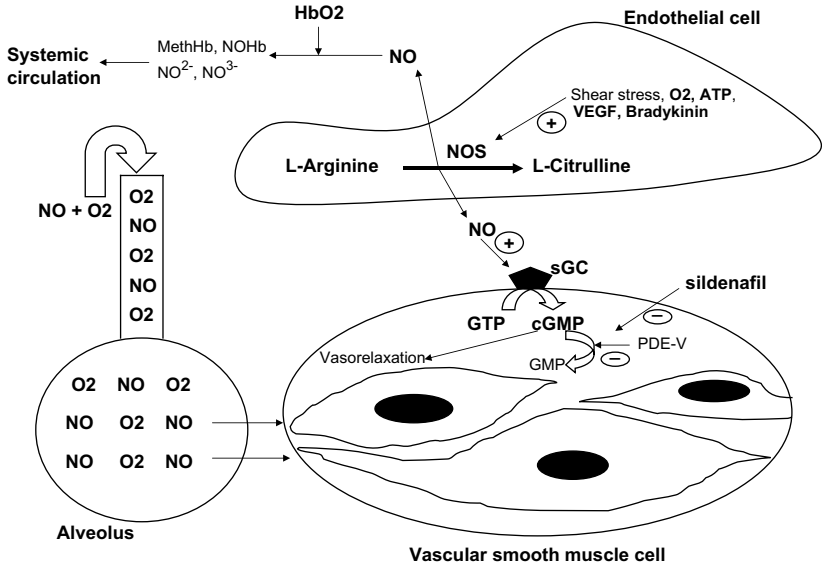

Fig. 1. Mechanism of action of NO. Endogenous NO diffuses from endothelial cells to the smooth muscle cells, whereas iNO diffuses across the alveolus and reaches the smooth muscle cells causing vasorelaxation by means of generation of cGMP. NO is quenched by hemoglobin on reaching the lumen of the pulmonary vessel. GTP, guanosine triphosphate; PDE-V, Phosphodiesterase-V.