EDITORIAL VIEWS

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Inhaled Nitric Oxide

The Past, the Present, and the Future

A decade ago, nitric oxide (NO) was viewed primarily as a toxic gas responsible for a portion of the morbidity related to air pollution. In contrast, NO currently is recognized as a major endogenous mediator of multiple physiologic processes, and the use of inhaled NO is expanding rapidly into anesthesia and critical care. This article will review the development of inhaled NO therapy, will summarize the current status of this agent, and will speculate on its eventual applications.

During the early 1980s, there developed an increasing understanding of the ability of the endothelium to modulate vascular tone. For example, acetylcholine may produce vasodilation in vessels with intact endothelium but vasoconstriction in vessels denuded of endothelium. Thus, when appropriately stimulated, the endothelium is able to produce substances that dilate the adjacent vascular smooth muscle. In 1987, NO was identified as the major endothelium-derived relaxing factor.[1] Nitric oxide diffuses from the endothelium into vascular smooth muscle, where it activates soluble guanylate cyclase; the subsequent increase in levels of intracellular cyclic guanosine monophosphate produces smooth muscle vasodilation. Endothelium-independent nitrovasodilators such as nitroglycerin and nitroprusside directly result in intracellular release of NO and subsequent guanylate cyclase activation. The role of endogenous NO in the regulation of vascular tone in normal and in disease states is a rapidly growing area of investigation in vascular biology.[1] Increased NO synthesis may be responsible for vasodilation in septic shock[2] so that inhibition of NO synthesis may be an effective therapy of hypotension.[3] In addition, NO appears to be a major endogenous neurotransmitter.[4]

The decision to use inhaled NO as a therapy for pulmonary disease required understanding several additional concepts. Nitric oxide is not effective during systemic administration because NO is extremely rapidly inactivated by hemoglobin.[5] Thus, exogenous inhaled NO may diffuse from the alveoli to pulmonary vascular smooth muscle and produce pulmonary vasodilation, but any NO that diffuses into blood will be inactivated before it can produce systemic effects. Therefore, inhaled NO may produce selective pulmonary vasodilation, a goal that has previously eluded research. The final concept required to develop the therapeutic use of inhaled NO was the understanding that NO *per se* has relatively low toxicity[6,7]; in contrast, nitrogen oxides such as NO_2 that form from NO over time are the major toxic compounds.[8] Thus, inhaled NO in theory may be both safe and effective as a selective pulmonary vasodilator.

The idea that inhaled NO may produce selective pulmonary vasodilation led to animal studies in which pulmonary hypertension was produced by global hypoxia, thromboxane-mimetic infusion, or heparin-protamine interactions.[9,10] These studies convincingly demonstrated that inhaled NO at concentrations of 5–80 ppm produces pulmonary vasodilation that is both rapid and completely reversible. Importantly, no systemic vasodilation or other adverse effects occurred in these studies.

These animal studies rapidly have led to clinical studies of the pulmonary vasodilator effects of inhaled NO. Two such studies appear in this issue of ANESTHESIOLOGY.[11,12] Frostell *et al.* describe the effects of inhaled NO during hypoxia in human volunteers. In the absence of hypoxia, inhaled NO did not alter pulmonary or systemic hemodynamics. Inhalation of 12% O_2 alone increased pulmonary artery pressure (PAP) from 15 to 20 mmHg and increased pulmonary vascular resistance (PVR) from 73 to 125 dynes · s · cm^{-5}. Addition of 40 ppm NO to the inhaled gas decreased PAP and PVR to control values but did not affect mean arterial pressure (MAP) or systemic vascular resistance (SVR). The effect of inhaled NO occurred within the first minute of inhalation. Studies in two subjects suggested that the maximal effect of inhaled NO occurred at concentrations of 10 ppm NO. Discontinuation of inhaled NO during hypoxia resulted in only a partial increase in PAP and PVR. These data confirm the results of animal

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