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Review

Inhaled nitric oxide: Current clinical concepts

Pavan Bhatraju [a], Jack Crawford[b], Michael Hall[c], John D. Lang Jr. [d, *]

[a] Department of Medicine, University of Washington Medical Center, Seattle, WA, United States
[b] Division of Cardiothoracic Anesthesiology, Pediatric Cardiac Section, Department of Anesthesiology, The University of Alabama at Birmingham, Birmingham, AL, United States
[c] Division of Cardiothoracic Anesthesiology, Department of Anesthesiology and Pain Medicine, University of Washington Medical Center, Seattle, WA, United States
[d] Department of Anesthesiology and Pain Medicine, University of Washington Medical Center, 1959 NE Pacific St., Suite EE-201, Seattle, WA 98195-6540, United States

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ABSTRACT

Nitric oxide (NO) has come far since being discovered serendipitously to relax vascular smooth muscle. Initially, administered to animals to reduce pulmonary artery pressures and improve oxygenation. It now enjoys FDA approval for administration to newborns with pulmonary hypertension but is used common place for other critical cardiopulmonary ailments. While never quite living up to expectations, newer applications show greater promise as a therapy especially in the area of ischemia-reperfusion. The following will give a clinical overview of inhaled nitric oxide as a gas, as applied to the pediatric patient population, and to those adults suffering with cardiopulmonary and hematologic disease. Lastly, due to more recent discoveries, the effects of how NO may be used to treat disorders such as ischemia-reperfusion, will also be reviewed.

Contents

* Corresponding author.
E-mail address: jdlang@uw.edu (J.D. Lang).

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1. Introduction

Nitric Oxide (NO) is an odorless, colorless gas first identified by Joseph Priestley in 1774. At that time, it was described to be toxic and highly reactive. Following this initial description, NO was largely thought of as a pollutant and discussion was generally limited to its toxic potential and industrial uses. It would not be until several centuries later that its role in biologic systems was suggested and subsequently proven.

In 1987, Palmer and colleagues published work in Nature characterizing endothelium-derived relaxing factor (EDRF) as NO [1–3]. This work demonstrated NO's critical role in biologic systems. Specifically, these investigators revealed that NO was released from vascular endothelium and played a crucial role in mediating smooth muscle vasorelaxation. Subsequently, numerous investigations have provided additional insights into the complexities and ubiquitous nature of NO. However, much remains to be learned.

Briefly, NO is a generated in vivo from the amino acid L-arginine in the presence nitric oxide synthase (NOS). NO exerts its effects as a vasorelaxant via activation of guanylate cyclase (sGC), which enhances cyclic guanosine monophosphate (cGMP), ultimately resulting in smooth muscle relaxation. However, its role in biologic systems extends way beyond vasomotor control. In fact, NO plays a dual role both as a pro- and anti-inflammatory mediator. Moreover, NO down regulates leukocyte responses, decreases platelet aggregation, facilitates neurotransmission, augments bronchodilation, and attenuates inflammatory responses from such perturbations as ischemia and reperfusion [4–7]. As its functions have been further elucidated, NO has attained a therapeutic role in a variety of disorders. Following Food and Drug Administration (FDA) approval in 1999 for a select group of neonatal patients, commercial availability of delivery systems and increased understanding of its role in disease states assisted in expanding the variety of applications it now enjoys [6,8]. Inhaled NO's utility in the modulation of pulmonary vasomotor tone is proven, and deemed part of standard clinical practice for pulmonary hypertension, especially in the pediatric population. Other disorders where inhaled NO has been used therapeutically include cardiac and lung transplantation, and acute respiratory distress syndrome (ARDS). Fittingly, continued work has focused on extending its therapeutic application in a host of other disorders such as acute myocardial infarction, sickle cell disease and solid organ transplantation. The information that follows presents a summary of NO biochemistry, potential NO toxicities, and will then expand on current clinical disorders where inhaled NO has demonstrated clinical efficacy or where there is emerging evidence of clinical promise.

1.1. NO biochemistry

NO is a highly reactive molecule with other free radical species and possesses an extremely short half-life [2]. NO is produced endogenously or delivered exogenously where it can react with a variety of cellular targets resulting in vasorelaxation, enhanced neuronal transmission, reduced apoptosis, inhibition of neutrophil aggregation and adhesion, and modulate vascular smooth muscle proliferation [9]. NO synthesis is dependent on the enzyme nitric oxide synthase (NOS). This complex enzyme system generates NO from the terminal nitrogen atom of L-arginine in the presence of NADPH and dioxygen. NOS binds flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), heme, tetrahydrobiopterin (BH4) and calmodulin from L-arginine and oxygen by a family of three NO synthases (NOS), all of which are expressed in numerous cell types. The generation of NO leads to several actions that promotes smooth muscle relaxation. First, activation of guanylate cyclase raises the level of intracellular cGMP which in turn inhibits the entry of calcium into the cell thereby inducing smooth muscle relaxation. Secondly, activation of K^+ channels leads to cellular hyperpolarization and relaxation. Finally, stimulation of cGMP-dependent protein kinase activates of myosin light chain phosphatase leading to dephosphorylation of myosin light chains resulting in smooth muscle relaxation. NOS proteins are related but encoded by distinct genes. Three distinct isoforms have been described. Neuronal NOS (NOS I), is produced in central and peripheral nerves and is pivotal in neuronal transmission and cell to cell communication within the central nervous system; Inducible NOS (NOS II), is exactly that, NOS that is induced by an inflammatory stimulus such as a microbe [10]. Unlike the other types of NOS (I and III), NOS II is generally not considered constitutive and is independent of calcium regulation. While NOS II is expressed by immune cells such as neutrophils and macrophages, it is also present in other cell lines including hepatocytes. Endothelial NOS (NOS III), is constitutively expressed by endothelial cells and is critical for the regulation of vascular function, more specifically vasorelaxation. Classically, the ability of NO to elicit vasorelaxation is due to its ability to increase intracellular levels of cyclic guanosine monophosphate (cGMP) through the activation of soluble guanylate cyclase (sGC). cGMP-dependent protein kinases in turn decrease the sensitivity of myosin to calcium-induced contraction and lower intracellular calcium by activation of calcium-sensitive potassium channels and inhibit the release of calcium from the sarcoplasmic reticulum.

1.2. Fate of inhaled NO

1.2.1. Chemical reactivity

Inhaled NO will react avidly with other free radical species,