

NITRIC OXIDE, (NO): A CLINICAL PRIMER

by David Wheeler RRT, NPS



Recently there has been a great deal of literature concerning my favorite free radical, Nitric Oxide (NO) and so I thought it valuable to catalog a brief review of the many wonders of this excessively obliging and adaptable signaling molecule.

Nitric Oxide, (NO), is a colorless gas that has gained a greater significance recently. NO was named "Molecule of the Year" in 1992 and it has experienced an exponential increase in attention since that time. Nitric Oxide is a ubiquitous signal molecule which has a role in regulating airway muscle tone, vasodilatation, ventilation and perfusion relationships, neuro-signaling, epidural defense, erectile function and stem cell differentiation.

NO is a competent vasodilator and it is this role that has gained NO the clinical function bedside clinicians are most familiar with. The principal clinical application of NO has been in the reversal of Persistent Fetal Circulation. The mechanism of vasodilatation has been well documented. Clinically, the dilation of the newborn pulmonary vasculature serves to normalize extrauterine circulatory patterns and facilitates the closure of intrauterine shunts. The foramen ovale and ductus arteriosus require a normalization of pulmonary capillary pressures to produce their closure and NO is a powerful vasodilator towards that end.

Indeed, the most frequent use of NO is in the treatment of Persistent Pulmonary Hypertension of the Newborn, (PPHN). This condition exists for any number of reasons and demonstrates

an elevated pulmonary vascular resistance, (PVR). This increased PVR creates significant right-to-left shunting that is eliminated with the vasodilatation of the pulmonary vascular bed. The rapid reduction of pulmonary vascular resistance allows the naturally occurring pressure gradients to initiate reversal of right-to-left shunting and normalization of cardiopulmonary hemodynamic pressures. Additionally, NO has been demonstrated to reduce the oxygen index and increase the PaO₂ of infants with hypoxic respiratory failure of varying etiologies. NO has been demonstrated in several studies to reduce both the need for infants to be given ECMO and the incidence of long term lung disease however, one should note that while low dose iNO (inhaled Nitric Oxide), may improve oxygenation it does not significantly impact survival in severely hypoxic preterm infants. It has been suggested that the preterm, severely hypoxic infant may experience a greater degree of toxicity from iNO.

The indispensable and fundamental role of endogenous Nitric Oxide is its function as a signaling molecule in maintaining basal vascular tone and the hypoxic vasoconstrictive response. The endogenous NO level unambiguously relates to the degree of vasoconstriction as it relates to hypoxia. Indeed the level of eNO, (exhaled NO), correlates directly with pulmonary blood flow.

One reasonably interesting study of Tibetans residing at 4,200 feet found the adaptive response to altitude of NO production and transfer was significant. The NO transfer rate of Tibetans was seven times higher than individuals at sea level. Tibetan NO consumption and eNO levels were elevated as well. This study also suggested that NO acts with oxygen to reduce Pulmonary Vascular Resistance, (PVR) and their actions are additive in effect.

NO is a very selective pulmonary vasodilator. NO is exceptionally selective as it vasodilates areas of the pulmonary vessels that are ventilated to the greatest degree.

One must be mindful of the fact that the pulmonary vasodilatation occurs primarily in the areas of the lung that are ventilated to the greatest degree. The pulmonary capillary blood flow is redirected from areas of hypoventilation through this extraordinarily selective vasodilatation.

The inverse relationship between pulmonary NO and pulmonary vascular pressure is well documented and appreciated by most informed clinicians. NO is regarded as an extremely potent vasodilator, may have a role a primary signaling molecule in the early differentiation events of embryonic stem cells, acts to signal adaptive responses of the cardiopulmonary vasculature, enhances endothelial barrier functions, NO has potential application as a topical antimicrobial agent, regulates vascular tone, neurotransmission, the regulation of cell death.

An additional clinical effect may be the enhancement of oxygenation in ALI and ARDS presentations. This outcome however must be tempered in the context of a greater pulmonary vasculature. The increased gas liquid inter-phase is the principal mechanism of the increased oxygenation in these states. Indeed, the prudent clinician will note that the NO levels of 10 ppm recommended in hypoxic ARDS are dramatically curtailed when con-

LÜČČĀ" ČĀ" āšě" đ



a? Vf e` _E> GV_eZRē` c € UVdZ_X VU Wc
 ^ Rdd TRdf Rlej UZRdeVcd Rd h V]] Rd
 VgVcj URj aReZ_e ecR_da` ced

č C d`MiZgZh" Vā VhgZVnid j hZ
 č EM Zci YhxcZX Vagb`
 č`eiZgMZY E: E`S8E6E
 č`B G>Xdb eM Vānid` (I
 č`C 78`xāgM`dc`[dg= 6OB 6I` hñj V`dch

TR]]))) Žžž Ž #S) mh h h žā? Vf e` _ZT` ^

CIRCLE READER ACTION CARD # 23

sidering the 40 ppm frequently utilized in the post operative setting. The clinical intention or goal will determine the dose of iNO. In high PVR states the clinical goal will be to decrease PVR and normalize pulmonary-capillary blood flow. The dose will begin at 40 ppm. In hypoxic states the clinical goal is to increase V/Q matching and the dose should be 10 ppm.

The role of iNO would seem to be the panacea for the attenuation of ischemia-reperfusion (IR), injury. It has been demonstrated that iNO is not clinically significant in the prevention or treatment of IR injury.

The measurement of exhaled NO plays a vital role in the assessment of the patient with reactive airways disease and asthma. NO levels rise commensurate with inflammatory responses in the larger and mid-range airways. There is a direct corollary between the level of exhaled NO and the level of airway inflammation. At one time it was suggested that the majority of NO was formed in the nares and sinuses however, recent investigations indicate that the majority of NO is produced below the glottis.

NO is a very powerful signaling molecule. This form of gaseous signaling molecule is very rare in nature however; the essential clinical utility of NO remains its potency as a vasodilator. The smooth muscle relaxation effect is produced through the activation of guanylate cyclase and resulting increase in intracellular cyclic guanosine 3-5-monophosphate.

Nitric Oxide is synthesized in three ways. Neuronal nitric oxide synthesis occurs, as the name implies, by isoforms in the nervous system. Inducible NO or Type II is released by macrophage activity and type III endothelial NO synthesis takes place in specialized endothelial cells.

Nitric Oxide is absorbed systemically via the pulmonary capillary bed. When the pulmonary capillaries are adequately oxygenated the NO combines with saturated hemoglobin to form methemoglobin and nitrite and these are the predominant byproducts that enter the systemic circulation. The excess nitrate is eliminated through normal urine output.

NO has been termed an extraordinary signaling molecule. This molecular messenger plays a major role in normal erectile function. NO mediators enhance vasodilation responsible for penile engorgement. NO production on the skin plays a vital role in barrier function and blood flow in the epidermal microvasculature. NO may also be responsible for protecting against Ultraviolet induced apoptosis. At least three different categories of NO production on the skin are requisite molecular signaling agents for both dermal barrier protection and wound healing.

This reactive free radical NO has a dramatic role in the immune response of the macrophage. The macrophage is capable of releasing massive burst of NO that play an indispensable role in the elimination of bacteria and certain types of tumor cells. NO has a pro-inflammatory mediator response. As a neurotransmitter NO is key in conduction to peripheral nerves and regulation of neuronal apoptosis.

SLEEP STUDY, EEG, RT & EMG SUPPLIES



INTEGRA NEUROSUPPLIES™

www.integraneurosupplies.com

800-638-7693 (Phone) • 800-303-3748 (Fax) • sales@integraneurosupplies.com

Integra NeuroSupplies is a trademark of Integra LifeSciences Corporation. © 2005 Integra LifeSciences Corporation. All rights reserved. NS861-05/05

CIRCLE READER ACTION CARD # 52

The astute practitioner will employ NO with both caution and discretion. Again, the current thought is that iNO is very beneficial in persistent fetal circulatory states, in reduction of elevated PVR and somewhat helpful in hypoxic ARDS. The informed clinician will note that the response to iNO should be rather immediate and that prolonged exposure to high concentrations of iNO may yield unsatisfactory or less than favorable consequences. In the infant with persistently high PVR one should see a rather prompt reduction in PVR with the administration of iNO so too in adults with elevated PVR. In ARDS hypoxic states iNO at 10ppm should yield an immediate increase in PaO₂.

One might call NO a Godsend in certain cases, however discretion and evidence must dictate clinical application. The mounting evidence suggests that we are just now beginning to appreciate the unlimited clinical potential of iNO. NO may have the greatest utility in the area of stem cell research as a signal molecule for undifferentiated cells. I feel we are barely capturing the potential of this fascinating molecule and thus I anticipate frequent readjustments to the current clinical practice.