Nitric Oxide in Anesthesia: When to Say "NO"

Robert N. Sladen, MB ChB

Introduction

The physiologic impact of nitric oxide (NO) was unleashed upon the scientific community as recently as 1987, when it was determined that endothelium-derived relaxing factor (EDRF) and NO were one and the same. Hitherto, this small, highly unstable diatomic free radical was considered to be an atmospheric pollutant derived from the combustion of fossil fuel (i.e. automobile exhaust), tobacco or lightning.[1] Its concentration in the atmosphere is 10-100 parts per billion (ppb); in heavy traffic it is often more than 1.5 parts per million (ppm) and in the depth of a glowing cigarette it may reach 400-1,000 ppm.

The last decade has seen an exponential growth in the scientific literature and knowledge of the multiple physiologic roles of endogenous NO and its therapeutic application by inhalation in the dose range of 1-80 ppm. This lecture will provide a basic review of the physiology, toxicity and therapeutic applications of NO, referred to by Scientific American in the mid-1990s as the "Molecule of the Decade". It is largely based on two excellent current reviews: a Medical Intelligence article in the October 1999 issue of Anesthesiology by Steudel et al,[2] and the March 1999 issue of Respiratory Care, which contains a number of detailed articles based on a multidisciplinary conference on nitric oxide.[1,3-7]

Endogenous Synthesis of Nitric Oxide

Endogenous formation of NO is controlled by the enzyme nitric oxide synthase (NOS), which catalyzes the hydroxylation of the non-essential amino acid L-arginine to L-citrulline (Figure 1).

There are several distinct subtypes of NOS, which determine the site and function of NO synthesis (Table 1).[2]

Constitutive NOS

Constitutive NOS (cNOS) is calcium and calmodulin dependent and releases small amounts of NO for short periods of time ("tonic" NO release).

There are two forms of cNOS:

NeuronaI NOS

Neuronal NOS (nNOS) is found predominantly in nerve tissue, where it modulates peripheral neurotransmission, induces cerebral vasodilation, and plays an important role in information storage, memory, pain and behavior. It also mediates smooth muscle relaxation in the GI tract, GU tract and respiratory tract.

Endothelial NOS

Endothelial NOS (eNOS) exists in the vascular endothelium and mediates the activity previously ascribed to EDRF. Its activity is increased by calcium releasing modulators (e.g. acetylcholine, bradykinin) and vascular shear stress. It is an important modulator of systemic and pulmonary vascular resistance, and in the myocardium it opposes catecholamine-induced inotropic effects.

Inducible NOS

Inducible NOS (iNOS) is calcium and calmodulin independent, and is induced by cytokines in inflammatory cells (macrophages, granulocytes), hepatocytes, myocardial cells and vascular smooth muscle.

At low levels of activation, iNOS enhances the response to infection (e.g. tuberculosis, parasites), and promotes inflammation and wound healing.

In severe sepsis, iNOS produces huge amounts of NO for protracted periods of time, and is largely responsible for the profound systemic vasodilation characteristic of the systemic inflammatory response syndrome (SIRS).

Actions of Nitric Oxide

Most actions of NO are mediated through its activation of soluble guanylate cyclase, which catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cyclic GMP).

Cyclic GMP has two major actions: relaxation of vascular smooth muscle and suppression of the inflammatory response. It inhibits leukocyte adhesion, platelet activation and aggregation, and cellular proliferation. Cyclic GMP is converted to GMP by phosphodiesterase I and V. Thus, the

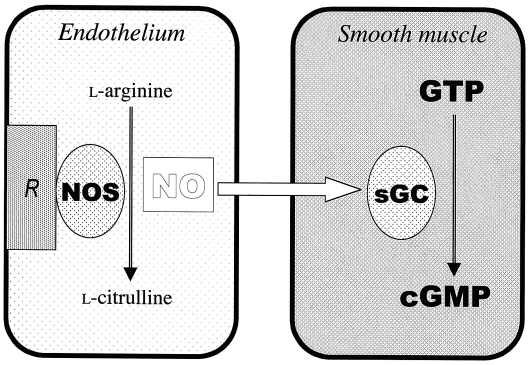

Figure 1: Endothelial synthesis of Nitric Oxide.
Schematic of endothelial synthesis and action of nitric oxide. Endothelial nitric oxide synthase (NOS) is activated by a G-protein coupled receptor complex (R) at the cell membrane. NOS acts on its primary substrate, L-arginine, which is converted to L-citrulline with the formation of nitric oxide (NO). NO diffuses into the smooth muscle cell where it activates soluble guanylate cyclase (sGC), which in turn catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGNW). In smooth muscle, the primary function of cGMP is to induce relaxation (vasodilation).

local action of NO can be enhanced by the administration of a selective phosphodiesterase V inhibitor, such as sildenafil (Viagra®). NO itself is rapidly inactivated by binding to intracellular heme and heme proteins (oxyhemoglobin, oxymyoglobin, guanylate cyclase, cyclooxygenase, cytochrome P450). This accounts for the selective effect of inhaled NO on the pulmonary circulation: it is inactivated in the blood and therefore does not enter the systemic circulation. It may also account for the vasospasm associated with bleeding (e.g. subarachnoid hemorrhage), due to the local inactivation of endogenous NO.

Role of Endogenous Nitric Oxide in Sepsis

The formation of huge quantities of inducible NO plays a central role in the inflammatory cascade of sepsis. It also contributes to many of the cardinal clinical manifestations of sepsis, including refractory vasodilation (and norepinephrine unresponsiveness), myocardial depression and loss of hypoxic pulmonary vasoconstriction.[4]

Numerous experimental studies have examined the role of blockade of endogenous NO production in animal models of sepsis. The most common approach is to use agents that compete with L-arginine such as L-NAME (N^G-nitro-L-arginine methyl ester) or L-NMMA (N^G-mono-methyl-L-arginine). These produce nonselective NOS blockade and impede the formation of NO from both iNOS and eNOS. In sepsis, the administration of L-NAME and L-NMMA effectively increases systemic vascular resistance and mean arterial pressure, i.e. it reverses the effect of iNOS. However, it also impairs eNOS and "tonic" NO-induced vasodilation. This increases pulmonary vascular resistance and significantly impairs cardiac output, oxygen delivery and regional organ perfusion, and actually worsens mortality.

Preliminary, uncontrolled clinical studies suggest that careful use of low doses of L-NAME or L-NMMA may help to support blood pressure until vascular responsiveness to vasopressor drugs is restored.[8] However, a beneficial effect on outcome has not yet been established.

Selective inhibition of iNOS has the theoretical advantage of preserving NO production from eNOS. Selective agents such as glucocorticoids and guanidine derivatives have had a more favorable effect on mortality in preliminary animal studies.

Methylene blue blocks soluble guanylate cyclase and blunts vasodilation without inhibiting NO production, and in low doses has shown some favorable effects on regional perfusion.[9]

Inhaled Nitric Oxide

Delivery and Toxicity of Inhaled Nitric Oxide

The most important consideration in the use of inhaled NO is to understand that it has a rather narrow therapeutic range. Pulmonary hypertension and hypoxemia may be considered states of endogenous NO deficiency which are corrected by the administration of I - 40 ppm inhaled NO. On the other hand, levels above 80 ppm. provide an increasing risk of toxicity from NO itself, or from NO reactive products. In other words, with regard to NO, "too little is bad, but too much is worse."

Commercial Manufacture

NO is produced commercially by the reaction of sulfur dioxide with nitric acid, sodium nitrite with sulfuric acid, or by the oxidation of ammonia over platinum at 500 °C. It is stored in aluminum alloy tanks, in which it is stable for up to two years.[1]

The most important hazard of its production is the formation of toxic nitrogen dioxide (NO_2), whose concentration must be kept less than 2% of NO concentration, and its reaction with water to form nitric acid:

$$2\ NO + O \rightarrow 2\ NO_2$$
$$2\ NO_2 + H_2O \rightarrow 2\ HNO_3 + NO$$

Nitric Oxide Toxicity[3]

Methemoglobinemia

The affinity of NO for hemoglobin is 1500 times greater than carbon monoxide. NO oxidizes the ferrous ion (Fe^{2+}) in hemoglobin to ferric ion (Fe^{3+}), to create methemoglobin

Table 1: Subtypes of Nitric Oxide Synthase (NOS)

Type	Subtype	Site	Actions
Constitutive (cNOS) *"Tonic" release of NO*	Neuronal (nNOS)	CNS, PNS viscera	neuronal function smooth muscle relaxation
	Endothelial (eNOS)	vascular endotheliurn leukocytes, platelets	smooth muscle relaxation inhibits inflammatory response
Inducible (iNOS) *"Phasic" release of NO*		vascular endothelium inflammatory cells	vasodilation enhanced inflammation

CNS = central nervous system, PNS = peripheral nervous system

(MetHb), which is incapable of binding oxygen. MetHb shifts the hemoglobin dissociation curve to the left thus decreasing tissue oxygen delivery. Normally MetHb levels are kept below 2% by red cell MetHb reductase, which is deficient in some segments of the population (e.g. native Americans).

Excess production of MetHb appears to be directly related to the dose of inhaled NO, and is extremely uncommon when the dose is kept less than 20 ppm.

Methemoglobinemia results in cyanosis, dyspnea and abnormal pulse oximetry readings. It can be treated by infusion of methylene blue (which increases levels of MetHb reductase) or ascorbic acid.

Nitric Oxide (> 80 ppm)

In animal studies low doses of NO attenuate acute inflammatory changes in induced lung injury (i.e. an antioxidant effect).

In contrast, high doses of NO are prooxidant, and induce changes consistent with ARDS (alveolar-capillary permeability, surfactant depletion and acute inflammation). Exposure to NO may also cause DNA alteration with either tumoricidal or tumorpromoting effects.[2]

Nitric Oxide Reactive Products

Nitrogen Dioxide

NO reacts very rapidly with oxygen to form NO_2, which is considerably more toxic. This is reflected by the OSHA workplace 8-hr exposure limits for NO_2,which are set at only 5 ppm, compared with 25 ppm for NO.

Formation of NO_2 is accelerated by the combination of a high NO concentration ($\geq$ 100 ppm) with a high FIO_2:

$$2NO+O_2 \rightarrow 2NO_2$$

In animals, levels of inhaled NO_2 above 10 ppm induce ARDS. Even levels as low as 2 ppm have been demonstrated to cause alveolar-capillary leak and airway hyperreactivity in animals and humans. In the administration of inhaled NO, the goal is always to keep NO_2 production below 1 ppm.

Peroxynitrite

NO also reacts with oxygen to form peroxynitrite ($ONOO^-$):

$$NO + O_2 \rightarrow ONOO^-$$

In turn, peroxynitrite rapidly decomposes to form NO_2 and the very reactive hydroxyl radical:

$$ONOO^- + H^+ \rightarrow OONOH \rightarrow NO_2 + OH^-$$

Endogenous peroxynitrite formation by inflammatory cells is important as it confers cytotoxicity to microorganisms or tumor cells. However, excess production of peroxynitrite as a by-product of inhaled NO induces peroxidation of lipids, proteins, DNA and surfactant.

Delivery Systems

Important considerations for the safe delivery of inhaled NO are summarized in Table 2.[1]

Table 2: Criteria for Delivery Systems for Inhaled Nitric Oxide

1. Must be simple, safe, reliable - it is used in critically ill patients.
2. NO delivery must be accurately monitored and not vary with ventilatory pattern or FIO_2.
3. NO_2 production must be limited and monitored.
4. Scavenging of NO is desirable.
5. Oxygen concentration must be measured downstream to NO entry (NO decreases FIO_2)

NO = nitric oxide, FIO_2= inspired oxygen fraction, NO_2 = nitrogen dioxide.

Modified from Branson et al[1]

Anesthesia ventilators pose a particular challenge in NO delivery because of recirculation of expired gas, which could cause NO to build up to undesirable concentrations. Options include using a critical care ventilator in the OR, or a commercial system such as the I-NOvent (see below). However, even if the fresh gas flow is kept at or above the minute ventilation, the I-NOvent flow readings may be rendered inaccurate by anesthetic gases and recirculation of NO can occur.

I-NOvent System (Ohmeda)

This is a versatile system, and the only one that has currently received FDA approval for use by hospitals with an INDN for NO administration. It can deliver 0-80 ppm NO from an 800 ppm tank. The injection module is inserted between the ventilator output and the humidifier, and NO is injected proportionally to the measured ventilator flow to provide the desired dose. Gas is sampled downstream in the inspiratory circuit and analyzed electrochemically, and the display provides FIO_2, NO and NO_2 concentrations, with multiple alarms. The system can also be adapted to a manual bag system for transport, providing NO at 20 ppm.

Physiologic Effects of Inhaled Nitric Oxide

The physiologic effects of inhaled NO are summarized in Table 3.

Inhaled NO provides selective pulmonary arterial and venous vasodilation. The effect is dose dependent in the range of 5-40 ppm, and is proportionately greater with increasing degrees of pulmonary vasoconstriction.[10] Elevated pulmonary vascular resistance and mean pulmonary artery pressure (MPAP) are consistently decreased. The decrease in right ventricular afterload in turn may enhance right ventricular performance, with improvement in ejection fraction and end-diastolic volume.

These beneficial effects on the pulmonary vascular bed and right ventricle are achieved without systemic effects on cardiac output or systemic vascular resistance because inhaled NO is inactivated by heme almost immediately that it enters the circulation. Coronary perfusion pressure is maintained, which is of particular benefit in the presence of right ventricular ischemia that may occur during and after aortic cross-clamping on cardiopulmonary bypass.

Inhaled nitric oxide improves oxygenation in hypoxemia due to acute ventilation-perfusion (V_A/Q) mismatch. Intrapulmonary shunt is improved because inhaled NO is carried to the alveoli with best ventilation, where it increases pulmonary blood flow by local vasodilation, and is then rapidly inactivated by binding to hemoglobin.[7] The improvement in oxygenation is often maximal with low doses of inhaled NO, i.e. 0.5 - 5 ppm. The response is variable, unpredictable and may be transient.

Oxygenation may be further enhanced by the simultaneous IV administration of pulmonary vasoconstrictors. Almitrine bismesylate is an investigational selective pulmonary vasoconstrictor. When administered concomitantly with inhaled NO it enhances its effect on oxygenation, presumably by increasing hypoxic pulmonary vasoconstriction". Its use is limited by its long half-life (12 hr) and potential peripheral neurotoxicity. Administration of phenylephrine, a nonselective vasoconstrictor, has been found to be successful in improving oxygenation in the presence of inhaled NO in about 50% of patients.[12] Its systemic vasoconstrictor effects limit its use.

Inhaled NO has been demonstrated to have some bronchodilator effects,[13] but these appear to be mild and variable.

Table 3: Physiological Effects of Nitric Oxide

1. Selective pulmonary arterial and venous vasodilation
   a. dose-dependent (5 - 40 ppm)
   b. decreased elevated mean pulmonary artery pressure (MPAP)
   c. may improve right ventricular performance (RVEF, RVEDV)
   d. no systemic effects on CO or SVR (inactivated by heme)
2. Improved intrapulmonary shunt
   a. NO carried to alveoli with best ventilation, in creases blood flow
   b. enhanced V_A/Q matching, oxygenation
   c. effect enhanced by IV administration of pulmonary vasoconstrictors
      i. selective: almitrine bimesylate
      ii. nonselective: phenylephrine
3. Bronchodilation

RVEF right ventricular ejection fraction, RVEDV = right ventricular end-diastolic volmne, CO cardiac output, SVR systemic vascular resistance, Va/Q = ventilation-perfusion ratio, IV = intravenous

Clinical Applications

Persistent Pulmonary Hypertension of the Newborn (PPHN)

This is a neonatal syndrome of sustained pulmonary hypertension, severe hypoxemia and cyanosis unresponsive to oxygen. It is confirmed by the echocardiographic display of a right to left shunt via the ductus arteriosus or patent foramen ovale. Conventional treatment consists of high FIO_2, mechanical ventilation, alkalosis, surfactant therapy and ultimately ECMO.

Use of inhaled NO in PPHN represents the most convincing evidence thus far of a positive impact on outcome, and is the basis for its current approval by the FDA. A number of multicenter studies have indicated that inhaled NO improves oxygenation and decreases the need for

ECMO from 55-70% to about 40% of patients.[14] However, this has not translated into improved survival rates compared with conventional therapy.

Perioperative Use of Inhaled Nitric Oxide

Lung Transplantation

Inhaled NO has a number of potential benefits in the intra- and postoperative management of patients undergoing single and double lung transplantation. By controlling pulmonary vascular resistance it may actually avoid the need for cardiopulmonary bypass is some cases. It can be used to attenuate acute pulmonary hypertension induced by underlying pulmonary vascular hyperreactivity, cardiopulmonary bypass or reperfusion injury. It is also very effective in the treatment of hypoxemia following lung transplantation, and at low doses may attenuate the inflammatory response to ischemic reperfusion injury.[15] In at least one retrospective study inhaled NO has been shown to decrease airway complications and in-hospital mortality.[16]

Cardiac Surgery

Cardiopulmonary Bypass

Inhaled NO is usually started prior to weaning from cardiopulmonary bypass, which may itself precipitate acute pulmonary hypertension in susceptible patients by inducing injury to the pulmonary vascular endothelium. It is continued into the postoperative period and gradually weaned and discontinued over the next 48 hours.

Congenital Heart Surgery

In surgery for congenital cardiac lesions with pulmonary hypertension, inhaled NO may decrease the requirement for ECMO (see PPHN).

Mitral Valve Replacement

Patients with severe mitral valve disease may have had longstanding pulmonary hypertension and pulmonary vascular remodeling. Valve replacement does not immediately ameliorate pulmonary hypertension, and the high afterload may induce acute postoperative right ventricular failure. Inhaled NO decreases pulmonary vascular resistance until the right ventricle can recover from the ischemic injury induced by cardiopulmonary bypass and aortic cross-clamping.

Cardiac Transplantation

Many patients with end-stage heart disease have longstanding severe pulmonary hypertension that persists after cardiopulmonary bypass. The transplanted heart easily develops acute right-sided failure because the compliant right ventricle is unused to high pulmonary vascular resistance. Inhaled NO can decrease elevated MPAP and thereby protect the right ventricle, while maintaining left ventricular filling by increasing pulmonary arterial blood flow.

Left Ventricular Assist Device (LVAD)

The left ventricular assist device (LVAD) was originally used as a last resort in patients unable to be weaned off cardiopulmonary bypass. However, with the development of the internal LVAD and portable drive, it is achieving increasing utility as a bridge to cardiac transplantation in patients who would otherwise not survive until a donor heart became available.

LVAD filling and stroke volume is very dependent on the sufficiency of pulmonary venous return to the left atrium and ventricle. Elevated pulmonary vascular resistance impedes pulmonary blood flow and restricts LVAD filling. Almost all patients requiring LVAD insertion have some degree of pulmonary hypertension, and since the right ventricle is usually involved in global cardiomyopathy, it may quickly fail. In this setting, the perioperative use of inhaled NO is very effective at decreasing high pulmonary vascular resistance and protecting the fight ventricle, while enhancing LVAD filling and flow.

ARDS

Inhaled NO can reverse pulmonary hypertension induced by models of acute lung injury (thromboxane, oleic acid, lung lavage, endotoxin, smoke inhalation). At low doses (5-10 ppm) it also attenuates neutrophil sequestration and oxidant activity, i.e. it appears to have an anti-inflammatory effect.[17] In models of pulmonary embolism, inhaled NO decreases pulmonary hypertension and platelet aggregation. The effect in models of oxygen toxicity is bimodal. Low doses (10 - 20 ppm) of inhaled NO protect against the effect of neutrophil oxidants such as peroxide (H_2O_2), alkyl peroxides, or superoxide (O_2^-). In contrast, high doses (100 ppm) result in peroxynitrite formation which exacerbates cell injury.

The potential benefits of inhaled NO in ARDS are summarized in Table 4. In patients with ARDS who have acute pulmonary hypertension, inhaled NO predictably decreases elevated pulmonary vascular resistance without causing systemic hypotension. Mean pulmonary artery pressure and right ventricular afterload are decreased as a consequence, and right ventricular function (as assessed by ejection fraction) may improve. The effect appears to be proportional to the degree of pulmonary hypertension present.

Permissive hypercapnia is a strategy used in the management of ARDS to attempt to decrease ventilator-induced lung injury caused by barotrauma or volutrauma. Tidal volume and minute ventilation are decreased and $PaCO_2$ is allowed to rise. However, hypercapnia exacerbates pulmonary vasoconstriction. Inhaled NO attenuates this increase and thus facilitates the use of permissive hypercapnia.[18]

In about two-thirds of patients with ARDS, inhaled NO enhances V_A/Q matching and improves arterial oxygenation

by more than 20%. This could affect outcome by decreasing the need for high FIO_2 and airway pressure therapy (PEEP, inverse ratio ventilation), thereby decreasing complications related to oxygen toxicity and barotrauma. However, prospective studies have not been able to demonstrate a significant improvement in mortality.[19,20] There are several possible reasons.[7] There is considerable inter-patient variability in the dose-response effect of inhaled NO, and even within an individual patient there may be a changing response over time. In many cases, ARDS mortality is related to sepsis and multisystem. failure rather than oxygen toxicity or ventilator-induced lung injury. Finally, there may have been inherent deficiencies in study design, such as exclusion of the sickest patients, or premature reduction of PEEP.

Table 4: Possible Benefits of Inhaled Nitric Oxide in ARDS

1. Decreases PVR and MPAP without decreased SVR.
   a. decreases RV afterload (improved RV function).
   b. maintains RV coronary perfusion.
   c. facilitates permissive hypercapnia.
2. Improves arterial oxygenation by enhanced V_A/Q matching.
   a. decreased FIO_2 (? decreased oxygen toxicity)
   b. decreased airway pressure therapy, i.e. PEEP, inverse ratio ventilation (? decreased barotrauma)
   c. ? decreased ECMO requirement, improved outcome as part of multimodal therapy.

PVR = pulmonary vascular resistance, MPAP = mean pulmonary artery pressure, SVR = systemic vascular resistance, RV = right ventricle, V_A/Q = ventilation-perfusion matching, $FI0_2$ = inspired oxygen fraction, PEEP = positive end-expiratory pressure, ECMO = extracorporeal membrane oxygenation.

An alternative approach is to use inhaled NO as one of several interventions in an integrated approach to ARDS. This takes advantage of the additive effect on improvement of oxygenation when several interventions are combined. For example, Germann et al demonstrated that inhalation of NO in the prone position halved the intrapulmonary shunt fraction and doubled the ratio of PaO_2 to FIO_2 compared to either modality used alone.[21] Using a treatment strategy that integrated pressure-controlled ventilation, dehydration, prone position and inhaled NO, Ulrich et al were able to restrict the use of ECMO to 15% of patients with ARDS, and achieved an overall survival rate of 80.%[21]

Sickle Cell Disease

Sickle cell disease results from the genetically induced replacement of the amino acid glutamine by valine in the hemoglobin ß-chain, resulting in the formation of HbS. In homozygotes, HbS predominates. Its oxygen-hemoglobin dissociation curve is right-shifted and has a P_{50} (the PaO_2 at which hemoglobin is 50% saturated) of about 32 mmHg. In other words, HbS has a markedly decreased oxygen affinity, which causes it to release oxygen at relatively high PaO_2. Deoxygenated HbS aggregates into large polymers which deform erythrocytes and cause sickling, resulting in the vasoocclusive, thrombotic and ischemic crises that epitomize the disease.

Inhaled NO at 80 ppm has been shown to shift the P_{50} back toward normal (i.e. 26 mmHg) without producing excessive methemoglobin, and thereby potentially protect against sickling.[6]

Primary Pulmonary Hypertension

In primary pulmonary hypertension, inhaled NO is used to test pulmonary vascular reactivity. A positive response (i.e. decreased MPAP) suggests a favorable response to long term vasodilator therapy with prostacyclin or calcium channel blockers. Inhaled NO avoids the limitation of systemic hypotension inherent in vasodilator drugs, and preliminary reports have appeared of the long-term ambulatory use of inhaled NO via nasal cannulas.[23]

Chronic Obstructive Pulmonary Disease (COPD)

The bronchodilator action of inhaled NO appears to be rather weak in patients with bronchospastic COPD.

There has been some controversy in its role in treatment of COPD-induced hypoxemia, which is related to ventilation-perfusion mismatch rather than intrapulmonary shunting. Some studies found that inhaled NO worsened oxygenation in these patients, presumably by overcoming hypoxic pulmonary vasoconstriction (HPV).[24] In others, where inhaled NO was added to supplemental oxygen, a beneficial effect has been observed on both hypoxemia and pulmonary hypertension.[25] A ceiling effect on oxygenation improvement was noted at 5 ppm inhaled NO, whereas a progressive decrease in MPAP was achieved through the dose range of 5-20 ppm.[26] This again attests to the disparity in dose response to inhaled NO between oxygenation and pulmonary vasoconstriction.

Adverse Effects of Inhaled Nitric Oxide

Increased Left Ventricular Filling Pressure

Nitric oxide is not indicated for patients with isolated left ventricular dysfunction and poor ventricular compliance. Modest increases in pulmonary blood flow induced by pulmonary vasodilation can rapidly increase left ventricular filling pressure and result in acute volume overload, ventricular failure and pulmonary edema.[27]

Rebound Hypoxemia and Pulmonary Hypertension

Acute cessation of inhaled NO after its administration for several days can precipitate rebound acute pulmonary

hypertension, right ventricular failure and acute hypoxemia.[28] It is thought that this is due to down-regulation of NOS, or its inactivation by peroxynitrite formation.

We have often observed little change in PaO_2 when inhaled NO is weaned from 20 to 5 ppm, but then a sudden deterioration when it is weaned below 5 ppm. This may be because of the ceiling in the dose-response effect of inhaled NO on intrapulmonary shunting, i.e. there was no further benefit to inhaled NO above 5 ppm.

When inhaled NO is weaned, close attention must be paid to indices of oxygenation (SpO_2, PaO_2) and pulmonary vascular resistance (MPAP, CVP). Strategies to avoid NO withdrawal rebound are summarized in Table 5.[3]

Table 5: Strategies to Manage Nitric Oxide Withdrawal and Rebound

1. Attempt to use the lowest effective dose of NO (< 10 ppm)
2. Do not withdraw NO until pulmonary status has sufficiently recovered (e.g. PaO_2 > 80 mmHg at FIO_2 < 0.4 and PEEP < 5 cm H_2O)
3. Increase FIO_2 to 0.6 - 0.7 prior to NO discontinuation
4. Use alternative methods to control pulmonary hyper tension (e.g. increased milrinone dosage)

Modified from Hess.[3]

Platelet Dysfunction

In animal and in vitro studies, inhaled NO consistently increases bleeding time, and inhibits platelet aggregation and agglutination by increasing platelet cGMP [29]. However, this has not translated into an observable increase in the incidence of bleeding.

Conclusions

Nitric oxide (NO) is a unique molecule that is ubiquitous in the human body and is responsible for normal neurologic function, vasodilator tone and modulation of the inflammatory response. Massive endogenous release of NO appears to play a central role in sepsis and the systemic inflammatory response syndrome. Inhaled NO (1-80 ppm) can markedly attenuate pulmonary vasoconstriction and improve hypoxemia due to ventilation-perfusion mismatch. However, excessive doses of inhaled NO exacerbate acute inflammation and induce lung injury by the action of NO itself or its reactive metabolites. Thus far, its use has received FDA approval only for persistent pulmonary hypertension of the newborn (PPHN). However, on an investigational basis it has achieved considerable acceptance for perioperative administration in lung and heart transplantation and LVAD insertion. Although prospective studies have not demonstrated that inhaled NO improves outcome in ARDS, its use as a component of an algorithmic approach has achieved an impressive survival rate. Other conditions in which inhaled NO shows promise include primary pulmonary hypertension, sickle cell anemia and hypoxic chronic obstructive lung disease.

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