# Nitric Oxide

## A guide to its use


SLE

When the smallest thing matters

## Nitric Oxide

Nitric Oxide is a highly diffusible, colourless gas with a sharp, sweet odour. It has a vapour density similar to that of air. It is a naturally occurring vasodilator.

The NO molecule is considered a “free radical” because it has an unpaired electron, making it able to react with other molecules. In the presence of oxygen, NO forms nitrogen dioxide ($NO_2$).

## Health and Safety Executive Safety Statement on Exposure Limits

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|---|---|
| NO Toxicity | 25 ppm for 8 hrs |
| $NO_2$ Toxicity | 3 ppm for 8 hrs |

## Nitric Oxide in Human Physiological Processes

- NO quickly diffuses into the pulmonary vascular smooth muscles.
- NO acts as a potent short-acting vasodilator with a half-life of three to five seconds.
- NO has a high affinity for haemoglobin combining with it five to twenty times faster than oxygen. Once NO combines with haemoglobin, methaemoglobin forms and the NO is quickly inactivated.
- NO also plays a role in several other physiological processes e.g. Neurotransmission and platelet aggregation.

## Nitric Oxide and the Lung

Sources of endogenous NO in the lung so far identified include pulmonary vascular endothelium, epithelium, alveolar macrophages and infiltrating inflammatory neutrophils.

In the absence of lung disease inhalation of exogenous NO appears to have no appreciable effects on pulmonary vascular resistance, airway resistance or gas exchange. However, in the presence of certain forms of lung diseases, inhaled NO reduces pulmonary hypertension.

Inhalation of exogenous NO selectively reduces pulmonary hypertension and improves ventilation/perfusion inequalities in a variety of pulmonary pathologic states.

This is a function of three properties:

- Its gaseous state permits delivery to ventilated alveoli by inhalation
- Its small size and lipophilicity allows ready diffusion to target cells
- Avid binding to, and rapid inactivation by haemoglobin prevents systemic vasodilation

These properties distinguish inhaled NO from intravenous vasodilators that exert their effects by releasing NO within both the systemic and pulmonary circulation.

## Inhaled Nitric Oxide and Gas Exchange

Various forms of acute and chronic lung disease associated with pulmonary hypertension are complicated by impaired gas exchange and hypoxaemia.

The effect of inhaled NO in oxygenation has been investigated in patients with ARDS, CPD, pneumonia and bronchospasm.

Inhaled NO is preferentially distributed to well ventilated alveoli. NO may redistribute pulmonary blood flow, diverting perfusion from poorly or unventilated lung regions thereby reducing shunting. Intravenous agents lack such regional specificity.

## Inhaled Nitric Oxide and Pulmonary Hypertension

Acute pulmonary hypertension is typically accompanied by severe cases of acute respiratory distress syndrome.

Human studies have documented the ability of inhaled NO to reduce the pulmonary hypertension associated with ARDS without the accompanying reductions in systemic arterial pressure.

In general, the degree of pulmonary hypertension predicts the degree of responsiveness to inhaled NO. However, although NO rapidly improves oxygenation, and can reduce the need for ECMO, it may not reduce the overall mortality.

## Persistant Pulmonary Hypertension of the Newborn

The failure to achieve and sustain a normal decline in pulmonary vascular resistance at birth results in PPHN.

Disorders that are associated with PPHN include congenital cardiac defects, birth asphyxia, meconium aspiration, Group B Strep sepsis, RDS, Congenital Diaphragmatic Hernia, hypoglycaemia and hypothermia.

PPHN results in the right-to-left shunting of blood across foetal circulatory channels away from the pulmonary vascular bed and structurally normal heart, causing severe systemic hypoxaemia.

Traditional treatment of PPHN includes hyperoxygenation, hyperventilation, fluids, colloids and if necessary intravenous vasodilators, correction of metabolic acidosis, and in some instances ECMO.

Hyperoxygenation increases the oxygen diffusion across the alveolar membrane promoting pulmonary vasodilation and decreasing pulmonary vascular resistance. However, the use of high oxygen concentrations may be toxic to alveolar tissues, destroying the cells needed to produce surfactant. High oxygen pressures increase the risk of long term complications such as Bronchopulmonary Dysplasia (BPD).

Mechanical hyperventilation produces alkalosis that should reduce pulmonary vascular resistance in patients with PPHN. However, ventilation rates need to be over 150 bpm for this to occur. The use of high peak inspiratory pressures to achieve adequate tidal volumes also increases the risk of pneumothoraces, other air leak syndromes and BPD.

## Nitric Oxide Therapy

NO may be used in conjunction with CMV or HFO ventilation. It is thought that NO used with HFO produces better results probably due to a more efficient distribution.

- The therapy system (e.g. Inosys) must be connected correctly as per the enclosed instructions.
- The therapy should only be commenced in the presence of a clinician at the bedside.
- The INNOVO trial (UK) suggests starting at 20 ppm in near term and term infants, and weaning down after stabilisation to the minimum dosage required to sustain clinical response.
- A response is defined as an increase in post ductal $PaO_2$ of more than 22.5 mmHg within 15 – 30 minutes after commencement of NO therapy.
- In preterm infants it is suggested that a starting dose be 5 ppm. The dosage may then be increased in increments to 20 ppm to achieve a satisfactory response. If still no significant response is achieved then an increase to 40 ppm may be attempted.
- If there is no response within 15 – 30 minutes, cessation of the therapy may need to be considered.
- NO binds to and is inactivated by haemoglobin forming methaemoglobin. This needs to be closely monitored as high levels of methaemoglobin can impair the oxygen carrying capacity. Initially, methaemoglobin levels need to be monitored 6 – 12 hourly then on a daily basis. The aim is to keep the methaemoglobin level at less that 2%.
- As NO affects platelet formation and bleeding time, it could potentially increase the risk of IVH in preterm infants.
- A hand-bagging system should always be available so that NO can be provided if the ventilator is not ventilating for any reason.

## Weaning

Weaning needs to be done very slowly and it may take several days. During weaning $FiO_2$ should be increased to help reduce the problems of vasoconstriction and a drop in $O_2$ saturation due to the withdrawal of exogenous NO.
If the decision to withdraw Nitric Oxide Therapy has been made, the infant must still be weaned from NO as per the above.

## The safe administration of Nitric Oxide

- The safe administration of NO requires the use of commercially prepared compressed gas cylinders containing NO diluted in Nitrogen.
- NO must be stored in Nitrogen and Helium as NO oxidises in the presence of oxygen, producing toxic $NO_2$. As NO quickly combines with oxygen to form toxic $NO_2$, the contact time between NO and oxygen should be as short as possible. Therefore NO should be diluted to the prescribed concentration just prior to inhalation.
- NO is delivered into the inspiratory limb of the patient circuit at a point between the humidifier and the ET tube. It must be at least 20 – 25 cm from the ET tube to allow for adequate mixing.
- The mixed gas is sampled at the patient connector, before inhalation, to confirm concentrations of NO and $NO_2$ reaching the patient.
- Exhaust gases are scavenged through scavenging filters containing active granules or soda lime.
- If there has been a leakage of NO into room air, the room should be evacuated and well aerated to clear the NO.
- Recommended exposure levels are a maximum of 25 ppm NO and 3 ppm $NO_2$ over eight hours.
- Exhaust gases should be routinely scavenged.
- If $NO_2$ is being purged from systems into room air, direct the flow away from the face and other staff.
- During hand-bagging, exhaust gases are not scavenged, so flow should be directed away from the face. Also, during hand bagging the ventilator should be capped to stop flow into room air.
- There are no guidelines about pregnant staff and the use of NO. This is a matter of informed choice by the staff. Working in the same room is not a concern as environmental levels are very low. Asthmatic staff should also not be concerned.

*N.B. There is evidence to show that traffic causes high $NO_2$ levels and therefore is present in city centres. Cigarette smoke contains up to 1000 ppm $NO_2$.*

SLE is a world leader in the design and manufacture of neonatal ventilators.

Years of ventilation experience have given the company an understanding of the challenges that nurses and clinicians are facing when caring for the tiniest and most critical babies.

From being the pioneers of neonatal Patient Triggered Ventilation (PTV) in the 1980's, to the introduction of combined HFO (High Frequency Oscillation) in the 1990's, and the design of the first touch-screen Neonatal Ventilator in the 2000's, SLE has maintained a position of strength in neonatal ventilation.

The company's guiding principle is to support clinical and nursing staff in their everyday work.

The knowledge and experience gained during years of development is evident in all SLE's products: the result of our ongoing commitments to innovation, competency and care.

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