# Pilbeam: Mechanical Ventilation, 4th Edition

## Special Techniques in Mechanical Ventilation

## SECTION IV: Nitric Oxide

### OUTLINE

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WITHDRAWAL OF INHALED NO

### LEARNING OBJECTIVES

Upon completion of this section the reader will be able to do the following:

1. Describe physical characteristics of nitric oxide.
2. List the normal concentration range for ambient nitric oxide, inhaled nitric oxide levels in smokers, and therapeutic levels of inhaled nitric oxide.
3. Explain the cellular process in which endogenous nitric oxide is produced.
4. Discuss the effects of inhaled nitric oxide on the pulmonary circulation, ventilation/perfusion matching, and pulmonary shunt.
5. Identify side effects and complications of inhaled nitric oxide.
6. Name the medication used in treating methemoglobinemia.
7. Compare the use of inhaled nitric oxide in patients with persistent pulmonary hypertension of the newborn and those with acute respiratory distress syndrome.
8. Describe the advantages and disadvantages of the four nitric oxide delivery systems presented.

In certain pulmonary disorders such as persistent pulmonary hypertension of the newborn (PPHN) and acute respiratory distress syndrome (ARDS), pulmonary vasoconstriction and pulmonary hypertension contribute to shunting and hypoxemia. In an effort to find a way to reverse these difficulties, a simple, common gas molecule called nitric oxide (NO) has been studied and used as a potential treatment to improve oxygenation and reduce shunting. This section reviews the use of NO as a therapeutic inhaled gas.

## PROPERTIES OF NO

NO is a highly reactive gaseous radical commonly found in the environment. Between 10 and 100 ppb are present in the atmosphere. Smokers may inhale as much as 400 to 1000 ppm when they inhale tobacco smoke.[1] Although NO is normally present in our environment, it is still considered an air pollutant.[2] In fact, NO is even present in the compressor gas supplies of hospitals, and breathing these gases may affect patients.[3]

NO is endogenous to and produced by a variety of body cells. It is also an important messenger molecule. For example, NO is accountable for the activity of the endothelium-derived relaxing factor, an agent that relaxes smooth muscles and augments blood flow in veins. The effectiveness of certain medications, such as sodium nitroprusside and nitroglycerin, is in fact attributed to their release of NO.

The formation of NO in cells is dependent on the presence of L-arginine, an amino acid. NO is produced in the presence of NO-synthase, an enzyme. The resulting NO typically diffuses to a neighboring cell where it binds with and activates guanylate cyclase. In the presence of guanosine triphosphate, activated guanylate cyclase increases production of cyclic guanosine 3′,5′-monophosphate, which produces certain biological effects within cells, such as smooth muscle relaxation (Figure 1).[4]

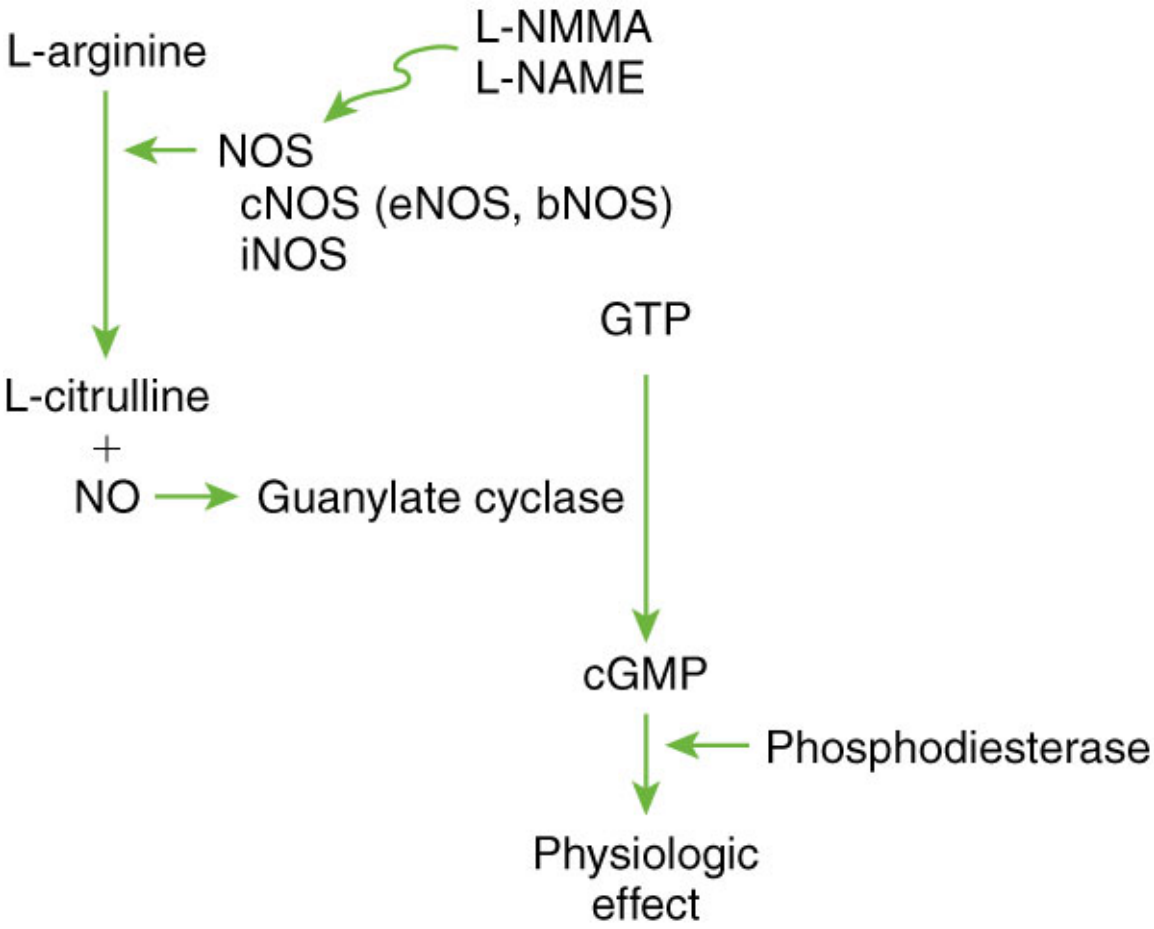


**Fig. IV-1**
Biological pathway for the endogenous production of NO. *bNOS,* Neuronal-type constitutive NO synthase; *cGMP*, cyclic guanosine 3′5′-monophosphate; *cNOS,* constitutive NO synthase; *eNOS,* endothelial NO synthase; *GTP*, guanosine triphosphate; *iNOS,* inducible NO synthase; *L-NAME, L-NG,* arginine methyl ester; *L-NMMA,* L-NG-monomethyl arginine; *NOS,* NO synthase. (From Hess D: Heliox and inhaled nitric oxide. In MacIntyre NR, Branson RD: *Mechanical ventilation*, Philadelphia, 2001, Saunders.)

NO has been measured in exhaled gases and within the nasopharynx and the paranasal sinuses in human beings.[5,6] The NO in the nasopharynx is actually inhaled and absorbed. NO present in the paranasal sinuses may have a bacteriostatic effect within the sinuses.[6] In inflammatory conditions such as asthma and bronchiectasis, the amount of exhaled NO increases above the normal amount. This may be a result of increasing NO synthesis from neutrophils and macrophages.[7]

## SELECTIVE PULMONARY VASODILATION

NO is important to pulmonary medicine because it can be inhaled through the lungs and cause selective pulmonary vasodilation. When very low concentrations of NO (0.25 to 20 ppm by volume) are inhaled in the lungs and delivered to ventilated alveoli, vasodilation

of adjacent pulmonary vessels occurs, resulting in improvement in ventilation/perfusion ($\dot{V}/\dot{Q}$) matching, reduction of shunting, and increase of $PaO_2$.[8,9] This occurs without dilating systemic vessels because the inhaled NO rapidly combines with hemoglobin once it diffuses into the blood stream and is inactivated. NO is not in itself a selective pulmonary vasodilator, but it becomes one when administered as an inhaled gas.[4] Other intravenous vasodilators such as nitroglycerin and sodium nitroprusside are not selective. These vasoactive agents result in lower systemic and pulmonary blood pressure. In addition, they increase blood flow to both ventilated and nonventilated alveoli, which increases intrapulmonary shunting and reduces arterial oxygenation.[10]

## TOXIC EFFECTS AND COMPLICATIONS OF INHALED NO

Inhaled NO, although beneficial as a selective vasodilator, has undesirable side effects. Most of these effects are minimal when NO is administered in appropriate amounts by experienced practitioners. However, clinicians using the gas should be familiar with the potential complications.

### Direct Inhalation of High Concentrations

Direct inhalation of extremely high concentrations of the NO gas either by accidental iatrogenic administration or in farmers exposed to the gas when filling silos (silo filler's disease) can result in shortness of breath, hypoxemia, pulmonary edema, and even death.[11,12] Although actual amounts of NO inhaled are not addressed in this section, one can only imagine the quantity of NO sufficient to cause death if cigarette smoke can contain as much as 1000 ppm. Table 1 illustrates some of the responses detected at various concentrations of NO administered to human beings.[4]

**Table 1**
**Response in Human Subjects Exposed to Various Concentrations of Inhaled NO**

| *Exposure Amount of NO* | *Response* |
|---|---|
| 1 ppm | Small decrease in specific airway conductance in healthy volunteers |
| 15-20 ppm | A decrease in $PaO_2$ and an increase in airway resistance in normal subjects after 15 min |
| 80 ppm | Decreased airway conductance in patients with chronic obstructive pulmonary disease |

### Nitrogen Dioxide

NO rapidly combines with oxygen to form the toxic irritant nitrogen dioxide ($NO_2$). Exposure to $NO_2$ has been shown to result in lung injury, loss of cilia, hypertrophy, and focal epithelial hyperplasia of the terminal bronchioles in rats.[13] In the presence of water, $NO_2$ forms nitric acid. The precise effects of these substances on human lungs are being investigated.

### Methemoglobin

After exposure to high levels of NO gas (80 ppm), the level of methemoglobin (metHb) in the blood increases.[4] (Note: Therapeutic inhalation of 20 ppm NO or less does not typically produce methemoglobinemia.) MetHb is a form of hemoglobin in which the iron molecule in the heme portion has been converted from the normal ferrous state ($Fe^{+2}$) to the oxidized ferric state ($Fe^{+3}$). MetHb is commonly present in concentrations less than 2%. This normal amount may actually exist because of the metabolism of endogenous NO.

When NO reacts with oxyhemoglobin it forms inorganic nitrate and methemoglobin. Inorganic nitrate is unstable and reacts with hemoglobin to form methemoglobin and NO. The NO reacts with oxyhemoglobin, and so on.

MetHb blood levels of less than 5% do not require treatment. However, higher percentages of metHb do require treatment because metHb interferes with the oxygen-carrying capacity of the blood. MetHb cannot bind to oxygen, and its presence actually interferes with the ability of normal hemoglobin to carry oxygen (leftward shift of the oxyhemoglobin dissociation curve). Methylene blue infusion is the common treatment for high metHb levels. Methylene blue increases reduced nicotinamide adenine dinucleotide metHb reductase. Ascorbic acid (vitamin C) can also be used for treatment.[4]

### Peroxynitrite

Peroxynitrite ($ONOO^-$) is a toxic substance produced when endogenous NO reacts with an oxide radical ($O_2^-$): $NO + O_2^-$ yields $ONOO^-$. This can occur in biological systems and may have toxic effects on these systems.[14] Whether inhaled NO produces a reaction is not currently known.[4]

### Platelet Inhibition

NO may inhibit platelet adhesion, aggregation, and agglutination. The importance of this clinical side effect has yet to be determined.[15]

### NO in Patients with Severe Left Ventricular Dysfunction

In some patients with severe left heart failure, high levels of inhaled nitric oxide (40 to 80 ppm) have been shown to reduce pulmonary vascular resistance and increase pulmonary artery occlusion pressure.[16] With a drop in pulmonary vascular resistance and therefore a decrease in afterload to the right heart, improvement in right heart output increases venous return to the left ventricle. If the left ventricle is functioning poorly, the resulting increased left ventricular filling may worsen pulmonary edema. This response may be dose related. In patients with elevated pulmonary artery occlusion pressure (25 mm Hg or greater) and severe left ventricular dysfunction, inhaled NO therapy should be avoided.[4]

## CLINICAL APPLICATION

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