Nitric oxide was first described as a vascular-derived relaxing factor that caused vasodilation via vascular smooth muscle relaxation. It is a highly lipid-soluble gas that allows for rapid diffusion through the alveoli-blood barrier into the pulmonary circulation, which improves matching of perfusion to ventilation. To reduce the risk of exposure to NO2, NO should be stored at concentrations no higher than 1000 ppm in a pure nitrogen environment and only exposed to oxygen at the time of administration.

- Adverse effects of NO include:
  - Formation of methemoglobin and the spontaneous oxidation to nitrogen dioxide (NO2).
  - NO and NO2 levels should be monitored closely on the inspiratory side of the Y-piece when using doses greater than 2 ppm.
  - An absolute contraindication to NO therapy is methemoglobinemia reductase deficiency (congenital or acquired).
- Relative contraindications include bleeding diathesis (secondary to reports of alteration in platelet function and bleeding time with inhaled NO), intracranial hemorrhage, and severe left ventricular failure (New York Heart Association grade III or IV).
  - Inhaled prostaglandins I2 (PGI2) and E1 (PGE1) are alternative medications that have effects similar to inhaled nitric oxide with minimal systemic effects.
  - Helium is an inert gas with a significantly lower density than room air (1.42 g/L for oxygen versus 0.17 g/L for helium).
  - By substituting helium for nitrogen in a helium-oxygen mix (heliox), the degree of reduction in density of the gas is directly proportional to the fraction of the inspired helium concentration in the mix.
  - Heliox reduces the Reynolds number and thereby results in more laminar flow, therefore reducing airflow resistance, work of breathing, and dynamic hyperinflation associated with a high resistance.
- Disadvantages of using heliox in critically ill patients include the cost of therapy and the high concentrations of helium required. Most studies utilize helium:oxygen mixes of 80:20 or 70:30 to achieve a therapeutic benefit. At higher concentrations of oxygen, the effect of helium is less and therefore is limited in use to those not requiring high FIO2. Ventilators also require recalibration for measured FIO2, flows, and tidal volumes when using heliox.
  - Heliox reduces the Reynolds number and thereby results in more laminar flow, therefore reducing airflow resistance, work of breathing, and dynamic hyperinflation associated with a high resistance.
  - Heliox is typically started at low doses ranging from 1 to 2 ppm and gradually increased until the desired effect is achieved.

- Clinical situations in which heliox may be used include conditions with high airflow resistance such as severe acute exacerbations of asthma or COPD, bronchiolitis, bronchopulmonary dysplasia, and extrathoracic or tracheal obstruction.