adjunctive therapies to improve oxygenation & ventilation

adverse effects of nitric oxide

- Adverse effects of NO include:
(i) the formation of methemoglobin and
(ii) the spontaneous oxidation to nitrogen dioxide (NO2). NO2 is known to be toxic to the respiratory system with maximal exposure limited to 5 ppm. Complications from NO2 exposure include airway irritation and hyperreactivity with levels as low as 1.5 ppm, pulmonary edema, and pulmonary fibrosis when exposed to higher levels.
(iii) Rebound pulmonary: vasoconstriction can occur with sudden discontinuation leading to rapid worsening of VQ mismatch and pulmonary hypertension with significant hemodynamic collapse

safe administration of nitric oxide

- 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.
- NO should be delivered into the ventilator circuit as close to the patient as possible.
- NO and NO2 levels should be monitored closely on the inspiratory side of the Y-piece when using doses greater than 2 ppm.

contraindications to nitric oxide

- 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

- Inhaled prostaglandins I2 (PGI2) and E1 (PGE1) are alternative medications that have effects similar to inhaled nitric oxide with minimal systemic effects.
- For PGI2, doses ranging from 1 to 25 ng/kg/min are favorably tolerated with similar reductions in pulmonary artery pressures and improvements in oxygenation as inhaled NO.
- PGE1 has the advantage of a more rapid degradation by the pulmonary endothelial cells, providing a selective advantage over PGI2 at higher doses.
- Additional studies are required to define a role for these agents, but they can be considered as alternatives for rescue therapy for similar conditions treated with inhaled NO.

heliox

- 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.
- 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.
- 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.

properties of NO

- 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 and smooth muscle cells of the vasculature.
- The main action of NO is mediated by activating guanylate cyclase and increasing intracellular cyclic guanylate monophosphate, thereby causing smooth muscle and subsequent vasomotor relaxation.
- The beneficial effects observed with inhaled NO are mediated primarily through this action on the pulmonary vascular smooth muscle. Pulmonary blood flow is specifically increased in well-ventilated regions, which improves matching of perfusion to ventilation.
- It also has anti-inflammatory effects

clinical trials of NO

- Numerous clinical observational studies in ALI/ARDS have demonstrated improvements in oxygenation by improving VQ mismatch as demonstrated by a 10% to 20% increase in PaO2/FIO2 ratio and a reduction on pulmonary vascular resistance and mean pulmonary arterial pressures by at least 5 to 8 mm Hg.
- Randomized controlled trials of varying sample size and design had similar findings. Typically, NO improved the PaO2 and PaO2/FIO2 ratios acutely, but by 24 to 72 hours those in the control group achieved the same level of improvement.
- Similarly, although a reduction in mean pulmonary artery pressure was also observed in these trials with the use of NO, this did not translate into clinically meaningful outcomes of a decrease in mortality, less organ failure, or days free of mechanical ventilation.
- Only 60% of ALI/ARDS patients respond to inhaled NO. No clear predictors of who will respond to NO exist.

clinical use of nitric oxide

- Given that doses below 40 ppm were safe without any significant adverse effects, it can be considered a "rescue" therapy to possibly allow for more protective forms of ventilation with decreases in FIO2 and mean airway pressures to maintain acceptable oxygenation or in situations in which secondary pulmonary hypertension leads to compromised hemodynamic function from right ventricular failure

potential indications include:

- Acute respiratory distress syndrome
- Severe primary and secondary pulmonary hypertension[79]
- Congenital cardiac syndromes[80,81]
- Right ventricular failure in acute pulmonary embolism or after cardiac surgery[82-85]
- Pulmonary ischemic-reperfusion injury after a heart-lung or lung transplant[63,85]
- Sickle cell crisis[86,87]

- Inhaled NO is typically started at low doses ranging from 1 to 2 ppm and gradually increased until the desired effect is achieved.
- One method, as recommended from the U.K. Consensus conference on NO use, is to perform a dose response test starting at 20 ppm and reducing the doses to 10, 5, and 0 ppm to find the lowest effective dose. A significant response should be considered as a 20% increase in the PaO2/FIO2 ratio or at least a 5 mm Hg decrease in the mean pulmonary artery pressure.
- The improvement in gas exchange is usually seen at lower doses. The dose required to reduce mean pulmonary artery pressure is usually higher. The usual dose ranges from 10 to 40 ppm.
- Doses greater than 80 ppm are associated with a higher risk for adverse effects.