cardiopulmonary bypass surgery. NRT has been successfully used in nonoperative pts after acute coronary syndrome.

Postoperative Period

- Smoking contributes to acute physiologic effects such as increased sympathetic tone, lung inflammation, and tissue hypoxia, as well as long-term pathophysiologic changes such as atherosclerosis and COPD, placing these pts at higher risk for postop complications.
- Nicotine withdrawal should be considered as a cause of postop agitation or anxiety.

Anticipated Problems/Concerns

- NRTs have proven to be both safe and effective in treating tobacco dependence in medically stable pts, even in those with smoking-related diseases. NRTs can be valuable tools to manage tobacco dependence in the periop period.
- Use of NRTs in the periop period is far preferable to continued smoking, per most experts in the field.

Acknowledgment

The author wishes to acknowledge the contribution of Dr. Esther Sung to this chapter in the previous edition.

Nitric Oxide, Inhaled

Warren M. Zapol

Uses

- Children: Acute or chronic pulm Htn associated with persistent pulmonary Htn of newborn (PPHN), meconium aspiration, CHD, and congenital diaphragmatic hernia
- Adults: Acute or pulm Htn associated with ARDS, pulm embolism, placement of a LVAD, and cardiac surgery

Perioperative Risks

- Methemoglobinemia (especially breathing >80 ppm NO)
- NO_2 and peroxynitrite formation

Worry About

- Methemoglobinemia; measure metHb, especially in infants, within 6 h and then every 24 h.
- Measure inhaled NO and NO_2 levels continuously.
- Do not give if high NO_2 levels (>2 ppm).
- Do not allow NO to stagnate in ventilator or breathing circuits; it slowly converts to toxic NO_2 gas.
- High inhaled NO levels may inhibit platelet aggregation.
- In severe heart failure, reducing PVR with NO may raise left atrial pressure.
- Rebound pulm Htn during acute NO withdrawal.

Overview/Pharmacology

- Inhaled NO activates guanylate cyclase in lung vessels and airways and increases levels of cGMP, causing selective pulm vasodilation.
- Very rapid and avid binding with RBCs. Hgb inactivates NO and thereby prevents systemic vasodilation.
- NO is metabolized to nitrate and excreted in urine.
- Supplied as stock gas of ≤1000 ppm by volume of NO in nitrogen or other inert gas.
- Inhaled NO is mixed with O_2-containing gas immediately before administration via intratracheal cath, ventilator, mask, or nasal prongs.

Drug Class/Mechanism of Action/Usual Dose

- NO is a free radical with a short $T_{½}$ in aqueous solutions (~17 sec)
- It combines with ferrous-heme ring of guanylate cyclase and thereby stimulates the conversion of GTP to cGMP; cGMP reduces intracellular Ca^{2+}, causing smooth muscle relaxation, and modulates other cell functions by regulating gene expression; cGMP is broken down by phosphodiesterases.
- Usual inhaled NO dose is 1-40 ppm by volume.

Assessment Points

System	Effect	PE	Test
RESP	Decreased PVR		Decreased PAP Increased CO
	Increased gas exchange	Skin color	Increased PaO_2 Increased SaO_2 Decreased $PacO_2$

Key References: Abman SH: Inhaled nitric oxide for the treatment of pulmonary arterial hypertension, *Handb Exp Pharmacol* 218:257–276, 2013; Rossaint R, Lewandowski K, Zapol WM: Our paper 20 years later: inhaled nitric oxide for the acute respiratory distress syndrome—discovery, current understanding, and focused targets of future applications, *Intensive Care Med* 40(11):1649–1658, 2014.

Perioperative Implications

Preoperative Concerns

- Check for heart failure; do not use in severe heart failure (e.g., PCWP >25 mm Hg) or with pulm venous disease (e.g., pulm vein stenosis, pulm venoocclusive disease). Use of inhaled NO in these settings can cause severe pulm edema with hypoxemia and decreased lung compliance. Some pts with mild left heart dysfunction (diastolic dysfunction) may also develop worsening pulm edema with iNO.

Monitoring

- Must monitor: Inhaled NO, NO_2 levels; metHb levels
- Consider monitoring: PA pressure; RV ECHO; ABGs, SpO_2

Induction/Maintenance

- For inhalation, 1–40 ppm in pts with ARDS (usual dose: 5–15 ppm). Initiate therapy with a higher dose (usually 40 ppm) in the setting of ARDS with moderate or severe pulm Htn and lower doses (5–10 ppm) to reduce intrapulmonary shunt (e.g., ARDS).
- In PPHN, begin therapy at 20 ppm and progressively reduce the dose to 5 ppm or less with improved oxygenation (e.g., FiO_2 <0.60) and PAP by ECHO. Inhaled NO therapy should not be initiated without first optimizing lung volume, ventilation, cardiac performance, and systemic BP.
- Ideal doses need better definition, but lower doses are most effective for improving oxygenation by matching ventilation and perfusion and higher doses to treat pulm Htn. Failure to respond in term infants with PPHN may reflect underlying lung developmental abnormality or structural (anatomic) heart disease.
- Give as little NO as possible to reduce oxidant burden of lung.

Adjuvants

- Phosphodiesterase inhibitors (e.g., sildenafil) increase sensitivity and duration of the dilatory effect of inhaled NO but must be used with caution as they can cause systemic hypotension.

Postoperative Period

- Slowly wean from NO over hours if possible watching for abrupt worsening of oxygenation or pulm Htn with the D/C of NO ("rebound" effect).

Anticipated Problems/Concerns

- Beware rapid D/C of iNO; reactive pulm vasoconstriction and hypoxemia leading to RHF may ensue. These effects may not be seen while doses are being reduced but can be dramatic with D/C of iNO therapy and can even occur after D/C low doses of NO.
- Do not allow NO stock tanks to deplete.
- Provide NO freshly mixed in O_2-containing gas for manual ventilation even when briefly disconnecting from ventilator for suctioning or moving pt.
- If iNO does not reverse hypoxemia despite mechanical ventilation with PEEP, high-frequency oscillatory ventilation, and so on, ECMO may be required.