Oxygen Toxicity

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Session Summary

Hypoxia can lead to pulmonary vasoconstriction and normoxia may lead to pulmonary vasodilation, but prolonged exposure to hyperoxia may be associated with oxygen toxicity. Excessive oxygen can damage lung tissue, partly through the production of oxidative stress. This presentation details the pathophysiology of hyperoxia and describes the clinical implications of excessive oxygen in patients of all ages. The importance of and insight into avoiding hyperoxia are also provided.

Session Objectives

Upon completion of this presentation, the participant will be able to:

- describe the role of oxygen in the clinical setting;
- understand the pathophysiological effects of hyperoxia;
- state the clinical effects of hyperoxia in different patient populations;
- outline strategies to avoid hyperoxia.

References


**Session Outline**

See presentation handout on the following pages.
**Oxygen Toxicity:**

Hyperoxia and the Risks to the Pulmonary System  
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**Oxygen Is a Drug**

- Oxygen is the second most abundant element in the Earth’s atmosphere (almost 21%)
- Molecular dioxygen, O₂, is essential for cellular respiration in all aerobic organisms
- Oxygen is a drug that has been administered to more newborns worldwide than any other treatment

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**History of Oxygen Therapy**

- 1775: Joseph Priestley invented the process of isolating O₂ and identified it as a gas
- 1800s: Sir Humphry Davy and others began using O₂ to treat diseases and injuries
- 1900s: Frederick Banting and others administered O₂ to premature infants
- 2000-2010: Discovery of a number of new ways to administer and monitor oxygen

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**Therapeutic Uses of Oxygen**

- **Uses of Oxygen**
  - Used in various medical and therapeutic applications
  - Oxygen Therapy for respiratory, cardiac, and neurological conditions
  - Oxygen therapy for sleep disorders
  - Oxygen therapy for cancer treatment
  - Oxygen therapy for wound healing
  - Oxygen therapy for dermatological conditions
  - Oxygen therapy for sports and fitness
  - Oxygen therapy for veterinary use
  - Oxygen therapy for aquatic sports

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Oxygen is Used by Cells to Produce Energy

- Oxygen consumption is regulated via:
  - Mitochondria
  - Hemoglobin (Hb)
- Hemoglobin is the oxygen transporter and oxygen regulator found in red blood cells.
- Oxygen is used in mitochondria to help generate adenosine triphosphate (ATP) during cellular respiration.
- Oxygen consumption is regulated to be maintained at an ideal level: “not too high, and not too low”

Differences Between Hyperoxemia and Hyperoxia

- Hyperoxia occurs when high concentrations of oxygen enter the lung, which can damage lung tissue and the pulmonary vasculature.
- Hyperoxemia is caused by high concentrations of oxygen in the blood, which can promote systemic damage and disease.

Defining Oxygen Levels for Inspired O₂ Therapy

- Normal: The optimal level for oxygen in the body or, more specifically, the level of oxygen required for normal physiological processes to occur.
- Hyperoxemia: Localized excess oxygen in the lungs or other body tissues.
- Hypoxemia: Abnormally high level of oxygen in the blood.

Hyperoxia and Hyperoxia Associated with Various Pulmonary-Related Conditions

- Hyperoxia is associated with:
  - Persistent pulmonary hypertension of the newborn (PPHN)  
  - Respiratory distress syndrome
  - Acute respiratory distress syndrome

- Hypoxia is associated with:
  - Retinopathy of prematurity
  - Bronchopulmonary dysplasia
  - Atelectasis
  - Damage to lung tissue

Hyperoxia Increases the Production of Reactive Oxygen Species (ROS)

- Hemoglobin oversupplies O₂ to tissue, stimulating ATP production in mitochondria that promotes the formation of reactive oxygen species.
- Enzymes like superoxide dismutase (SOD) and antioxidants like glutathione (GSH) help convert ROS to less reactive molecules.
Hyperoxia May Have Cytotoxic Effects

- ROS damages cellular components
- Damage from ROS promotes cell and tissue injury/death

Effects of Hyperoxia on Clinical and Pre-Clinical Outcomes in Preterm Infants

Hyperoxia Led to Proliferative Changes in the Lung Tissue of Preterm Infants

Assessing Oxidative Stress in Preterm Lamb Models

Objective

A lamb ductal ligation model of PPHN was used to examine whether inhaled NO (iNO) or recombinant human SOD (rhSOD) can reduce oxidative stress and restore endothelial nitric oxide synthase expression in PPHN lambs ventilated with 100% O₂.

Methods

5 groups of subjects were analyzed:
1. One-day spontaneously breathing lambs, as a negative control
2. Nonventilated preterm PPHN lambs, as an age-matched, disease state control
3. Preterm PPHN lambs ventilated with 100% O₂ for 24 hrs alone
4. Preterm PPHN lambs ventilated with 100% O₂ and 20 ppm NO for 24 hrs (data not presented)
5. Preterm PPHN lambs ventilated with 100% O₂ for 24 hrs and a single dose of rhSOD (5 mg/kg) given intratracheally at delivery (data not presented)

Ventilation of Preterm PPHN Lambs with 100% Oxygen Showed Oxidative Stress

Images of Frozen Lung Cross-Sections from a Term (145 Days) Lamb and Preterm (135 Days) PPHN Lambs Stained with 5 μM Dihydroethidium (DHE) to Visualize Concentrations of ROS

- Ventilation withbaseline of O₂ was associated with ANO in present PPHN lambs that was greater than ROS accumulation in full-term control and fetal nonventilated PPHN lambs (P < 0.05).
Oxygen Concentration and Pulmonary Hemodynamics in Preterm Lambs With PPHN

**Objective**
- A lamb ductal ligation model of PPHN was used to examine the effect of oxygen concentration on lowering pulmonary vascular resistance (PVR) during resuscitation

**Methods**
- Following delivery by cesarean section, PPHN lambs were resuscitated with 21%, 50%, or 100% O₂ (n=6 each) for 30 min
- The effect of oxygen concentration during resuscitation on the ability of iNO therapy (20 ppm) to decrease PVR was also elucidated

**Recommendations for Treating Preterm Infants (<28 Weeks’ Gestation) Based on NEO PROM**

**Neonatal Oxygenation Prospective Meta-Analysis (NEOPROM)**
- NEOPROM is a meta-analysis of 5 clinical trials
- 4911 infants (<28 weeks’ gestation) were randomized to either a low (85-89%) or high (91-95%) functional oxygen saturation (SpO₂) within the first 24 hours after birth

**Results of NEO PROM**
- Low saturation targets (85-89%) until 36 weeks postmenstrual age are associated with more deaths and greater incidences of necrotizing enterocolitis
- Higher saturation targets (91-95%) are associated with greater incidences of retinopathy of prematurity

**European Guidelines**
- Control the oxygen for resuscitation using a blender. Start stabilization with 21-30% oxygen; adjustments up or down should be guided by heart rate and saturation
- Target SpO₂ between 90 and 95% in premature infants <28 weeks’ gestation

Hyperoxia and the Risks to the Pulmonary System

**Effects of Hyperoxia on Clinical and Pre-Clinical Outcomes in Late-Preterm and Term Infants**

**PVR Reduction with Varied Oxygen Levels in Response to iNO in Preterm PPHN Lambs**

Decline in Pulmonary Vascular Resistance in Preterm PPHN Lambs (155-136 Days) Resuscitated with 21%, 50%, or 100% Oxygen for 30 Minutes and Treated With 20 ppm iNO for 60 Minutes

**Many Preterm Infants Receive Oxygen Outside the Intended Study Range**

Percentage of Oxygen Saturation Measurements That Were Within the Intended Range Set by Local Policy in 84 Preterm Infants (<28 Weeks’ Gestation)

- Participating units in the study maintained infants within the intended range 16-64% of the time but were above the intended range 20-73% of the time

**Oxidative Stress Occurs During Birth**

- Birth is a hyperoxic challenge that is accompanied by an increase in oxidative stress
- Newborns are far more exposed to ROS than they would be if they had remained in utero
- The fetus transfers from an intratracheal hypoxic environment (PO₂, 20-25 mm Hg) to an extratracheal normoxic yet relatively hypoxic environment (PO₂, 100 mm Hg)

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A2a: OXYGEN TOXICITY
Hyperoxia and the Risks to the Pulmonary System

### Effects of Hyperoxia on Clinical Outcomes in Adults

**Objectives**
- The effects of hyperoxia exposure were assessed in mechanically ventilated patients with acute lung injury, the effects of high oxygen exposure on clinical outcomes (ICU stay, hospital stay, duration of mechanical ventilation, and 28-day mortality) were also evaluated.

**Methods**
- 210 intensive care unit patients (aged 51–81) with acute lung injury were identified for this study using prospective electronic medical record screening.
- The ventilator settings (FiO₂ and SpO₂) for these patients were collected and assessed.
- Patients included in the study underwent invasive mechanical ventilation for >48 hours:
  - 155 patients were exposed to hyperoxia (defined as FiO₂ >0.5 despite SpO₂ >92%)
  - 55 patients were not exposed to hyperoxia.

### Hyperoxia in Adult Patients with Acute Lung Injury Can Worsen Oxygenation Index (OI)

**Mean Changes in Oxygenation Index at 48 Hours in 155 Adult Patients (Aged 52–79 Years) with Acute Lung Injury, by Duration of Hyperoxia Exposure**

<table>
<thead>
<tr>
<th>Duration of Hyperoxia</th>
<th>Mean Change in Oxygenation Index (OI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;24</td>
<td>10.6±*</td>
</tr>
<tr>
<td>24–30</td>
<td>9.2±*</td>
</tr>
<tr>
<td>18–24</td>
<td>6.9±*</td>
</tr>
<tr>
<td>12–18</td>
<td>2.3±*</td>
</tr>
<tr>
<td>0–12</td>
<td>0.4±*</td>
</tr>
</tbody>
</table>

*OI, oxygenation index

Hyperoxia Exposure in Adults with Acute Lung Injury Was Associated with Poor Clinical Outcomes

**Effect of Hyperoxia on the Clinical Outcome of 210 Adult Patients (Aged 51–81 Years) with Acute Lung Injury**

There was no significant difference in mortality between the hyperoxia-exposed and non-exposed groups (48.4% vs 54.5%, *P*=0.4).

Hyperoxia and the Risks to the Pulmonary System

### Avoidance of Hyperoxia in Neonates

**Term Lambs Resuscitated with 100% Oxygen Display Greater Amounts of Oxidative Stress**

Images of Frozen Lung Cross-Sections from Asphyxiated Term Lambs (139–141 Days) Resuscitated with 21% or 100% Oxygen Stained with 5 μM DHE to Visualize Concentrations of ROS

**Effects of Hyperoxia on Clinical Outcomes in Adults**

Adapted from Rachmale S. et al. Respir Care. 2012;57:1887-1893.

*OI, oxygenation index*

Adapted from Rachmale S. et al. Respir Care. 2012;57:1887-1893.
Optimization of PaO₂: A Balancing Act

PaO₂, partial pressure of oxygen in arterial blood.

Focus on FiO₂: Barriers to Avoiding Hyperoxia

- In clinical practice, supplemental FiO₂ is adjusted based on blood gas values or arterial O₂ saturation measured by pulse oximetry.
- These adjustments may not always be effective:
  - Since fully dedicated attention to FiO₂ adjustment is not usually possible, the response is often delayed when SpO₂ is outside the intended range.
  - This circumstance often results in exposure to unnecessarily high FiO₂.

Study Design

- A study by Claure et al hypothesized that a reduction of hyperoxemia, hypoxemia, and FiO₂ can improve maintenance of SpO₂ within the intended range by automated adjustments when compared with routine care by a dedicated nurse.

Results

- Adjusting the FiO₂ in response to hypoxemia must be appropriate and timely to avoid “overshoot” into hyperoxemia.
- Claure et al reported an “overshoot” into hyperoxemia in 1 out of 10 episodes observed.

Avoiding Hyperoxia

- The goal is oxygen delivery with minimal toxicity.
- Neonates may suffer undue oxidative stress as a result of the administration of excessive oxygen.
- Determining and implementing appropriate oxygen levels is a multifactorial issue.
- The solutions require strategies that are multidisciplinary.

Oxygen Supplementation Is Not Always the Best Therapy

Potential Treatments for Four Physiologic Conditions That Can Lead to Arterial Hypoxemia

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxemia</td>
<td>Increase alveolar ventilation</td>
</tr>
<tr>
<td>Low ventilation/perfusion ratio</td>
<td>CPAP</td>
</tr>
<tr>
<td>Intrapulmonary shunt</td>
<td>CPAP</td>
</tr>
<tr>
<td>Low FiO₂ (&lt;0.21)</td>
<td>Oxygen</td>
</tr>
</tbody>
</table>

Discussion

- What is the goal of increasing FiO₂ beyond 0.60?
- What methods do you use to avoid hyperoxia?
- Is there an established protocol for managing neonates with oxygen?
Summary

- Oxygen is a drug: at appropriate doses, oxygen has benefits, but at high doses, the risks may be increased without additional benefits.
- Hyperoxia increases production of reactive oxygen species and may have cytotoxic effects.
- Hypoxia can lead to pulmonary vasoconstriction and normoxia may lead to pulmonary vasodilation, but prolonged exposure to hyperoxia may be associated with oxygen toxicity.
- Incorporating methods for avoiding hyperoxia in clinical protocols may prevent undue oxidative stress and damage to the lungs.

Adverse Effects of Oxygen Therapy on the Neonate Lung

Objective

- The evaluation of pulmonary alterations occurring in infants exposed to hypoxia was examined postmortem in T4 infants who were administered high levels of oxygen (frequently exceeding 80%) for varying periods of time.

Methods

- In the study population exposed to hypoxia:
  - >70% of the infants in the study were premature at birth.
  - The birth weights ranged from 600g to 2748g.
  - Most of the infants weighed >1500g.
  - All of the infants manifested respiratory distress within the first day of life and required assisted ventilation.
  - The infants examined in the study survived from 3 hours to 135 days.
  - A control population of 16 infants with baseline membrane disease who were exposed to 30-42% oxygen was used for histological comparison.
  - Changes to the lung tissue were identified using light and electron microscopy.

Evidence of Oxidative Stress in Healthy, Full-Term Newborns

Objective

- Determine whether oxidative stress occurs during early infancy following adaption to ambient oxygen at birth.

Methods

- The level of oxidative stress was measured in blood samples drawn from 77 full-term infants (38-42 weeks) at 1, 3, 5, 6, and 12 months of age utilizing the following markers of oxidative injury:
  - F2-isoprostanes - lipid peroxidation
  - Catalase and SOD activity - antioxidant enzyme activity (data not presented)
  - Ferric reducing ability of plasma - ability to resist oxidative stress (data not presented).

Hyperoxia and the Risks to the Pulmonary System

Study Design Slides

Examination of Compliance with SpO2 Target Ranges Among 14 NICU Centers

Objective

- Achieved SpO2 levels in infants who were born at <28 weeks’ gestation were compared with SpO2 levels that were recommended by local NICU policy to examine characteristics that are associated with successful maintenance of a target range.

Methods

- In this prospective, multicenter cohort study, infants from 14 centers in 3 countries were enrolled to document their pulse oximeter saturation levels achieved within their first 4 weeks of life.
  - The study population was composed of 84 infants <28 weeks’ gestation and 186 hours of age (mean birth weight of 813 g and gestational age of 26 weeks).
  - The oxygen saturation levels of these infants were recorded and compared with the levels targeted by local policy.
  - Factors associated with compliance with the target range were examined.

Pulmonary Hemodynamics and Vascular Reactivity in Asphyxiated Term Lambs

Objectives

- Determine whether resuscitation of asphyxiated term lambs with 100% oxygen would decrease PVR, improve oxygen uptake, and increase PaO2 significantly better than 21% oxygen.
- Determine whether use of 100% oxygen for resuscitation would increase pulmonary arterial contractility by enhancing the formation of superoxide anions.

Methods

- Term fetal lambs (139-141 days of gestation) were asphyxiated by intratracheal umbilical cord occlusion for 10 min; lambs were then resuscitated for 30 min with either 21% or 100% oxygen.
- Lung sections were isolated and analyzed for immunochemistry and superoxide generation.