No Excellence Without Evidence: The Therapeutic Use of Oxygen

Penelope S. Benedik PhD, CRNA, RRT
Associate Professor of Clinical Nursing
UTHealth Houston, Texas
Drug levels must be accurately monitored

Oxygen is a DRUG
Oxygen overuse is toxic

Oxygen dose affects both short- and long-term outcomes

Hyperoxia-induced acute lung injury (HALI) may be an under recognized comorbidity
Oxygen—the Context

- Makes up 53.8% of earth’s crust
- Diatomic gas in atmosphere
  - 20.9% of air
  - colorless, tasteless
- Essential for life – within a narrow range
Like any drug, oxygen has a therapeutic range

• Healthy people can adapt to both low or high levels
• There are acceptable limits for both deficient and excessive levels
  • lowest acceptable 19.5% although some argue for 16%
  • highest acceptable limit 60%
Room air at sea level
\[ \text{PO}_2 \text{ 159 mmHg (21.2 kPa)} \]

Dilution by water vapor and \( \text{CO}_2 \)

Alveoli \( \text{PO}_2 \text{ 100 mmHg (13.3 kPa)} \)

Physiologic shunt

Arterial \( \text{PO}_2 \text{ 95 mmHg (12.7 kPa)} \)

\( \text{O}_2 \) tissue uptake

Tissue \( \text{PO}_2 \text{ 20-30 mmHg (2.7 to 4 kPa)} \)

Mitochondrial \( \text{PO}_2 \text{ 1 mmHg (0.13 kPa)} \)
How are the patient’s oxygen levels measured clinically?

- **Dissolved oxygen**
  - PaO$_2$ or PO$_2$
  - Partial pressure exerted by oxygen in the arterial blood

- **Oxygen carried by hemoglobin**
  - O$_2$ saturation or SO$_2$%
  - Percent of hemoglobin that is saturated with oxygen in the arterial blood
The relationship between PO$_2$ and SaO$_2$% is defined by the Oxyhemoglobin Dissociation Curve—it is not linear.

<table>
<thead>
<tr>
<th>PO$_2$ mmHg</th>
<th>SaO$_2$ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>97.5</td>
</tr>
<tr>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>40</td>
<td>75</td>
</tr>
</tbody>
</table>
To increase oxygen delivery, the most effective intervention is to increase the patient’s PO$_2$. 

1. True  
2. False  
3. Not sure
Oxygen Delivery =

Total Oxygen Content x

How much oxygen is in the arterial blood?

Cardiac Output

How much arterial blood is perfusing the tissue bed?
Total oxygen content
≈ 20 ml O₂/dL blood

= Dissolved oxygen \( (PO₂) \)
  0.3 ml O₂/dL blood
 +

Oxygen bound to hemoglobin \( (SaO₂) \)
19.7 ml O₂/dL blood

1 gram of Hb carries 1.36 ml O₂ per dL of blood
At PO₂ 100 torr, blood carries only 0.3 ml dissolved O₂ in each dL
Is a higher $\text{PaO}_2$ really better . . .
PO\textsubscript{2} above 100 does little to increase overall oxygen delivery to the tissues. Why?

There is \textbf{65x more} oxygen carried by hemoglobin than dissolved in the blood.

Typically with 15 grams of Hb, PO\textsubscript{2} 100, SaO\textsubscript{2} 98%:

- Carried by hemoglobin: 19.7 ml O\textsubscript{2}/dL blood
- Dissolved O\textsubscript{2}: 0.3 ml O\textsubscript{2}/dL blood

Increasing the PO\textsubscript{2} to 500 increases dissolved oxygen content by 1.2 ml and hemoglobin-bound oxygen by 0.4 ml per dL blood.

Total O\textsubscript{2} content has only increased by 1.6 ml !!
1. Oxygen lack is dangerous

2. “Haemoglobin is almost completely saturated with oxygen when exposed to ordinary inspired air, and therefore the administration of oxygen to a healthy person does little to increase the quantity of oxygen taken up by the blood.”

3. Lack of oxygen is rarely a direct cause of dyspnea

4. If oxygen is given, it should be given continuously
<table>
<thead>
<tr>
<th>Technique</th>
<th>Flow in liters/minute</th>
<th>Approximate* Percent Oxygen Delivered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal cannula/nasal prongs</td>
<td>1</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>32%</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>44%</td>
</tr>
<tr>
<td>Simple $\text{O}_2$ mask</td>
<td>6 to 10</td>
<td>35 to 50%</td>
</tr>
<tr>
<td>Partial rebreathing mask</td>
<td>10 to 15</td>
<td>35 to 60%</td>
</tr>
<tr>
<td>Non-rebreathing mask</td>
<td>10 to 15</td>
<td>55 to 70%</td>
</tr>
</tbody>
</table>

*Depends upon respiratory rate, tidal volume and breathing pattern.
The 8 rights of drug administration do apply to oxygen therapy!

1. Right patient
2. Right medication
3. Right dose
4. Right route

1. Right time
2. Right documentation
3. Right reason
4. Right response
Firefighters improvised to save the life of the bearded dragon ‘Thorn’
Any oxygen delivered greater than room air is a drug—are you administering oxygen for the right reason?

• Not enough $\rightarrow$ $PO_2 < 60$, $SO_2 < 90$
  • potential for cellular hypoxia
  • oxygen deficit

• Too much $\rightarrow$ $PO_2 > 100$, $SO_2 > 98$
  • potential for oxygen toxicity
There are disparate views on restoring the oxygen deficit versus the risk of oxygen toxicity.


- So now there is experimental evidence suggesting that oxygen toxicity does occur during reperfusion after resuscitation and first aid, rather than the opposite. Resuscitation. 2001 Feb;48(2):188.
Does your unit routinely administer oxygen to patients with chest pain/suspected acute coronary syndrome?

1. Yes
2. No
3. I don’t know
Oxygen for Acute MI

- Does the routine use of inhaled O₂ in acute myocardial infarction (AMI) improve patient outcomes, in particular pain and death?
  - 3 RCT, 387 people, 14 deaths
    - 3x more deaths in patients given oxygen
  - Small sample, few deaths → chance?
  - Evidence suggests the oxygen may be harmful
    - *Hyperoxia causes coronary & systemic vasoconstriction* → *decreases coronary blood flow and cardiac output!*

Oxygen therapy for acute myocardial infarction (Review)
Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Recent review looked at the effect of oxygen on **infarct size** in patients with acute MI and concluded:

- Little evidence by which to determine the efficacy and safety of high flow oxygen therapy in MI
- Evidence that does exist suggests that the **routine use of high flow oxygen in uncomplicated MI may result in a greater infarct size** and possibly increase the risk of mortality

Oxygen for Acute MI--Conclusions

• The evidence in this area is sparse, of poor quality and pre-dates the advances in reperfusion techniques and trial methods

• The evidence available is suggestive of harm but lacks power so this could be due to chance
AHA Recommendations for oxygen use in acute coronary syndrome (ACS)

- Oxygen should only be given initially...
- NO evidence for routine use in uncomplicated ACS
- NO evidence for administering O₂ for > 6 hours
- Give oxygen if patient is dyspneic, hypoxic, in heart failure or in shock
  - Titrate oxygen to SpO₂ 94% or above
Persons resuscitated with 100% oxygen have better outcomes after CPR.

1. True
2. False
• All available evidence from animal models says that resuscitation with 100% oxygen may be HARMFUL
  • worse neurologic outcome at 12 and 24 hours
  • higher levels of oxidized brain lipids & lipid peroxidation → neurologic damage

• Despite this, both AHA and UK Resuscitation Council recommend high-flow oxygen until the return of spontaneous circulation

Should we give high-dose oxygen *during* CPR? Yes
Well, we should definitely be giving 100% oxygen to patients POST-CPR to improve outcomes!

1. True

2. False
With the return of spontaneous circulation (ROSC), monitoring of oxygenation is paramount to prevent hyperoxia.

- IMPACT trial (N = 6326 patients who received CPR with 24 hours of arrival in ICU)

3 group comparison

**Hyperoxic group** (PO$_2$ > 300)

- Higher mortality
- Less likelihood of independent functional status at discharge
Forest plot of odds ratio of in-hospital mortality (10 studies)

Forest plot: OR 1.4 (95% CI 1.02–1.93) p = 0.004

Recommendations for Post-CPR care from the American Heart Association (AHA) and UK Resuscitation Council

- *Monitor* oxygen saturation as soon as the return to spontaneous circulation occurs

- **AHA**: Titrate $F_1O_2$ to maintain saturation $\geq 94\%$

- **UK**: Titrate to maintain saturation 94 to 98% administering not more 2 to 4 lpm
Newborns in distress or who appear cyanotic should be resuscitated with 100% oxygen.

1. True
2. False
Major new recommendations related to oxygen therapy for neonatal resuscitation emphasize *limiting oxygen exposure* in the delivery room.

1. Oximetry should be used —assessment of color is unreliable.
2. For term babies, resuscitation should begin with air not 100% oxygen.
3. Supplemental O₂ should be delivered with a blender to control F₁O₂ and O₂ concentration guided by oximetry.

Laboring women should receive supplemental oxygen when they are in Stage II or if there is any evidence of fetal distress.

1. True

2. False
Comparison 1. Maternal oxygen for fetal distress

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Assisted vaginal delivery</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2 Caesarean section</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3 Maternal dissatisfaction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4 Abnormal fetal heart rate tracing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5 Cord arterial pH &lt; 7.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6 Apgar score &lt; 7 at 1 minute</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7 Apgar score &lt; 7 at 5 minutes</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8 Neonatal resuscitation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9 Neonatal encephalopathy</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10 Serious neonatal morbidity or death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11 Childhood disability</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
The only studied interaction between the use of prophylactic maternal oxygen and fetal outcome was a negative one.

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Assisted vaginal delivery</td>
<td>1</td>
<td>85</td>
<td>1.07 [0.07, 16.60]</td>
</tr>
<tr>
<td>2 Caesarean section</td>
<td>1</td>
<td>85</td>
<td>0.54 [0.05, 5.70]</td>
</tr>
<tr>
<td>3 Maternal dissatisfaction</td>
<td>0</td>
<td>0</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>4 Abnormal fetal heart rate tracing</td>
<td>1</td>
<td>85</td>
<td>1.25 [0.46, 3.42]</td>
</tr>
<tr>
<td>5 Cord arterial pH &lt; 7.2</td>
<td>2</td>
<td>245</td>
<td>3.51 [1.34, 9.19]</td>
</tr>
<tr>
<td>6 Apgar score &lt; 7 at 1 minute</td>
<td>1</td>
<td>85</td>
<td>0.15 [0.01, 2.88]</td>
</tr>
<tr>
<td>7 Apgar score &lt; 7 at 5 minutes</td>
<td>1</td>
<td>85</td>
<td>0.36 [0.01, 8.53]</td>
</tr>
<tr>
<td>8 Neonatal resuscitation</td>
<td>1</td>
<td>85</td>
<td>0.92 [0.34, 2.51]</td>
</tr>
<tr>
<td>9 Neonatal encephalopathy</td>
<td>0</td>
<td>0</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>10 Serious neonatal morbidity or death</td>
<td>0</td>
<td>0</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>11 Childhood disability</td>
<td>0</td>
<td>0</td>
<td>0.0 [0.0, 0.0]</td>
</tr>
<tr>
<td>12 Cord arterial blood oxygen content (ml/dl)</td>
<td>1</td>
<td>67</td>
<td>-0.80 [-2.29, 0.69]</td>
</tr>
<tr>
<td>13 Cord arterial blood oxygen saturation (%)</td>
<td>1</td>
<td>67</td>
<td>-4.40 [-11.22, 2.42]</td>
</tr>
</tbody>
</table>
Maternal oxygen administration for fetal distress

- 2 RCTs assessed use of prophylactic maternal oxygen during 2\textsuperscript{nd} stage of uncomplicated labor

- N = 245

- Abnormal cord blood pH (< 7.2) was significantly more frequent in the oxygenation group compared to the controls
  - Relative risk 3.31 (95\%CI 1.34 to 9.19)
Patients under anesthesia should receive very high concentrations of oxygen...just to be safe.

1. True
2. False
Why is 100% oxygen often used perioperatively?

Preoxygenation prior to anesthesia induction.

Anesthesiology 2003;98:28–33.

What if we cannot ventilate, cannot intubate?
One “down” side of routine administration of 100% oxygen is the development of significant atelectasis.

Shunt = hypoxemia.
Higher $F_{I}O_{2}$ causes significantly more atelectasis formation than lower $F_{I}O_{2}$.

![Graph showing the relationship between $F_{ET}O_{2}$ and atelectasis formation. The graph indicates that higher $F_{I}O_{2}$ values lead to a greater atelectasis area compared to lower values.](image)
Other purported reasons to use a very high FIO$_2$ perioperatively...

- Prevention of surgical site infection?
  - Studies show equivocal results
  - Meta-analysis: hyperoxia only beneficial if patients with colorectal surgery do not receive neuraxial analgesia

- Prevention of postoperative nausea & vomiting?
  - Initial reports not reproducible
  - Meta-analysis: no evidence to support use of hyperoxia for preventing PONV

---

Anesth Analg 2012;114:334–42
• 1386 patients underwent elective or emergency laparotomy and were randomized to receive either 80% or 30% oxygen during and for 2 hours after surgery
• Underpowered to detect risk factors that might influence outcomes
• 99.7% follow-up

Anesth Analg 2012;115:849–54
More patients in the 30% oxygen group survived at 2.3 years (N=1386)

For ALL study patients:

23.2% died in 80% $O_2$ group
18.3% died in 30% $O_2$ group

$p=0.03$
Improved survival with 30% O₂ versus 80% O₂ only occurred in cancer surgery patients (N=714)

In non-cancer surgery patients:
No significant difference in mortality between oxygen group (p=0.79)

In CANCER surgery patients:
33.5% died in 80% oxygen group
24.6% died in 30% oxygen group (p=0.009)
Why might this have occurred?

- Study not large enough . . .
- Groups not different enough . . . or
- High oxygen fraction may have adverse effects--
  1. increases *neovascularization of tumor cells* that remain in the body
  2. increases *cellular growth*
  3. promotes *formation of reactive oxygen species* & oxidative stress
     - airway inflammation especially in COPD patients
     - arterial vasoconstriction, reduced coronary blood flow, DNA damage leading to atherosclerotic plaque rupture
Hyperoxia causes systemic vasoconstriction

- Can increase vascular resistance (SVR) in patients with CV disease
- Coronary artery resistance increased by hyperoxia
  - Resistance increased 23% when patients with ischemic heart disease breathe 100%
  - Attenuated by giving vitamin C infusion . . . suggesting a relationship to reactive oxygen species (ROS)

ROS can damage cells; excessive exposure induces oxidative stress and causes genetic mutations
In inflamed areas

Relatively unreactive

Limited reactivity

Moderate reactivity

High reactivity
Virtually all experiments have found that most animals die 3 to 6 days after breathing $F_1O_2 > 0.8$

- Progressive respiratory failure
  - ranging from mild tracheobronchitis to diffuse alveolar damage
- Depends on age and species of animal

- KEY: *individual variation* for development of lung injury and mortality

Respir Care 2013;58(1):123–140.

What about in humans?
The term "oxygen toxicity" is usually reserved for the presence of *tracheobronchial and pulmonary parenchymal damage* →

**Hyperoxic Acute Lung Injury (HALI)**

- Excess oxygen injures alveolar walls
  - Alveolar type II cells proliferate adaptively—increased mitochondria, increased antioxidant activity, more surfactant production
- Pulmonary epithelial thickness increases by 60%
  - Increased diffusion distance
- No clinical signs of recovery until $F_1O_2 < 0.7$
- Immune suppression ↑ risk of developing HALI
Mechanisms governing the initial burst in ROS in the primary target cell

1. ROS generation is proportional to $\text{PO}_2$

2. Plasma membrane produces 1$\text{st}$ ROS

3. Damage to lipid bilayer

4. Most ROS produced inside mitochondria

5. Endothelial nitric oxide reacts with $\text{O}_2$
Mechanisms governing the secondary burst of reactive oxygen species (ROS) and basic pathways of cell death from hyperoxia

1. Loss of plasma membrane integrity
2. ROS damage to mitochondria & enzymes
3. Release of cytochrome c into cell cytoplasm
4. ROS damage to nuclear membrane and DNA
5. Pro-inflammatory cytokines released
6. Activation of platelets, neutrophils, macrophages → burst of additional ROS

Respir Care. 2013 January; 58(1): 123–141.
Is there a “safe” oxygen concentration?

- $F_1O_2$ from 0.6 to 0.7 generally safe
- Longer exposure times less safe

- Oxygen is a drug and its use requires:
  - an indication
  - appropriate monitoring
  - reduction in therapy based on patient response
Comments, questions, stories?

Email: penelope.s.benedik@uth.tmc.edu