Oxygen Never Hurt Anyone
– Or Did It?

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Goals for this talk:

- Hypoxia
- Hyperoxia
- Oxidative stress
  - Theory and research
  - Implications
- Practice pearls
  - Monitoring
  - Standards of Care
  - Unanswered questions
Hypoxia

Mt. Kilimanjaro
19,340 ft
# Altitude And Hypoxia

Hecht, AJM 1971;50:703

<table>
<thead>
<tr>
<th>Feet</th>
<th>Meters</th>
<th>Baro Press</th>
<th>PiO₂</th>
<th>PaO₂</th>
<th>SaO₂</th>
<th>PaCO₂</th>
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<td>253</td>
<td>43</td>
<td>28</td>
<td>40</td>
<td>7.5</td>
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Effects of sudden hypoxia
(Removal of oxygen mask at altitude or in a pressure chamber)

- Impaired mental function; onset at mean SaO2 64%
- No evidence of impairment above 84%
- Loss of consciousness at mean saturation of 56%

Notes:
- Absence of breathlessness when healthy resting subjects are exposed to sudden severe hypoxia
- Mean SpO2 of airline passengers in a pressurised cabin falls from 97% to 93% (average nadir 88.6%) with no symptoms and no apparent ill effects

References:
Aker A et al Eur Respir J. 2005;25:725-30
“Normal” Oxygen Saturation

Normal range for healthy young adults is approximately 96-98\% \cite{CrapoAJRCCM19991601525}

Previous literature suggested a gradual fall with advancing age…

However, a Salford/Southend UK audit of 320 stable adults aged >70 found:
Mean SpO2 = 96.7\%
(2SD range 93.1-100\%)
“Normal” nocturnal SpO$_2$

- Healthy subjects in all age groups routinely desaturate to an average nadir of **90.4%** during the night (SD 3.1%)*

  (Gries RE et al  Chest 1996; 110: 1489-92)

*Therefore, be cautious in interpreting a single oximetry measurement from a sleeping patient. Watch the oximeter for a few minutes if in any doubt (and the patient is otherwise stable) as normal overnight dips are of short duration.
What happens at 9,000 metres (approximately 29,000 feet)?

It Depends…

SUDDEN
Passengers unconscious in <60 seconds if depressurized

ACCLIMATIZATION
Everest has been climbed without oxygen
Lowest Recorded $\text{PaO}_2$

- 7.5 mmHg (1.0 kPa)
- 20-year old male breathing room air following a heroin overdose 2 hours before ABG (+ 40 min for lab result)
- Unremarkable recovery

Is Hypoxia Bad?

“Hypoxia not only stops the motor, it wrecks the engine.”

- John Scott Haldane, 1917
Chemistry Warning – $O_2$
Oxygen

- Diatomic gas
- Atomic weight = 15.9994 g⁻¹
- Invisible
- Odorless, tasteless
- Third most abundant element in the universe
- Present in Earth’s atmosphere at 20.95%
Oxygen

- Essential for animal life.
Oxygen

- Oxygen therapy has always been a major component of emergency care.
- Health care providers believe oxygen alleviates breathlessness.
Oxygen

We began giving oxygen because it seemed like the right thing to do...

Documented benefits:

✓ Hypoxia
✓ Nausea/vomiting
✓ Motion sickness
Today, there are numerous textbooks on the reactive oxygen species.
Oxygen

- We are learning that oxygen is a two-edged sword
- It can be beneficial
- It can be harmful
The Chemistry of Oxygen

- Oxygen is highly reactive; it has 2 unpaired electrons
- Molecules/atoms with unpaired electrons are extremely unstable and highly reactive
- Referred to as “free radicals”
The Chemistry of Oxygen

How are free-radicals produced?

- Normal respiration and metabolism
- Exposure to air pollutants
- Sun exposure
- Radiation
- Drugs
- Viruses
- Bacteria
- Parasites
- Dietary fats
- Stress
- Injury
- Reperfusion
The Chemistry of Oxygen

- Most cells receive approximately 10,000 free-radical hits a day
- Enzyme systems can normally process these
The Chemistry of Oxygen

- Changes associated with aging are actually due to effects of free-radicals
- As we age, the antioxidant enzyme systems work less efficiently
The Chemistry of Oxygen

- An excess of free-radicals damages cells and is called oxidative stress.
Oxygen Free Radicals

- Develop during reperfusion—not during hypoxia (when $O_2$ enters damaged area)
- Flooding ischemic cells with oxygen worsens oxidative stress (proportionate)
Not a new concept

ACLS Guidelines 2000:
- Supplemental oxygen only for saturations < 90%
- 2005: ditto
- 2010: < 94%
## Stroke

<table>
<thead>
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<th>Variable</th>
<th>Minor or Moderate Strokes</th>
<th>Severe Strokes</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Oxygen Control</td>
<td>Oxygen Control</td>
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<tr>
<td>Survival</td>
<td>81.8% 90.7%</td>
<td>53.4% 47.7%</td>
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<tr>
<td>SSS Score</td>
<td>54 (54-58) 57 (52-58)</td>
<td>47 (28-54) 47 (40-52)</td>
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<tr>
<td>Barthel Index</td>
<td>100 (95-100) 100 (95-100)</td>
<td>70 (32-90) 80 (47-95)</td>
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</table>


![Graph](https://via.placeholder.com/150)
“Supplemental oxygen should not routinely be given to non-hypoxic stroke victims with minor to moderate strokes.” - AHA 1994

“Further evidence is needed to give conclusive advice concerning oxygen supplementation for patients with severe strokes.”
Neonates

- Prevailing wisdom: oxygen is harmful to neonates
- Transition from intrauterine hypoxic environment to extrauterine normoxic environment leads to an acute increase in oxygenation and development of ROS
Neonates

• 1,737 depressed neonates:
  – 881 resuscitated with room air
  – 856 resuscitated with 100% oxygen

• Mortality:
  – Room air resuscitation: 8.0%
  – 100% oxygen resuscitation: 13.0%

• Room air superior to 100% oxygen for initial resuscitation


Neonatal Studies - Summary

Newborn resuscitation with 100% oxygen increases:

- Mortality
- Myocardial injury
- Renal injury
- Childhood leukemias and cancers

Therapeutic Hypothermia

Vanderbuilt Univ – TH post ROSC

- 170 patients - highest PaO$_2$ during 24° TH (32-34°C):
  - Survivors had significantly lower PaO$_2$ (198) vs non-survivors (254)
  - Higher PaO$_2$ ↑ risk death (OR 1.439)
  - Favorable neuro outcomes (CPC 1-2) also linked to lower PaO$_2$
  - Higher PaO$_2$ ↓ neuro outcomes (OR 1.485)

Trauma

- Charity Hospital (1/1 ➔ 9/30/2002):
- 5,549 trauma patients by EMS

Mortality:

<table>
<thead>
<tr>
<th>Category</th>
<th>Oxygen</th>
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<tr>
<td>Penetrating</td>
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</table>
“Our analysis suggest that there is no survival benefit to the use of supplemental oxygen in the prehospital setting in traumatized patients who do not require mechanical ventilation or airway protection.”

Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial

Michael A Austin, honorary associate,1 emergency medicine registrar,2 wilderness helicopter, intensive care paramedic,3 Karen E Wills, biostatistician,1 Leigh Blizzard, senior biostatistician,1 Eugene H Walters, professorial fellow,1 Richard Wood-Baker, honorary fellow,1 director2

ABSTRACT
Objectives To compare standard high flow oxygen treatment with titrated oxygen treatment for patients with an acute exacerbation of chronic obstructive pulmonary disease in the prehospital setting.
Design Cluster randomised controlled parallel group trial.
Setting Ambulance service in Hobart, Tasmania, Australia.
Participants 165 patients with an exacerbation of chronic obstructive pulmonary disease were randomly assigned to standard high flow oxygen or titrated oxygen.139 patients were eligible for analysis.
Interventions Standard high flow oxygen via face mask or nasal cannula at a rate of 6 l/min; titrated oxygen at a rate of 6 l/min to achieve an oxygen saturation of 93% to 95%. The median (interquartile range) partial pressure of oxygen was 99 (97) mm Hg in the high flow group and 99 (96) mm Hg in the titrated group (P=0.76; n=28).

Conclusions Titrated oxygen treatment significantly reduced mortality, hypercapnia, and respiratory acidosis compared with high flow oxygen in acute exacerbations of chronic obstructive pulmonary disease. These results provide strong evidence to recommend the routine use of titrated oxygen treatment in patients with breathlessness and a history or clinical likelihood of chronic obstructive pulmonary disease.
405 diff breathers randomized:
- NRBM (n=226)
- NC to SpO₂ 88-92% (n=179)

Titrated O₂ reduced mortality:
- all patients 58%
- COPD patients 78%
ACS (Acute Coronary Syndrome)

• $O_2$ shows little benefit, may harm
• No analgesic effect
• Harm study needed since 1976
• Dangers:
  – Increases myocardial ischemia (Nicholson, 2004)
  – Triples mortality (Rawles, 1976)
  – Increases infarct size (Ukholkina, 2005)
• No benefit when sats $>90$

Within 5 minutes of 100% $O_2$ (vs. RA):

- $\uparrow$ coronary resistance ~ 40%
- $\downarrow$ coronary blood flow (CBF) ~ 30%
- Blunted CBF response to Ach
- Marked $\downarrow$ NO

CBF (Coronary Blood Flow)

- Room air
  - APV: 24
  - pO2 = 73

- 100% oxygen
  - APV: 16
  - pO2 = 289
Right Heart Cath:

Where to from here?
British Thoracic Society

- O₂ therapy guideline (2008)
- All this... and more:
  - Routine administration can be harmful
  - O₂ does not affect dyspnea unless hypoxic
  - Hyperoxia may decrease target organ perfusion (when given needlessly)
  - Unnecessary O₂ delays recognition of deterioration by providing false reassurances with high O₂ saturations

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... and more:

- Absorption atelectasis @ FiO$_2$ 0.3-0.5
- O$_2$ risk to some COPD patients
- ↑ SVR, coronary vasospasm
- No demonstrated clinical benefit of keeping O$_2$ sat > 90% in any patient

Kaneda T et al. Jpn Circ J 2001; 213-8
Thomaon AJ et al. BMJ 2002; 1406-7
Ronning OM et al. Stroke 1999; 30
Downs JB. Respiratory Care 2003; 48:611-20
British Thoracic Society

O₂ therapy guideline (everywhere):

- Keep normal/near-normal O₂ sats
  - All patients except hypercapnic resp. failure and terminal palliative care
  - Keep sat 92-96%, tx only if hypoxic
  - Use pulse oximetry to guide tx – max 98%

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But this is not the UK...

Guidelines 2010:

- Oxygen for saturations < 94%
- Target range 94 – 96%
Got oxygen?
Oxygen?
Implications: Oximetry mandatory
Implications: Precise Control

• Both hypo/hyperoxia seem bad
  – We often tx hypoxemia & ignore hyperoxia

• Individual responses vary widely

• No biomarkers to identify damage

• Time for PCAO?
  – Precise Control of Arterial Oxygenation
  – FiO₂ directly linked to SpO₂ or PaO₂
  – Clinician sets upper & lower limits

Implications: Venturi Comeback
Prehospital Implications

- Pulse oximetry guided supplemental oxygen
- Protocols needed!
Can We Attenuate Oxidative Stress?

- Perhaps
- Clues lie with **Carbon Monoxide**
  - Known in vitro and in vivo antioxidant and anti-inflammatory properties
  - Critically ill patients ↑ CO production
    - Survivors produce more CO
    - Non-survivors produce less or no CO
  - Multiple human studies now using CO to attenuate oxidative pulmonary stress
Endogenous Sources of CO

- Normal heme catabolism (breakdown):
  » Only biochemical reaction in the body known to produce CO
- Hemolytic anemia
- Sepsis, critical illness...
Laboratory CO-oximetry
Pulse CO-oximetry
Take Home Messages

• Oxygen can hurt
• CO may help
• Empiric use is not a good practice - \( \text{O}_2 \) tx must be focused
• Use oximetry to guide care: prevent hypoxia and hyperoxia
Questions?

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