Can Oxygen Be Bad?

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Disclosures

- I serve on the speakers bureau for Masimo Corporation.
- I have no other financial relationships to disclose.
- I am the EMS editor for Fire Engineering magazine.
- I do not intend to discuss any unlabeled or unapproved uses of drugs or products.
Mike McEvoy - Books:

- Emergency & Critical Care
  Pocket Guide™ ACLS Version

- Critical Care Transport
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**

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Physics

Hypobaric hypoxia

Alveolar gas equation:

\[ P_{A}O_2 = ( F_{i}O_2 \times (P_{atmos} - P_{H2O})) - (P_{a}CO_2 / RQ) \]

\( P_{A}O_2 \) varies in direct proportion to \( P_{atmos} \)

Himalayan Peaks over Kathmandu, Nepal
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*
“Normal” Oxygen Saturation

Normal range for healthy young adults is approximately 96-98% (Crapo AJRCCM, 1999;160:1525)

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 SpO₂

- 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.
Technology
Nasal Alar SpO$_2$™ Sensor

- Xhale.com FDA approved 3-17-15
Nasal Ala

- Last branch external carotid
- First branch internal carotid

Cardiopulmonary Bypass

Finger PPG

Alar PPG
Response to Neosynephrine

- IV bolus
- Alar PPG signal
- Finger PPG signal
Know Your Equipment
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
How High Is Too High?

- High altitude: 1500-3000m above sea level
- Very high altitude: 3000-5000m
- Extreme altitude: above 5000m

- For sea level visitors, 4600-4900m = highest acceptable level for permanent habitation (15-16Kft)
- For high altitude residents, 5800-6000m = highest so far recorded (19Kft)
Deaths at Extreme Altitude

UIAA Mountain Medicine Study Himalayan peaks above 22,960 ft

- All British expeditions to peaks over 7000 m were collected from Mountain Magazine 1968 - 1987.
- 535 mountaineers, 23 deaths on 10 of 51 peaks visited, 4.3% overall mortality (1 fatality every 5th expedition).

Everest - 29,032 ft

- 121 individuals, 11 expeditions, 7 deaths, 5.8% overall mortality

K2 - 28,250 ft

- 28 individuals, 5 expeditions, 3 deaths, 10.7% overall mortality

Source: UIAA Mountain Medicine Centre, June 1997
Mike 73%
Godlisten 84%
Pete 41%
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

Everest Ascent – It’s Dangerous Up There

- Summit: 8848 m (29,029')
- Base Camp: 5380 m (17,700')
- High Camp: 7920 m (26,000')
- Southeast Ridge
Acclimatization

Process by which people gradually adjust to high altitude

- Determines survival and performance at high altitude
- Series of physiological changes
  1. ↑ O₂ delivery
  2. hypoxic tolerance +++
- Acclimatization depends on:
  - severity of the high-altitude hypoxic stress
  - rate of onset of the hypoxia
  - individual’s physiological response to hypoxia
**Ventilatory Acclimatization**

- **Hypoxic ventilatory response**
  - Starts within 1 – 3 hours of exposure ≥ 1500m

- **Mechanism:**
  - Ascent to altitude
  - Hypoxia
  - Decreased $\text{PCO}_2$
  - Carotid body stimulation
  - Respiratory center stimulation
  - Increased ventilation
  - Improved hypoxia

**Degree of HVR**

$$\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{HCO}_3^- + \text{H}^+$$
Lung Gas Diffusion

High altitude = ↓ $O_2$ diffusion:

1. Lower $O_2$ driving pressure (atmospheric air to blood)
2. Lower Hb affinity for $O_2$ (on the steep portion of the $O_2$/Hb curve)
3. Inadequate time for equilibration
$O_2$ Hgb Dissociation Curve

Left shift
- Decreased temp
- Decreased 2-3 DPG
- Decreased $[H+]
- CO

Right shift (reduced affinity)
- Increased temp
- Increased 2-3 DPG
- Increased $[H+]$
Consequence = \downarrow \text{O}_2 \text{ Saturation}
AMS
Acute Mountain Sickness

Trekkers on the Annapurna Circuit
AMS - Signs & Symptoms

Lake Louise Consensus 1993:

- **Headache** in an unacclimatized individual who recently arrived at > **2500m plus** one or more:
  - n/v, anorexia, insomnia, dizziness or fatigue.
- 1-10h after ascent, remits in 4-8days.
- No diagnostic physical findings except low O$_2$sat.

(Hackett & Roach, 2001, Forwand et al. 1968)

Machhapuchhre, 6993m
Red cell moving out of the capillary lumen (c) into an alveolus (a)

Costello et al., 1992

West et al., 1995

- Circular break of the epithelium
- Full break of the blood-gas barrier
HAPE - prevention

**Slow ascent** (HAPE-S <300m/day over 2000m)
(Dumont et al. BMJ 2000)


**CPAP** (Schoene et al. Chest, 1985)
HAPE – what doesn’t work

Simulated descent  (Bärtsch et al. BMJ, 1993; Pollard et al, BMJ, 1995)

Practice (repeated exposures)  (Burse et al. Aviat Space Environ Med, 1988)


Thorung La, 5415m
Bottom Line: prevent/correct hypoxia and you will prevent/correct PE!
Is Hypoxia Bad?

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

- John Scott Haldane, 1917
Chemistry Warning – $\text{O}_2$
“Not all chemicals are bad. Without chemicals such as hydrogen and oxygen, for example, there would be no water, a vital ingredient for beer.”

-Dave Barry
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
Oxygen

• 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
Destructive power of oxidation
Have You Seen Oxygen Harm?
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

• Free radicals, in normal concentrations, are important in intracellular bacteria and cell-signaling

• Most important free radicals:
  – Superoxide ($\bullet O_2^-$)
  – Hydroxyl radical ($\bullet OH$)
The Chemistry of Oxygen

- Oxygen produces numerous free-radicals—some more reactive than others:
  - Superoxide free radical (\(\cdot O_2^-\))
  - Hydrogen peroxide (\(H_2O_2\))
  - Hydroxyl free radical (\(\cdot OH\))
  - Nitric oxide (\(\cdot NO\))
  - Singlet oxygen (\(^1O_2\))
  - Ozone (\(O_3\))
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.
The Chemistry of Oxygen

Diseases associated with free-radicals:

- Arthritis
- Cancer
- Atherosclerosis
- Parkinson’s
- Alzheimer’s
- Diabetes
- ALS

Neonatal diseases:

- Intraventricular hemorrhage
- Periventricular leukomalacia
- Chronic lung disease / bronchopulmonary dysplasia
- Retinopathy of prematurity
- Necrotizing enterocolitis
The Chemistry of Oxygen

Lifespan = 3.5 years

H$_2$O$_2$ Leakage from Cardiomyocytes

Lifespan = 21 years

Lifespan = 24 years
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%
• 2015: ditto
### Stroke

<table>
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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</td>
<td>Control</td>
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<tr>
<td>Survival</td>
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<tr>
<td>SSS Score</td>
<td>54 (54-58)</td>
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<tr>
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</tbody>
</table>


![Graph showing probability of survival over time with and without oxygen](image)
Stroke

• “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


Cardiac Arrest

- Emphasis on circulation
  - Compression only CPR may be better
  - Known dangers of oxidative stress
- Study on Room Air vs. FiO₂ 1.0
  - In-hospital med/surgical wards
  - Standard ACLS, change only FiO₂ (30 days)
  - Study halted by IRB: use of 100% oxygen harmful to human subjects!

McEvoy et al. (Unpublished) Comparison of Normoxic to hyperoxic ventilation during In-Hospital Cardiac Arrest. Germany 2008.
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$_2$ $\uparrow$ risk death (OR 1.439)
  – Favorable neuro outcomes (CPC 1-2) also linked to lower PaO$_2$
  – Higher PaO$_2$ $\downarrow$ neuro outcomes (OR 1.485)

Trauma

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

Mortality:

\[
\begin{array}{c|c|c}
\text{Oxygen} & \text{None} \\
\hline
\text{PENETRATING} & \text{O} & \text{R} \\
\text{OVERALL} & \text{O} & \text{R} \\
\text{BLUNT} & \text{O} & \text{R} \\
\end{array}
\]
• “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 195 patients with acute exacerbation of chronic obstructive pulmonary disease presenting to hospital emergency department.

Interventions Oxygend delivery at high flow rate compared with titration of oxygen by the paramedic.

Main outcome measures Mortality and subsequent treatment at hospital emergency department. Blood pressure and arterial oxygen pressure.

Results Times to high flow oxygen treatment were not significantly different. Titrated oxygen patients had a lower arterial oxygen pressure (−33.6 (16.3) mm Hg; P=0.02; n=29) than were patients who received high flow oxygen.

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%

ACS: Why, why, why?

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

- ↑ coronary resistance ~ 40%
- ↓ coronary blood flow (CBF) ~ 30%
- Blunted CBF response to Ach
- Marked ↓ NO

CBF (Coronary Blood Flow)

Room air
pO2 = 73

100% oxygen
pO2 = 289
Where to from here?
British Thoracic Society

• Issued an $O_2$ therapy guideline 2008

• All this… and more:
  – Routine administration can be harmful
  – $O_2$ does not affect dyspnea unless hypoxic
  – Hyperoxia may decrease target organ perfusion (when given needlessly)
  – Unnecessary $O_2$ delays recognition of deterioration by providing false reassurances with high $O_2$ saturations

www.brit-thoracic.org.uk
… and more:

- Absorption atelectasis @ FiO\textsubscript{2} 0.3-0.5
- O\textsubscript{2} risk to some COPD patients
- SVR, coronary vasospasm
- No demonstrated clinical benefit of keeping O\textsubscript{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
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%

www.brit-thoracic.org.uk
But this is not the UK...

Guidelines 2010 and 2015:

• Oxygen for saturations < 94%
• Target range 94 – 96%
Got oxygen?
Oxygen?
Implications: Oximetry mandatory
Implications: Venturi Comeback
Prehospital Implications
Prehospital Implications

- Pulse oximetry guided supplemental oxygen
- Protocols needed!
Prehospital Implications

- Rationalizing the O$_2$ administration using pulse-oximetry reduces O$_2$ usage.
- Oxygen cost-saving justifies oximeter purchase:
  - Where patient volume > 1,750 per year.
  - Less frequently for lower call volumes, or
  - Mean transport time is < 23 minutes.

Oxidative Stress?
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?

NEED CASH FOR ALCOHOL RESEARCH

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