

Can Oxygen Be Bad?

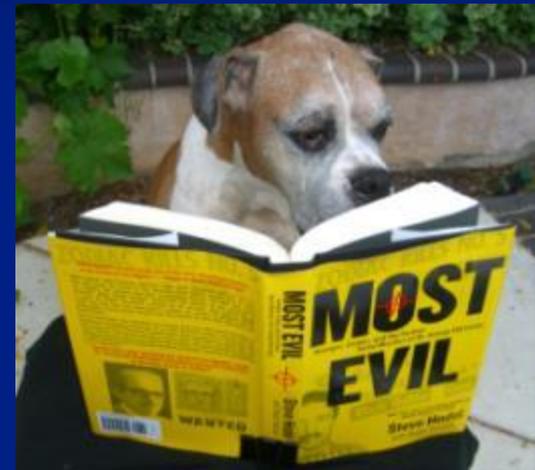
Mike McEvoy, PhD, NRP, RN, CCRN

EMS Coordinator – Saratoga County, New York

EMS Editor – Fire Engineering Magazine

Chair – Resuscitation Committee, Albany Medical Center

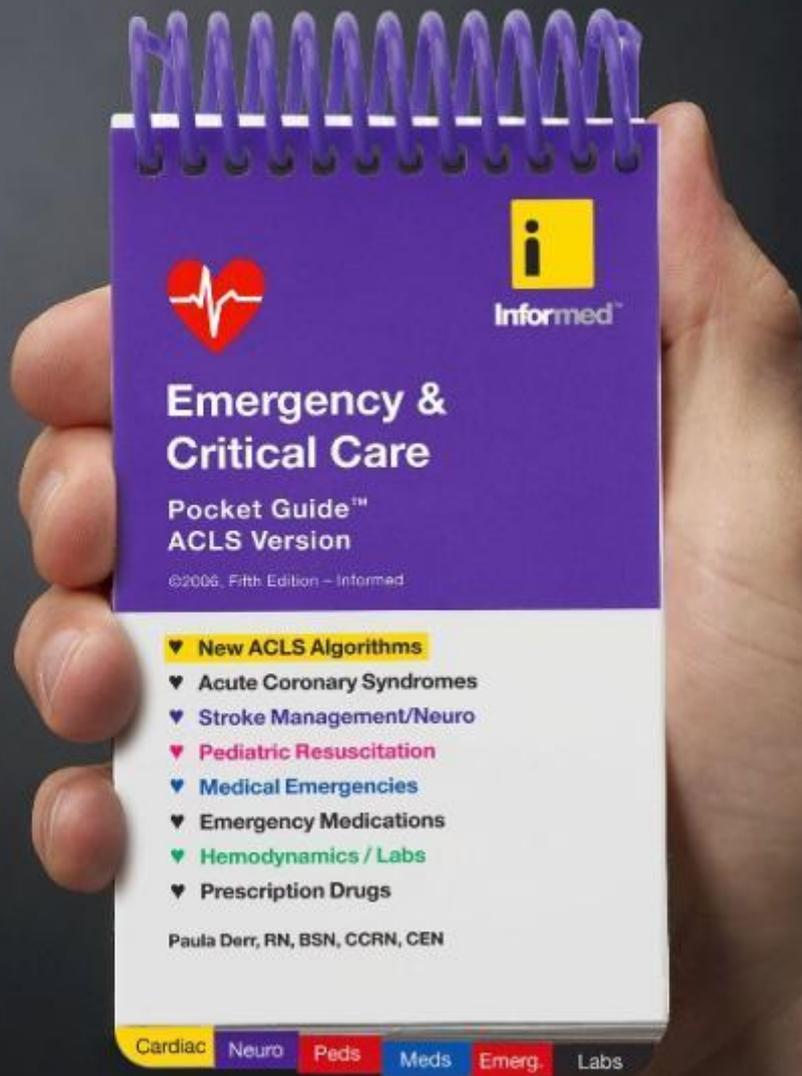
Sr. Staff RN – Cardiac Surgical ICUs – Albany Med Ctr



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:



AAOS

Critical Care Transport





Mike McEvoy, PhD, RN, CCRN, NRP

**Power Point version of these slides
available at www.mikemcevoy.com**

(Click on Open Bar tab)



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

<u>Feet</u>	<u>Meters</u>	<u>Baro Press</u>	<u>PiO₂</u>	<u>PaO₂</u>	<u>SaO₂</u>	<u>PaCO₂</u>
0	0	760	149	94	97	41
5,000	1,500	630	122	66	92	39
8,000	2,400	564	108	60	89	37
10,000	3,000	523	100	53	83	36
12,000	3,600	483	91	42	85	35
15,000	4,600	412	76	44	75	32
18,000	5,500	379	69	40	71	29
20,000	6,100	349	63	38	65	21
24,000	7,300	280	62	34	50	16
29,029	8,848	253	43	28	40	7.5

Physics

Hypobaric hypoxia

Alveolar gas equation:

$$P_A O_2 = (F_i O_2 * (P_{atmos} - P_{H_2O})) - (P_a CO_2 / RQ)$$

$P_A O_2$ varies in direct proportion to P_{atmos}

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

Akero A et al Eur Respir J. 2005;25:725-30

Cottrell JJ et al Aviat Space Environ Med. 1995;66:126-30

Hoffman C, et al. Am J Physiol 1946;145:685-692

“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)

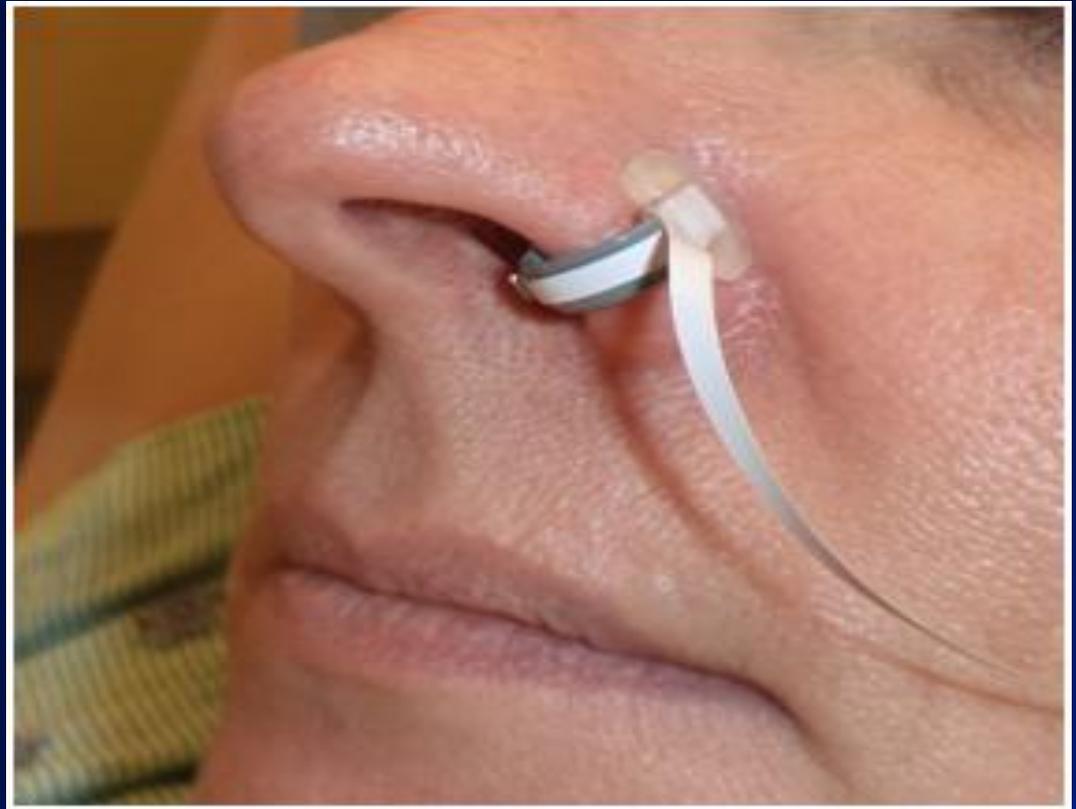
**Therefore, be cautious in interpreting a single oximetry measurement from a sleeping patient. Watch the oximeter for a few minutes if in any doubt (and the patient is otherwise stable) as normal overnight dips are of short duration.*

Technology



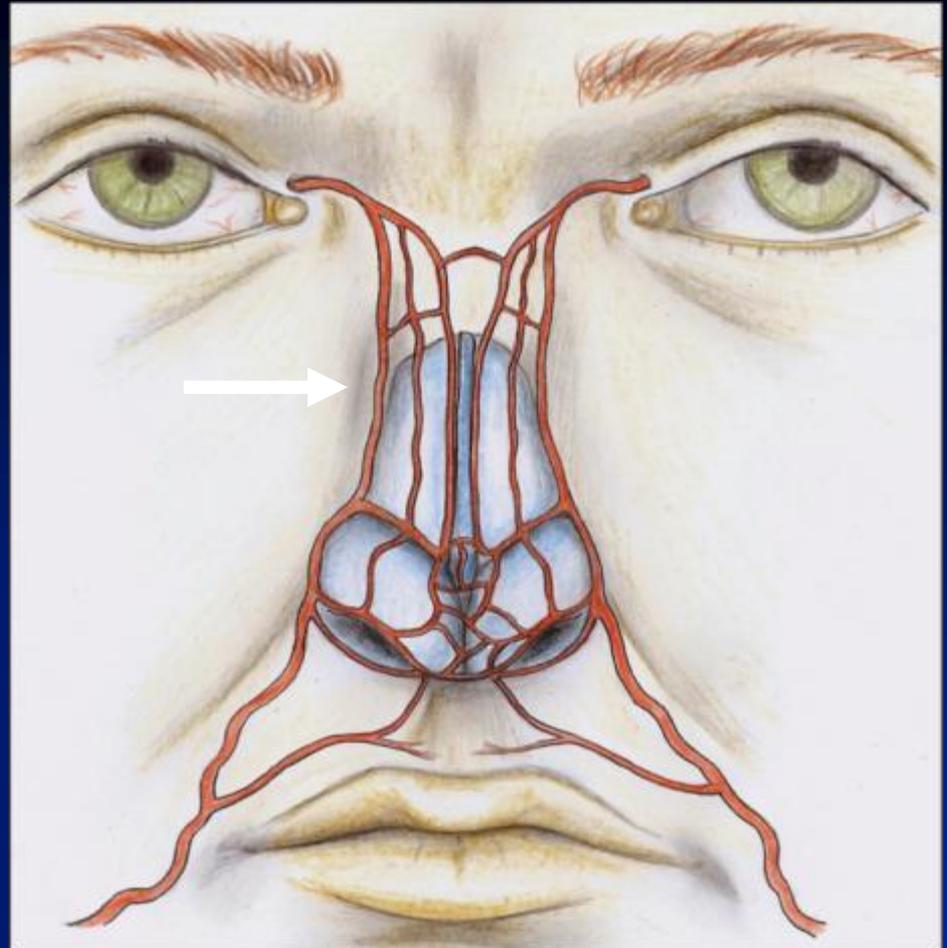
Nasal Alar SpO₂™ Sensor

- **Xhale.com FDA approved 3-17-15**



Nasal Ala

- Last branch external carotid
- First branch internal carotid



Saban, et al. Nasal Arterial Vasculature: Medical and Surgical Applications Arch Facial Plast Surg. 2012;14:429-436.

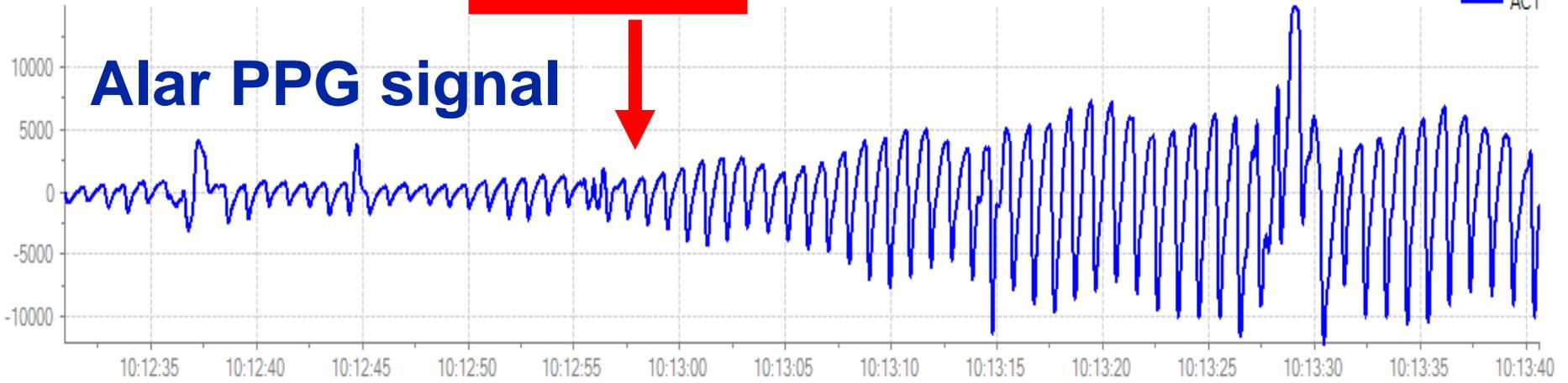
Cardiopulmonary Bypass



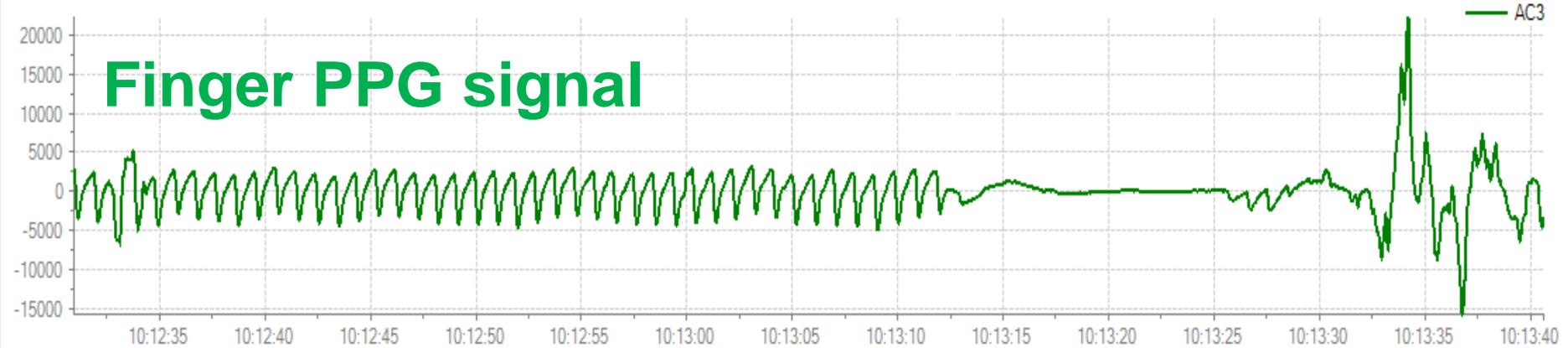
Response to Neosynephrine

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



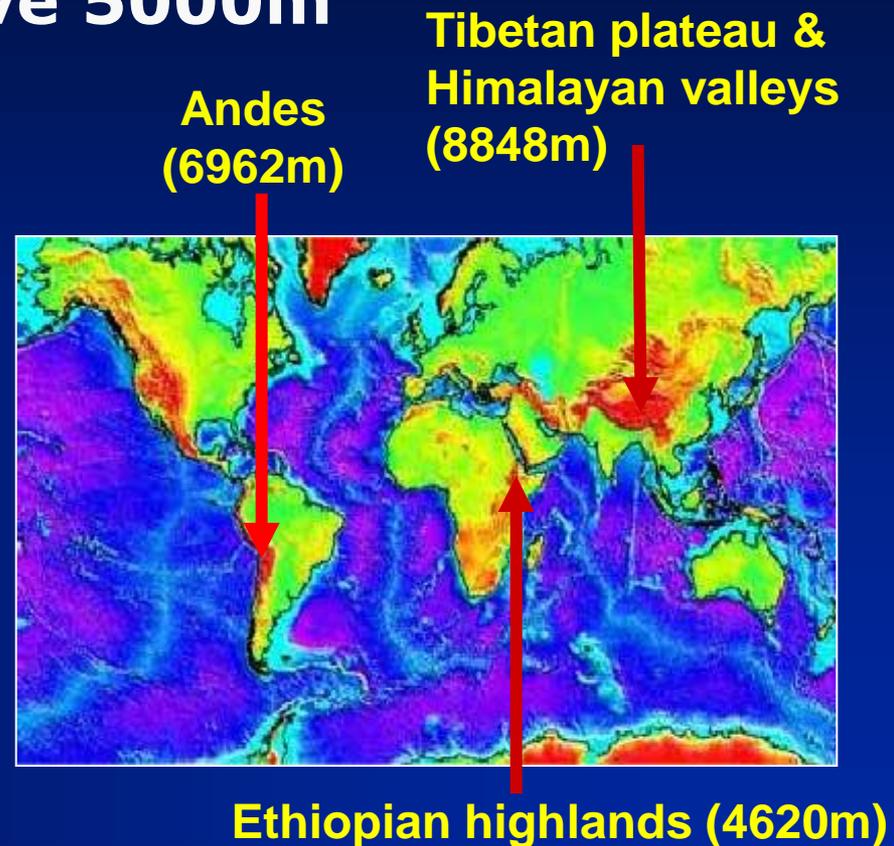
ACCLIMATIZATION

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%

Pete
41%

Godlisten
84%

Lowest Recorded PaO₂

- 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



Gray FD, Horner GJ. Survival following extreme hypoxemia. *JAMA* 1970; 211:1815-1817.



← LAVA TOWER
← ARROW GLACIER

Everest Ascent – It's Dangerous Up There

A photograph of Mount Everest with a red line tracing an ascent route. The line starts at the Southeast Ridge, goes up to Base Camp, then to High Camp, and finally to the Summit. Each point is marked with a red dot and a callout box.

Summit
8848 m (29,029')

Base Camp
5380 m (17,700')

High Camp
7920 m (26,000')

Southeast Ridge

Acclimatization

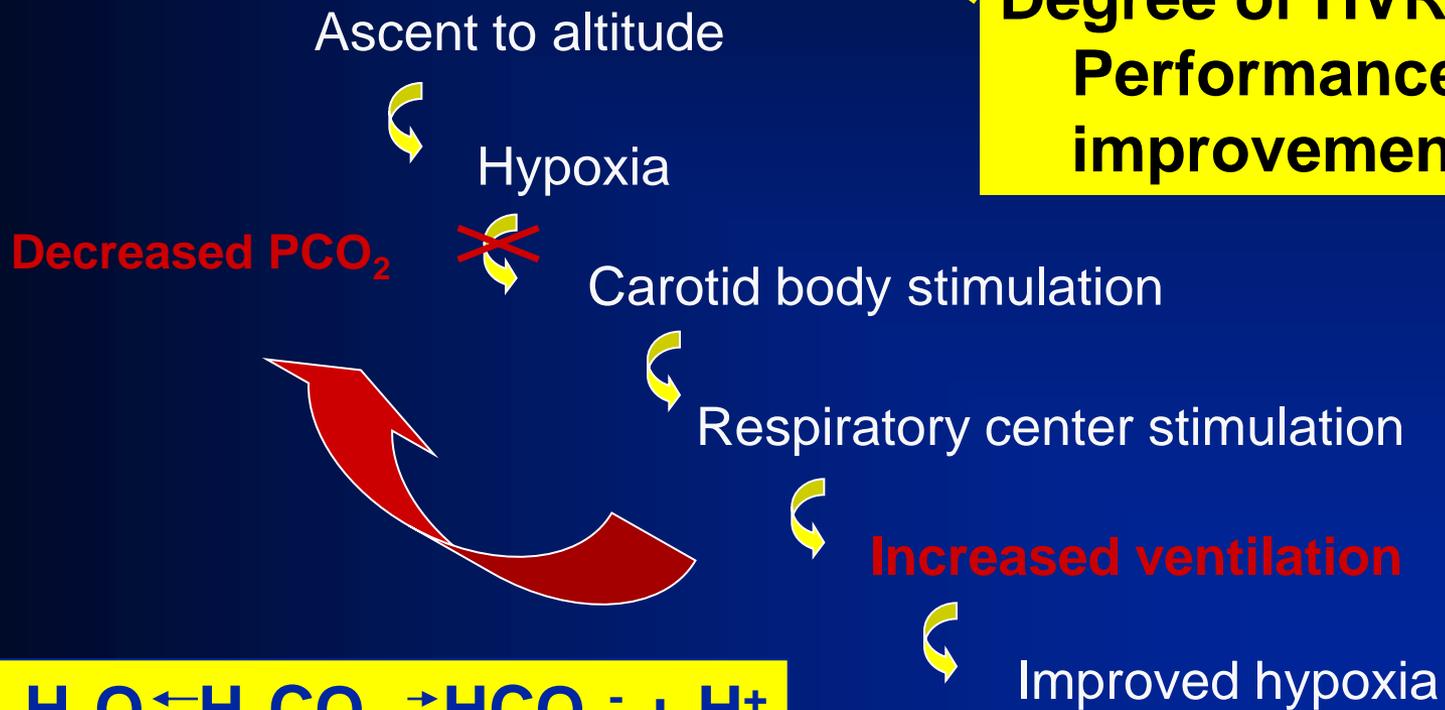
Process by which people gradually adjust to high altitude

- **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**

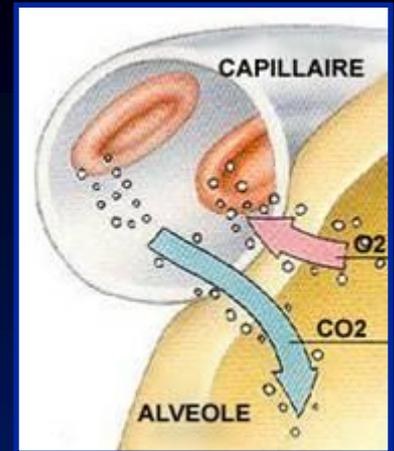
Ventilatory Acclimatization

- Hypoxic ventilatory response = $\uparrow V_E$
- Starts within 1 – 3 hours of exposure $\geq 1500\text{m}$
- Mechanism:

Degree of HVR =
Performance
improvement



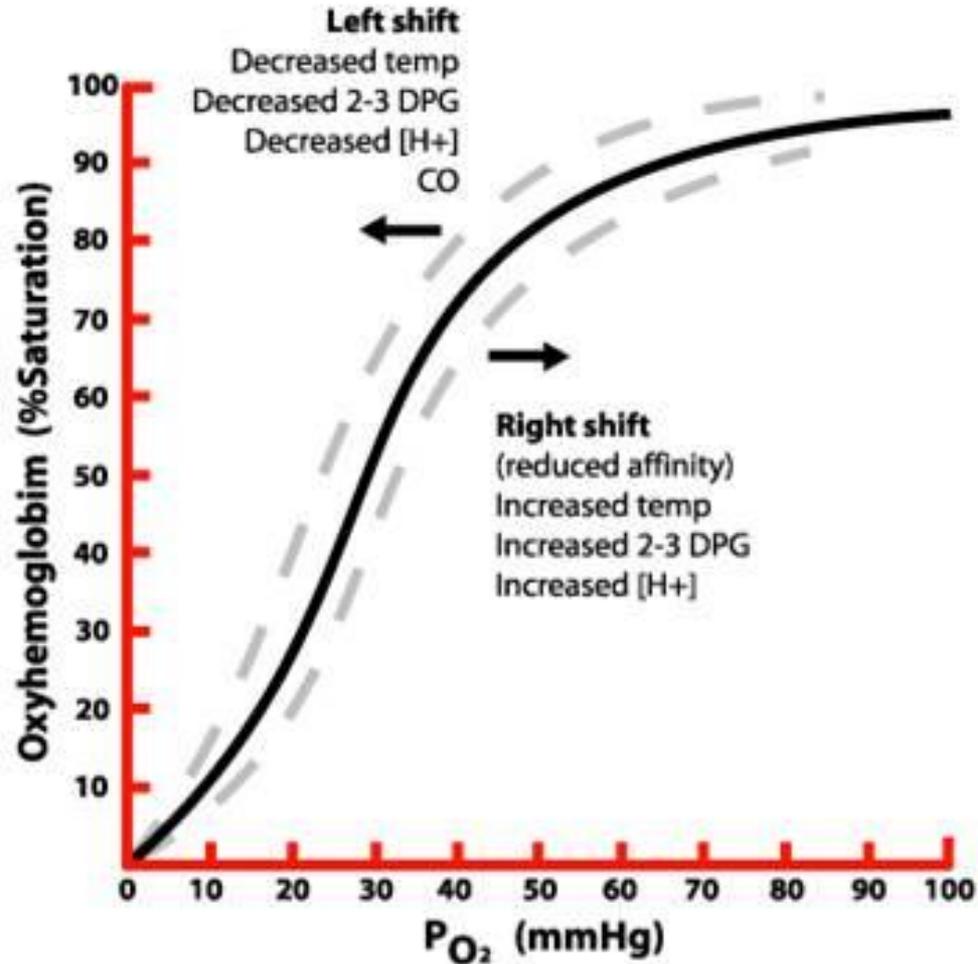
Lung Gas Diffusion



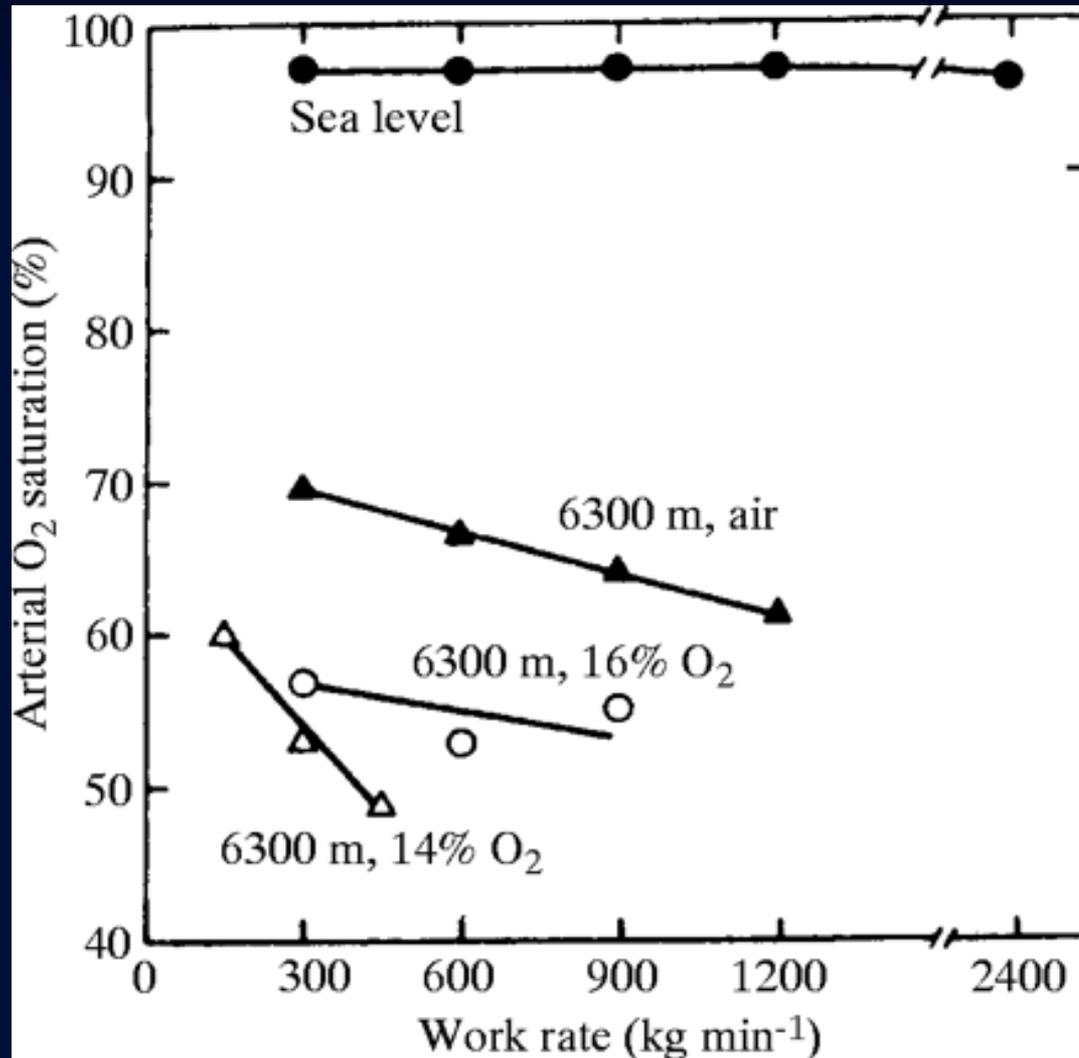
High altitude = ↓ O₂ diffusion:

- 1. Lower O₂ driving pressure (atmospheric air to blood)**
- 2. Lower Hb affinity for O₂ (on the steep portion of the O₂/Hb curve)**
- 3. Inadequate time for equilibration**

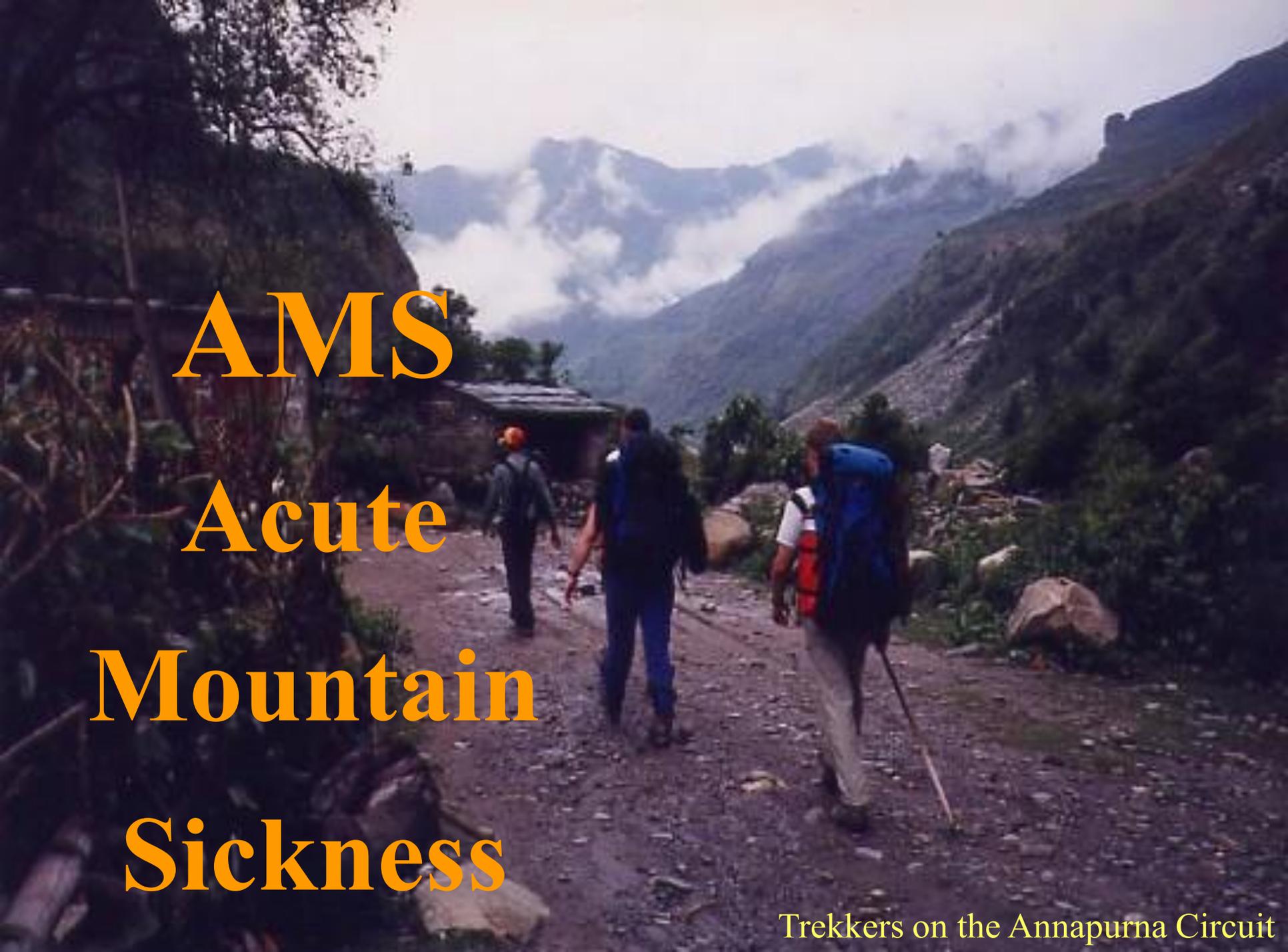
O₂ Hgb Dissociation Curve



Consequence = ↓ O₂ Saturation



West et al., 1983



AMS
Acute
Mountain
Sickness

Trekkers on the Annapurna Circuit

AMS - Signs & Symptoms

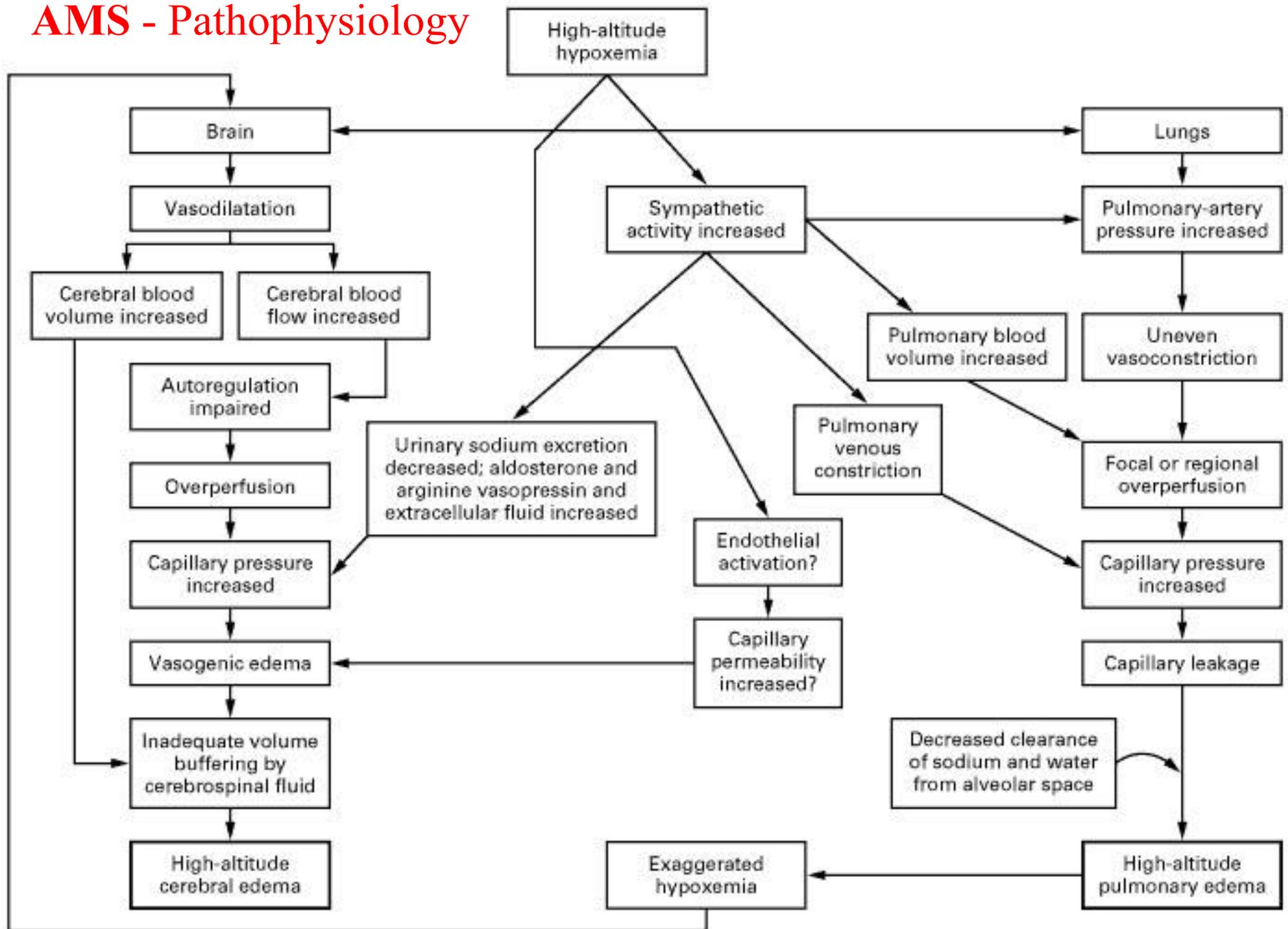
Lake Louise Consensus 1993:

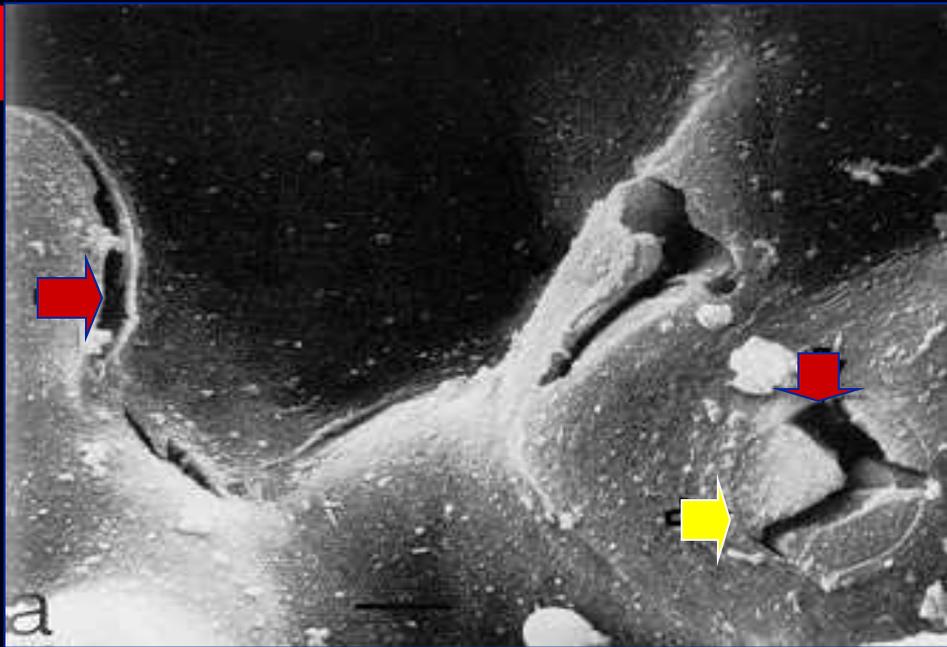
- **Headache** in an unacclimatized individual who recently arrived at $> 2500\text{m}$ **plus** one or more:
n/v, anorexia, insomnia, dizziness or fatigue.
- 1-10h after ascent, remits in 4-8days.
- No diagnostic physical findings except low O₂sat.

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

Machhapuchhre, 6993m

AMS - Pathophysiology

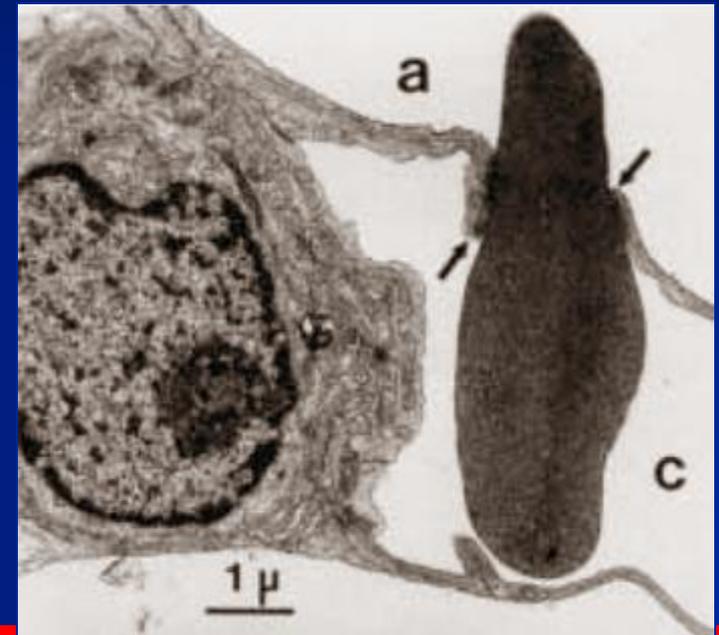




Costello et al., 1992

- Yellow arrow: Circular break of the epithelium
- Red arrow: Full break of the blood-gas barrier

Red cell moving out of the capillary lumen (c) into an alveolus (a)



West et al., 1995

HAPE - prevention

Slow ascent (HAPE-S <300m/day over 2000m)

(Dumont et al. BMJ 2000)

Steroids (Keller et al. BMJ, 1995; Reid et al. J Wild Med, 1994; Johnson et al. NEJM, 1984)

Pulmonary vasodilators (PDI) & NO (Dumont et al. BMJ 2000; Hohenhaus et al. Am J Resp Crit Care Med, 1994; Fallon et al. Amer J Physiol, 1998; Oelz et al. Lancet, 1989)

PCO₂ reducers (acetazolamide) (Grissom et al. Ann Int Med, 1992; Reid et al. J Wild Med, 1994; Forwand et al. NEJM, 1968)

CPAP (Schoene et al. Chest, 1985)

HAPE – what doesn't work

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

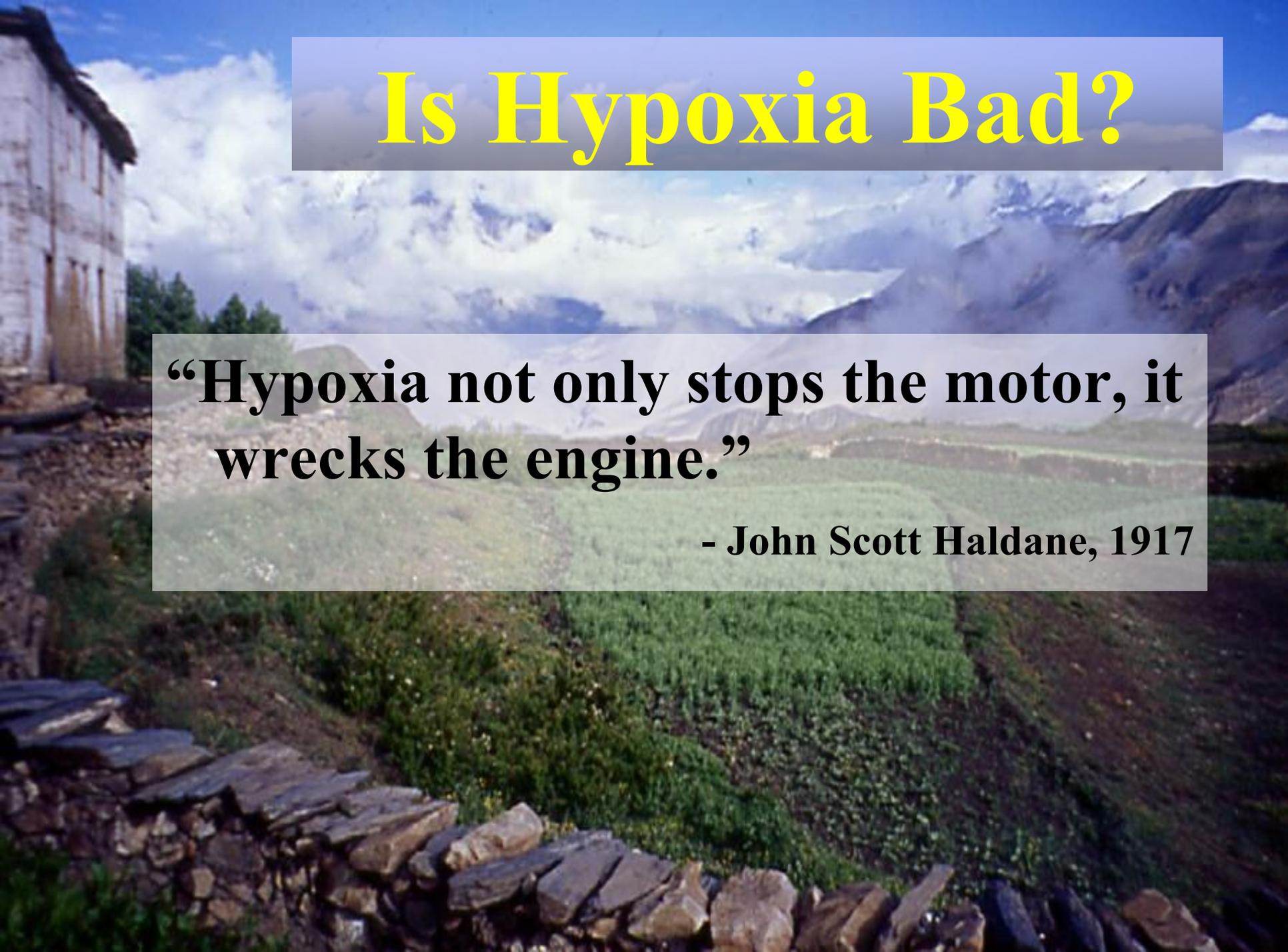
Practice (repeated exposures) (Burse et al. Aviat Space Environ Med, 1988)

? **Antioxidants** (Bailey et al. High Alt Med Biol, 2001)

**Bottom Line: prevent/correct hypoxia
and you will prevent/correct PE !**



Heading towards Muktinath, 5000m

A scenic view of a mountain valley. In the foreground, a stone wall runs across the bottom. A dirt road leads up a hillside covered in green vegetation. On the left, a building with a thatched roof is visible. In the background, there are mountains with patches of snow and a blue sky with white clouds.

Is Hypoxia Bad?

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

- John Scott Haldane, 1917

Chemistry Warning – O₂



Oxygen

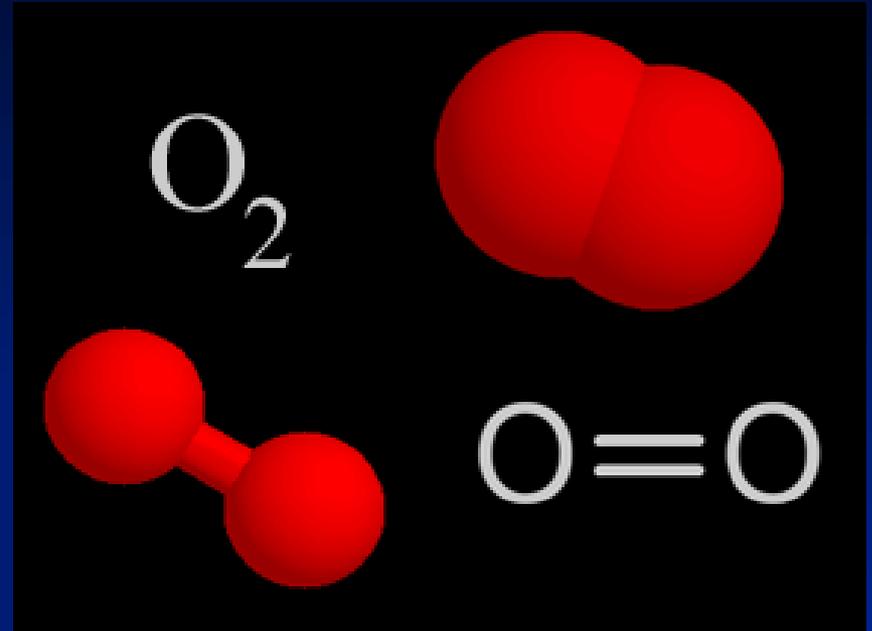
“Not all chemicals are bad. Without chemicals such as hydrogen and **oxygen**, for example, there would be no water, a vital ingredient for beer.”

-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 emergency care
- Health care providers believe oxygen alleviates breathlessness



Oxygen

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

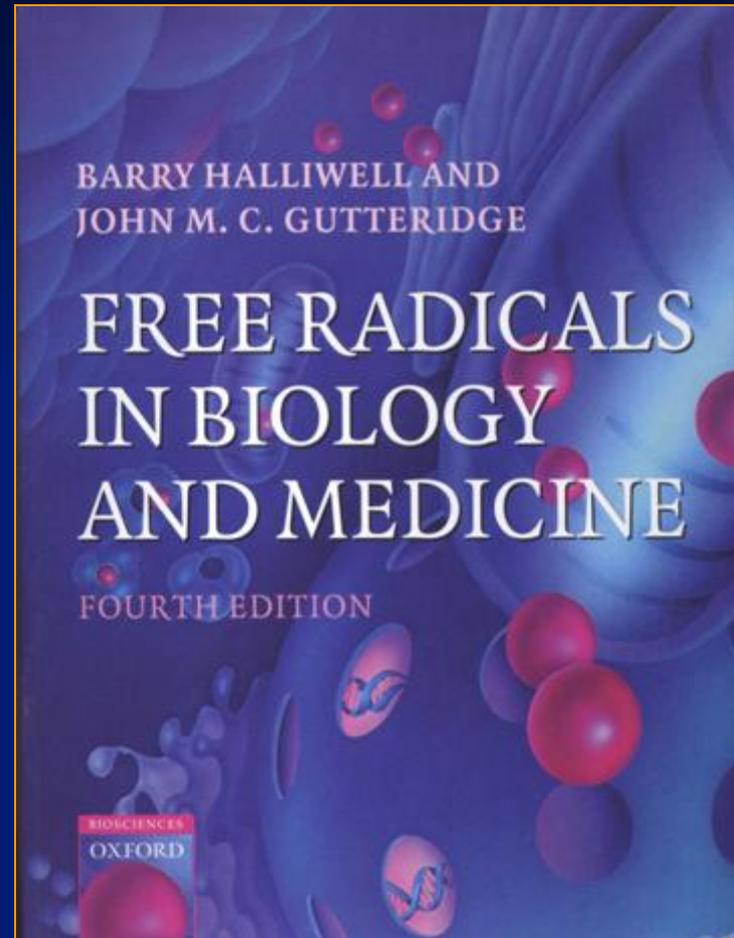


Documented benefits:

- ✓ Hypoxia
- ✓ Nausea/vomiting
- ✓ Motion sickness

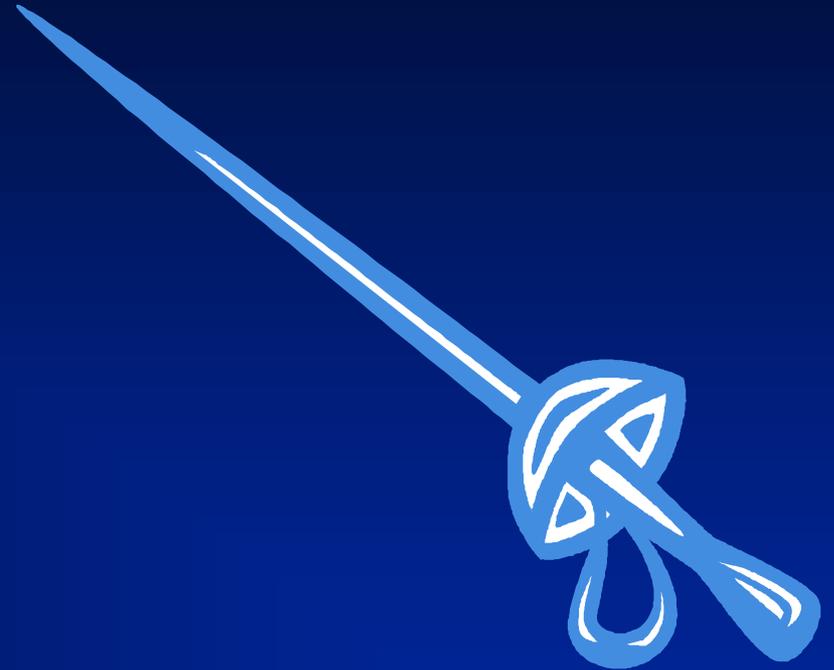
Oxygen

- 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**

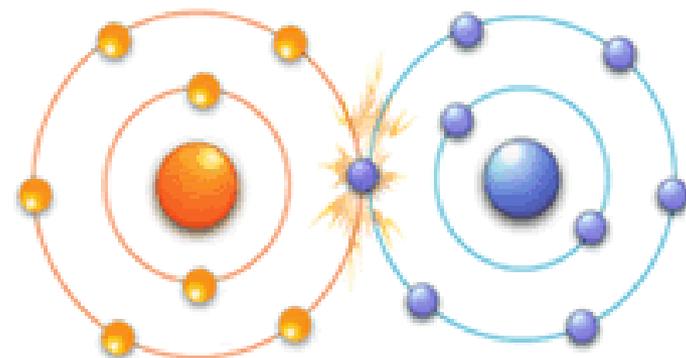


Have You Seen Oxygen Harm?

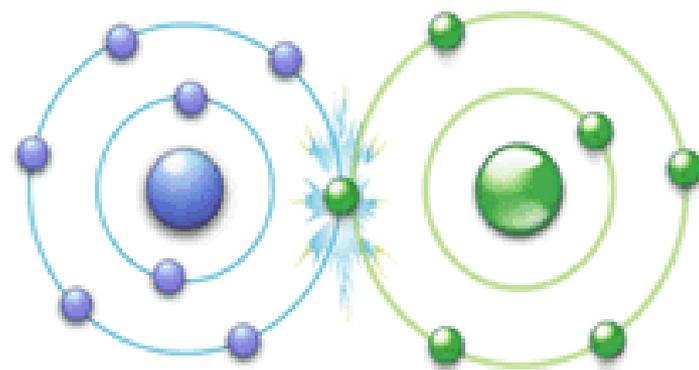


The Chemistry of Oxygen

- 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**”



Free radical steals an electron from another molecule.



Antioxidant stabilizes the molecule by giving an electron.

The Chemistry of Oxygen

- Free radicals, in normal concentrations, are important in intracellular bacteria and cell-signaling
- Most important free radicals:
 - Superoxide ($\cdot\text{O}_2^-$)
 - Hydroxyl radical ($\cdot\text{OH}$)

The Chemistry of Oxygen

- Oxygen produces numerous free-radicals—some more reactive than others:
 - » Superoxide free radical ($\cdot\text{O}_2^-$)
 - » Hydrogen peroxide (H_2O_2)
 - » Hydroxyl free radical ($\cdot\text{OH}$)
 - » Nitric oxide ($\cdot\text{NO}$)
 - » Singlet oxygen ($^1\text{O}_2$)
 - » Ozone (O_3)

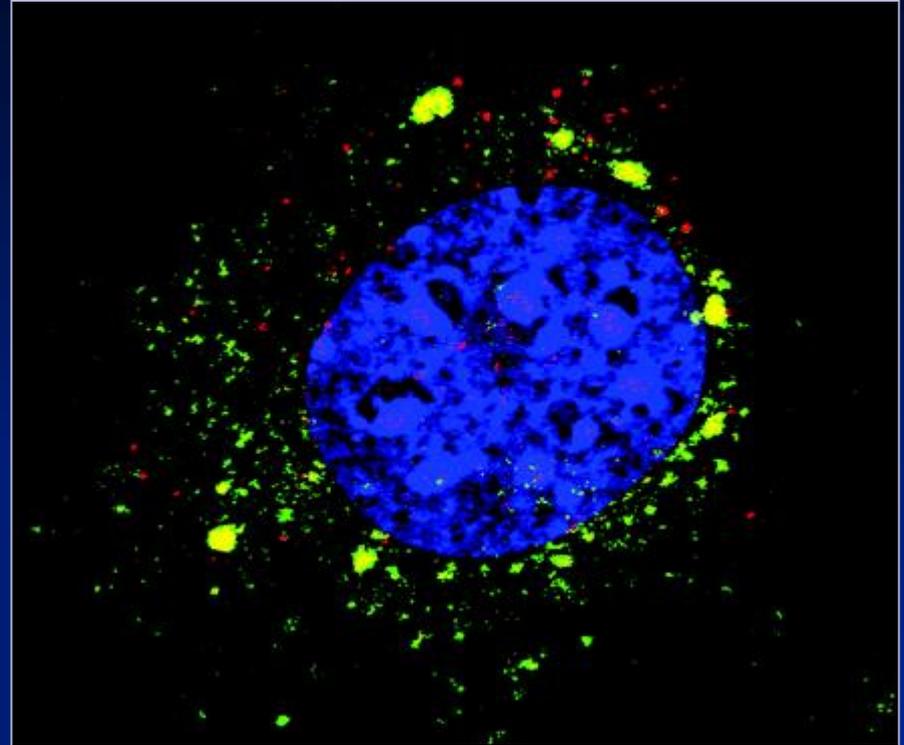
The Chemistry of Oxygen

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



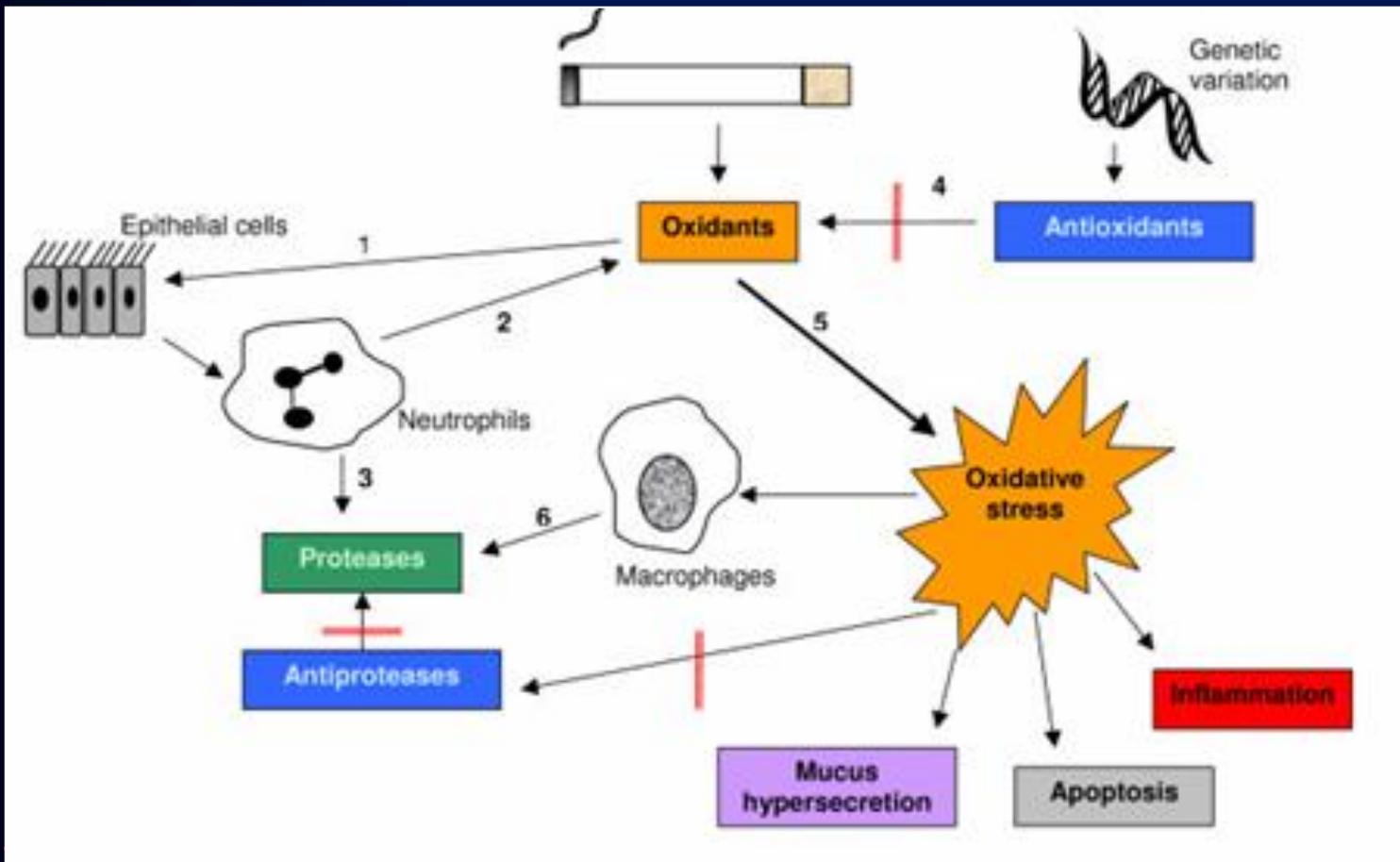
The Chemistry of Oxygen

- 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.

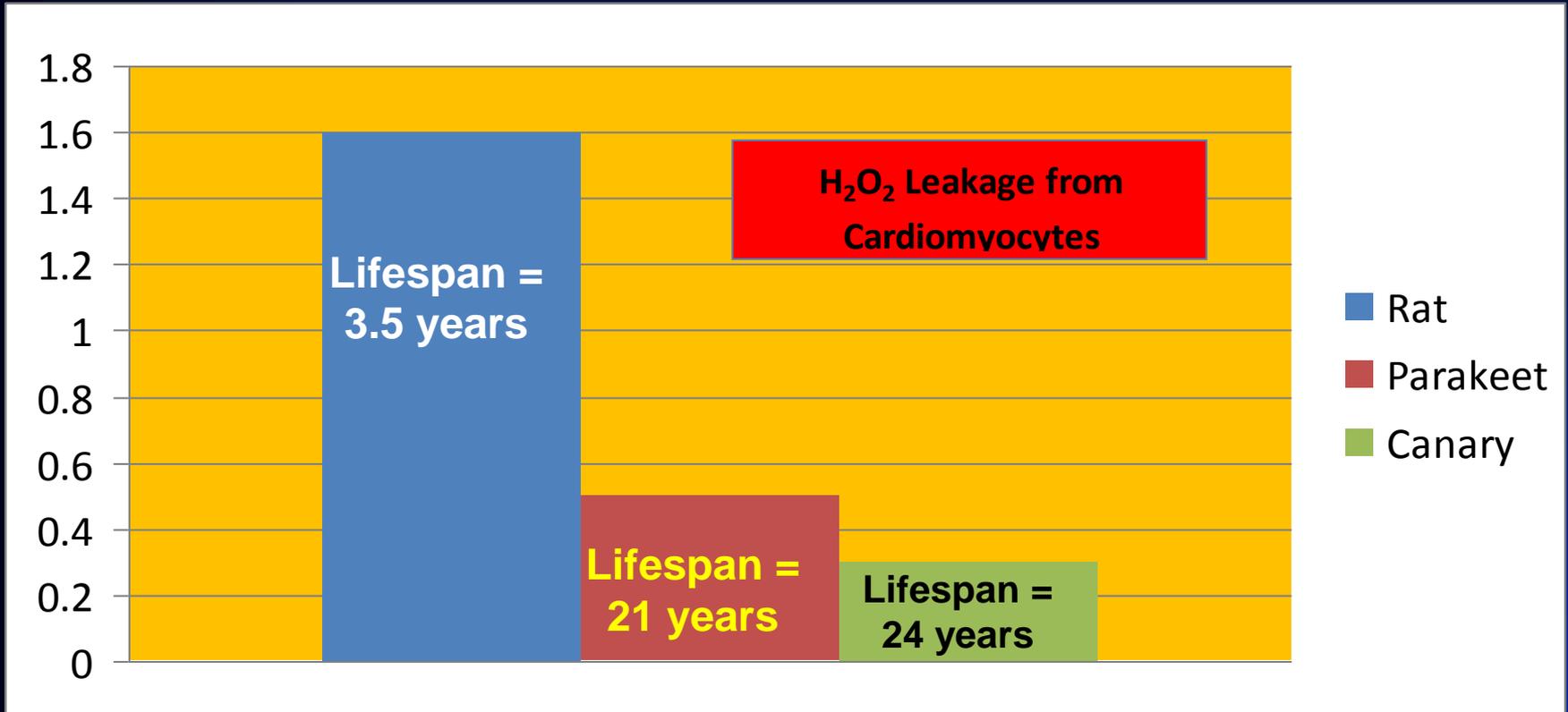


The Chemistry of Oxygen

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



Oxygen Free Radicals

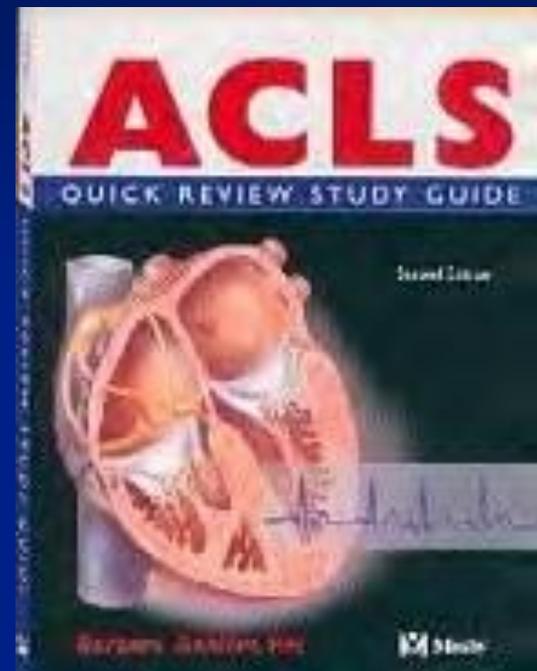
- Develop during reperfusion—not during hypoxia (when O₂ enters damaged area)
- Flooding ischemic cells with oxygen worsens oxidative stress (proportionate)



Not a new concept

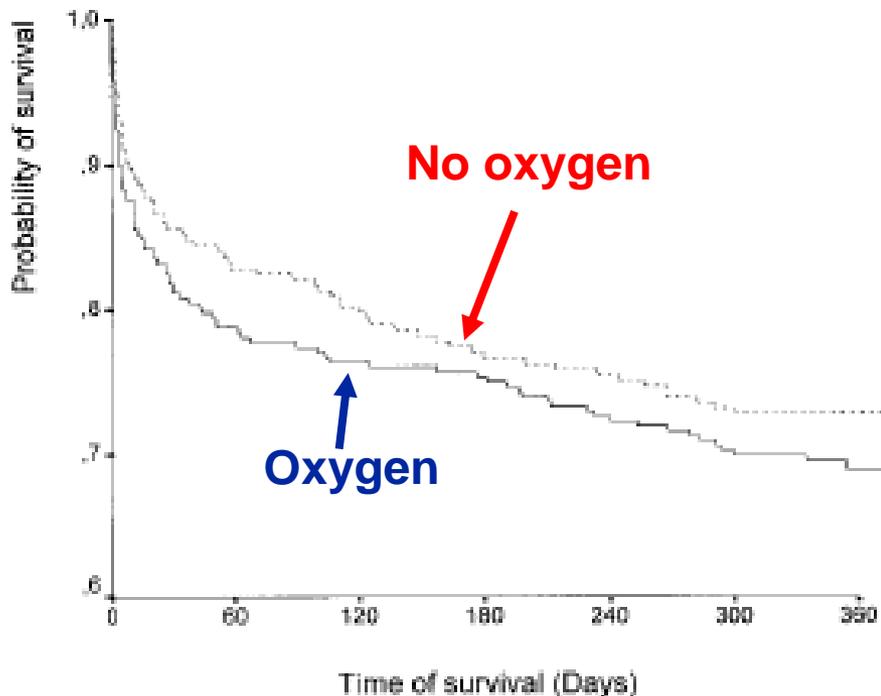
ACLS Guidelines 2000:

- Supplemental oxygen only for saturations $< 90\%$
- 2005: ditto
- 2010: $< 94\%$
- 2015: ditto



Stroke

	Minor or Moderate Strokes		Severe Strokes	
Variable	Oxygen	Control	Oxygen	Control
Survival	81.8%	90.7%	53.4%	47.7%
SSS Score	54 (54-58)	57 (52-58)	47 (28-54)	47 (40-52)
Barthel Index	100 (95-100)	100 (95-100)	70 (32-90)	80 (47-95)



Ronning OM, Guldvog B. Should Stroke Victims Routinely Receive Supplemental Oxygen? A Quasi-Randomized Controlled Trial. *Stroke*. 1999;30:2033-2037.

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**

Rabi Y, Rabi D, Yee W: Room air resuscitation of the depressed newborn: a systematic review and meta-analysis. *Resuscitation* 72:353-363, 2007

Davis PG, Tan A, O'Donnell CP, et al: Resuscitation of newborn infants with 100% oxygen or air: a systematic review and meta-analysis. *Lancet* 364:1329-1333, 2004

Cardiac Arrest

- **Emphasis on circulation**
 - Compression only CPR may be better
 - Known dangers of oxidative stress
- **Study on Room Air vs. FiO_2 1.0**
 - In-hospital med/surgical wards
 - Standard ACLS, change only FiO_2 (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

Vanderbilt Univ – TH post ROSC

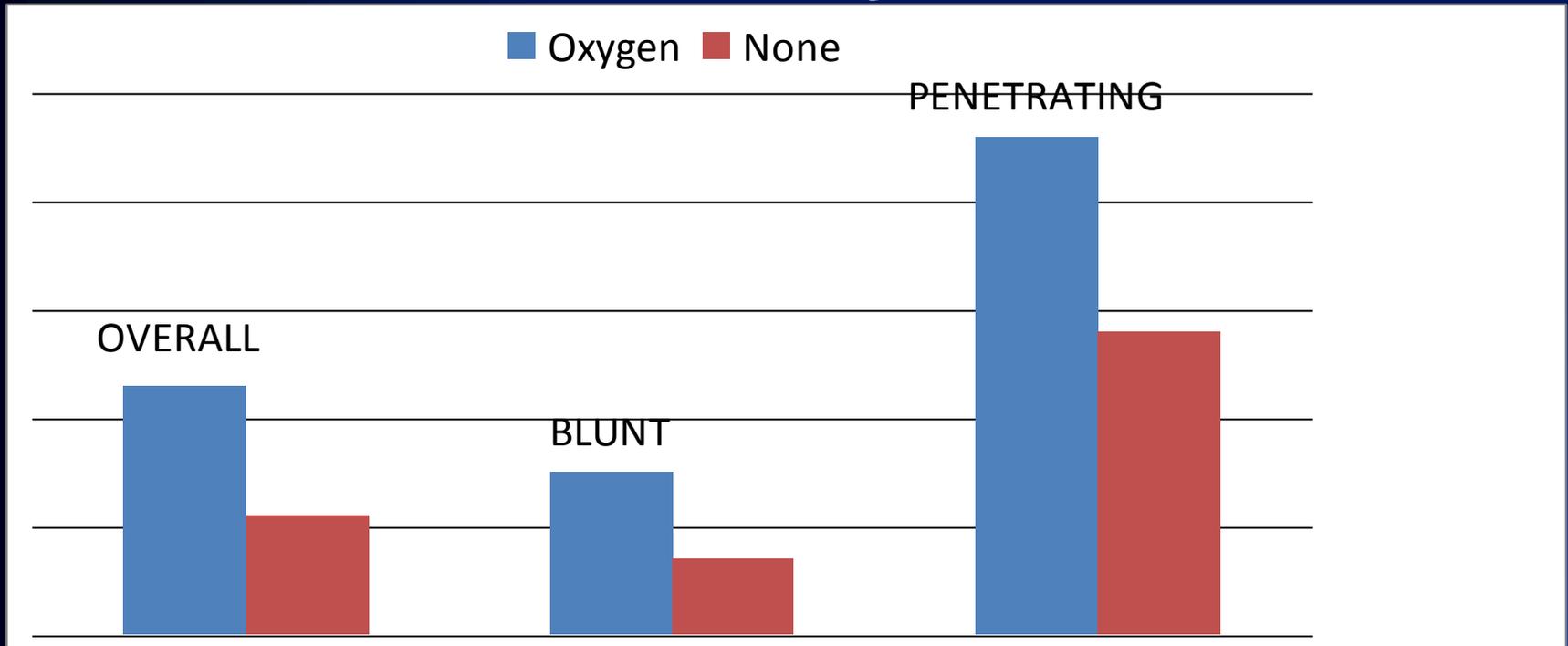
- 170 patients - highest PaO₂ during 24° TH (32-34°C):
 - Survivors had significantly lower PaO₂ (198) vs non-survivors (254)
 - Higher PaO₂ ↑ risk death (OR 1.439)
 - Favorable neuro outcomes (CPC 1-2) also linked to lower PaO₂
 - Higher PaO₂ ↓ neuro outcomes (OR 1.485)

Janz et al. Hyperoxia is associated with increased mortality in patients treated with mild therapeutic hypothermia after sudden cardiac arrest. Crit Care Med 2012; 40(12): 3135-3139.

Trauma

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

Mortality:



Trauma

- “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.”

Stockinger ZT, McSwain NE. Prehospital Supplemental Oxygen in Trauma Patients: Its Efficacy and Implications for Military Medical Care. *Mil Med.* 2004;169:609-612.

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.

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 history of clinical likelihood of chronic obstructive pulmonary disease.

¹Menzies Research Institute, University of Tasmania, Hobart, Tasmania, 7001 Australia

²Department of Respiratory Medicine, Royal Hobart Hospital, Hobart, Tasmania

³Tasmanian Ambulance Service, Hobart, Tasmania

Correspondence to: M A Austin
maustin@utas.edu.au

B 405 diff breathers randomized:

- NRBM (n=226)
- NC to SpO₂ 88-92% (n=179)

Titrated O₂ reduced mortality:

- all patients 58%
- COPD patients 78%

¹Menzies Research Institute,
University of Tasmania,
Tasmania, 7000

²Department of Respiratory
Medicine, Royal Hobart Hospital,
Hobart, Tasmania

³Tasmanian Ambulance Service,
Hobart, Tasmania

Correspondence to: M A Austin
maustin@utas.edu.au

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.

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 of clinical likelihood of chronic obstructive pulmonary disease.

ACS (Acute Coronary Syndrome)

- O₂ 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?

Effects of supplemental oxygen administration on coronary blood flow in patients undergoing cardiac catheterization

Patrick H. McNulty,¹ Nicholas King,¹ Sofia Scott,¹ Gretchen Hartman,¹ Jennifer McCann,¹ Mark Kozak,¹ Charles E. Chambers,¹ Laurence M. Demers,² and Lawrence I. Sinoway¹

Departments of ¹Medicine and ²Pathology, Pennsylvania State College of Medicine, Milton S. Hershey Medical Center, Hershey, Pennsylvania

Submitted 23 June 2004; accepted in final form 5 October 2004

Within 5 minutes of 100% O₂ (vs. RA):

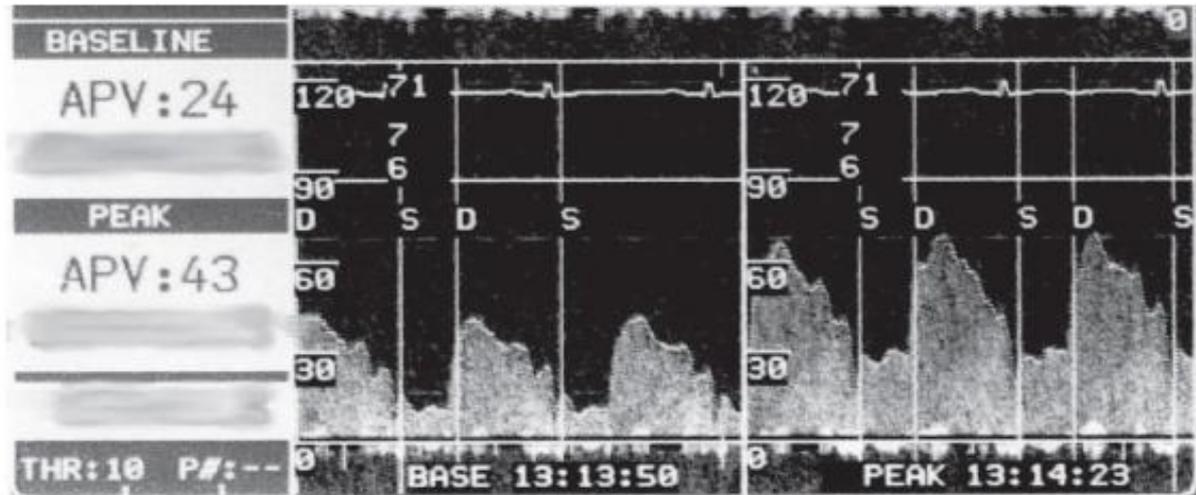
- **↑ coronary resistance ~ 40%**
- **↓ coronary blood flow (CBF) ~ 30%**
- **Blunted CBF response to Ach**
- **Marked ↓ NO**

McNulty PH, et al. Effects of supplemental oxygen administration on coronary blood flow in patients undergoing cardiac catheterization. *Am J Physiol Heart Circ Physiol.* 2005; 288: H1057-H1062.

CBF (Coronary Blood Flow)

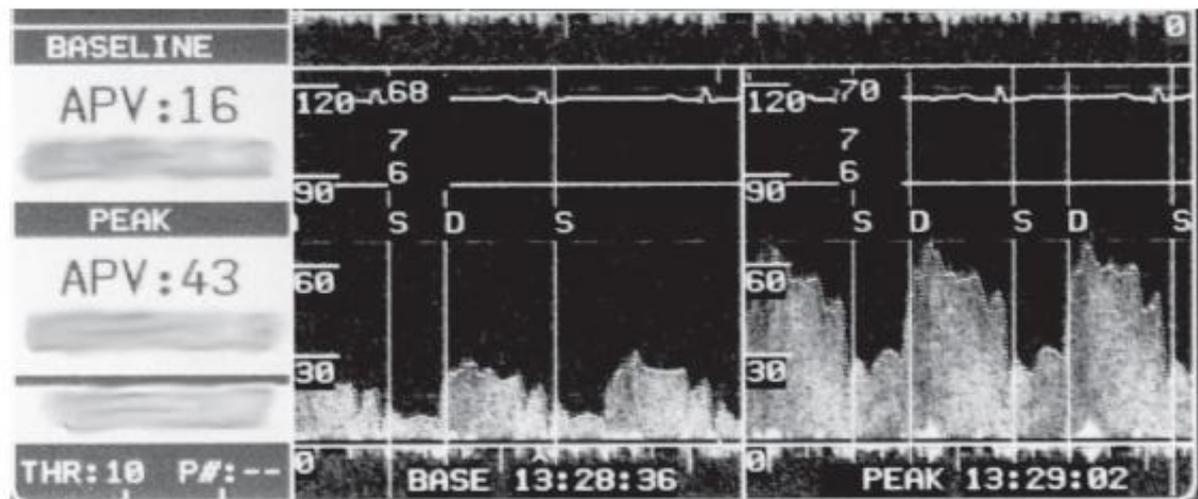
Room air

pO₂ = 73



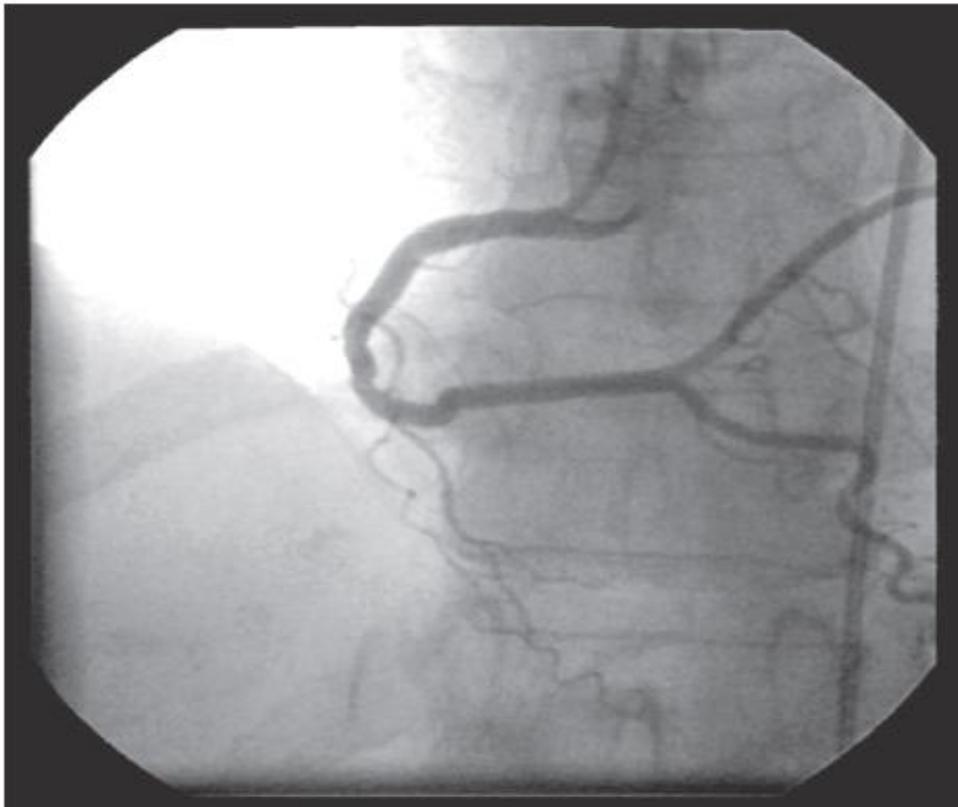
100% oxygen

pO₂ = 289

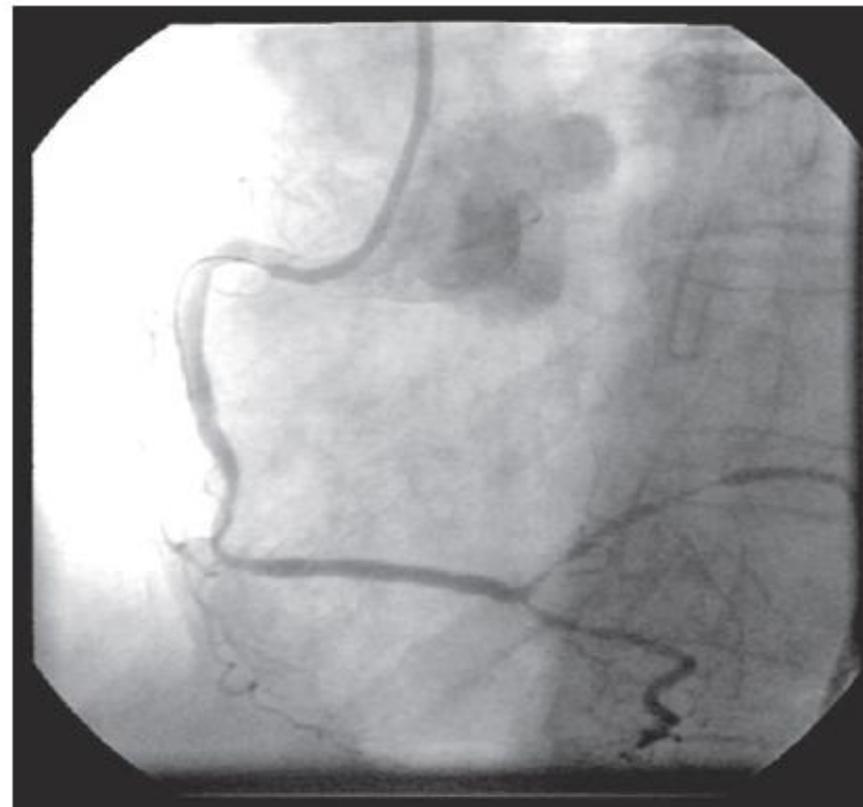


Right Heart Cath:

Room air



100% oxygen



McNulty PH, et al. Effects of supplemental oxygen administration on coronary blood flow in patients undergoing cardiac catheterization. *Am J Physiol Heart Circ Physiol.* 2005; 288: H1057-H1062.

Where to from here?



British Thoracic Society



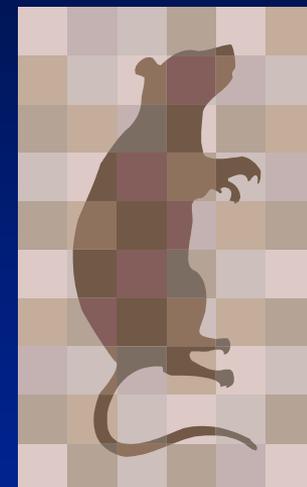
- Issued an O₂ therapy guideline 2008
- All this... and more:
 - Routine administration can be harmful
 - O₂ does not affect dyspnea unless hypoxic
 - Hyperoxia may decrease target organ perfusion (when given needlessly)
 - Unnecessary O₂ delays recognition of deterioration by providing false reassurances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

British Thoracic Society



... and more:

- Absorption atelectasis @ FiO_2 0.3-0.5
- O_2 risk to some COPD patients
- \uparrow SVR, coronary vasospasm
- No demonstrated clinical benefit of keeping O_2 sat $>$ 90% in **any patient**



Harten JM et al. *J Cardiothoracic Vasc Anaesth* 2005; 19: 173-5

Kaneda T et al. *Jpn Circ J* 2001; 213-8

Frobert O et al. *Cardiovasc Ultrasound* 2004; 2: 22

Haque WA et al. *J Am Coll Cardiol* 1996; 2: 353-7

Thomaon AJ et al. *BMJ* 2002; 1406-7

Ronning OM et al. *Stroke* 1999; 30

Murphy R et al. *Emerg Med J* 2001; 18:333-9

Plant et al. *Thorax* 2000; 55:550

Downs JB. *Respiratory Care* 2003; 48:611-20



O₂ therapy guideline (everywhere):

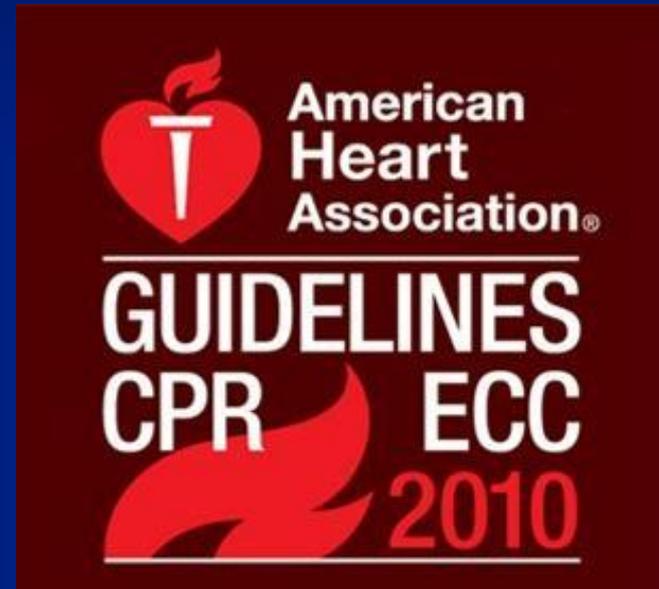
- **Keep normal/near-normal O₂ sats**
 - All patients except hypercapnic resp. failure and terminal palliative care
 - Keep sat 92-96%, tx only if hypoxic
 - Use pulse oximetry to guide tx – max 98%



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 O₂ administration using pulse-oximetry reduces O₂ 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?

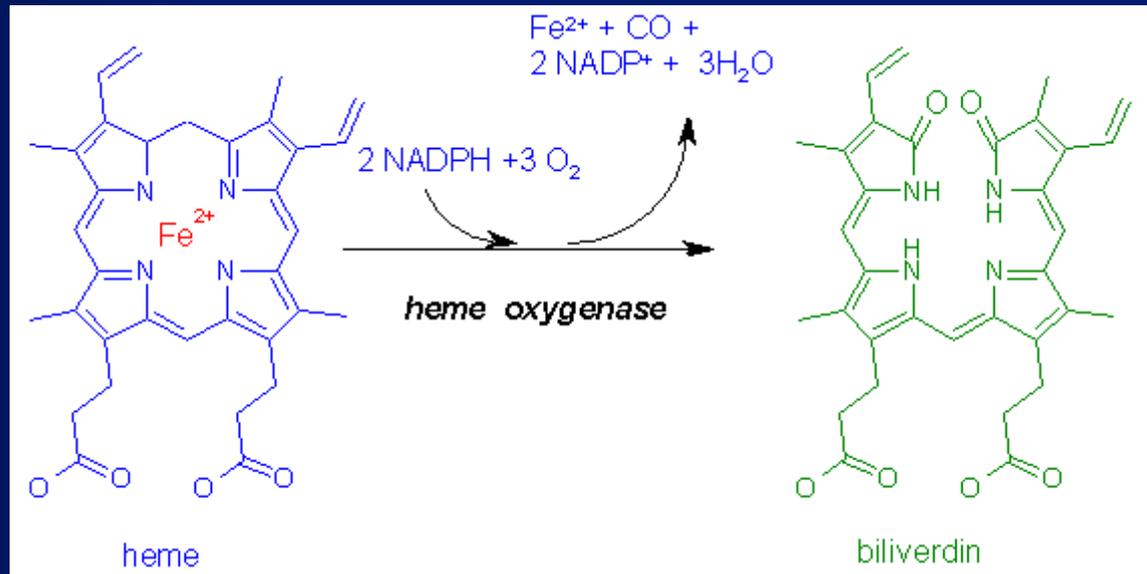


Can We Attenuate Oxidative Stress?

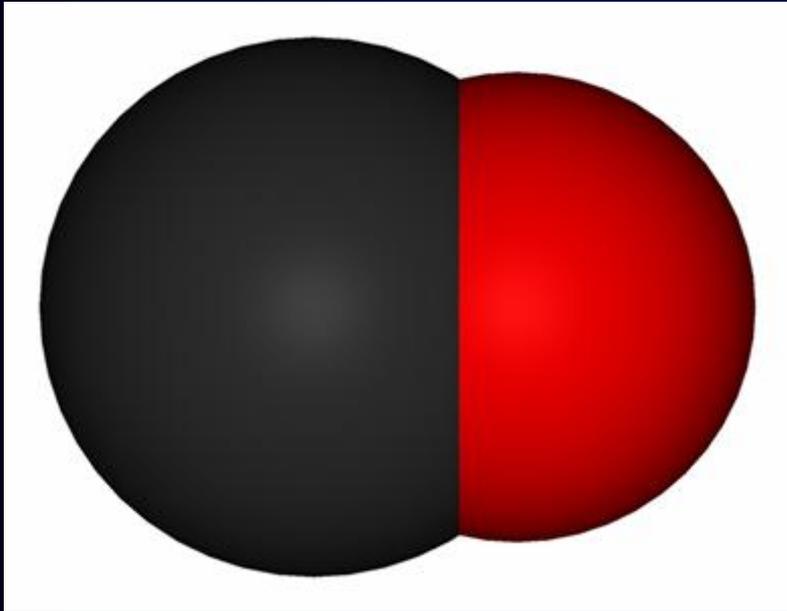
- Perhaps
- Clues lie with **Carbon Monoxide**
 - Known in vitro and in vivo antioxidant and anti-inflammatory properties
 - Critically ill patients ↑ CO production
 - » Survivors produce more CO
 - » Non-survivors produce less or no CO
 - Multiple human studies now using CO to attenuate oxidative pulmonary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



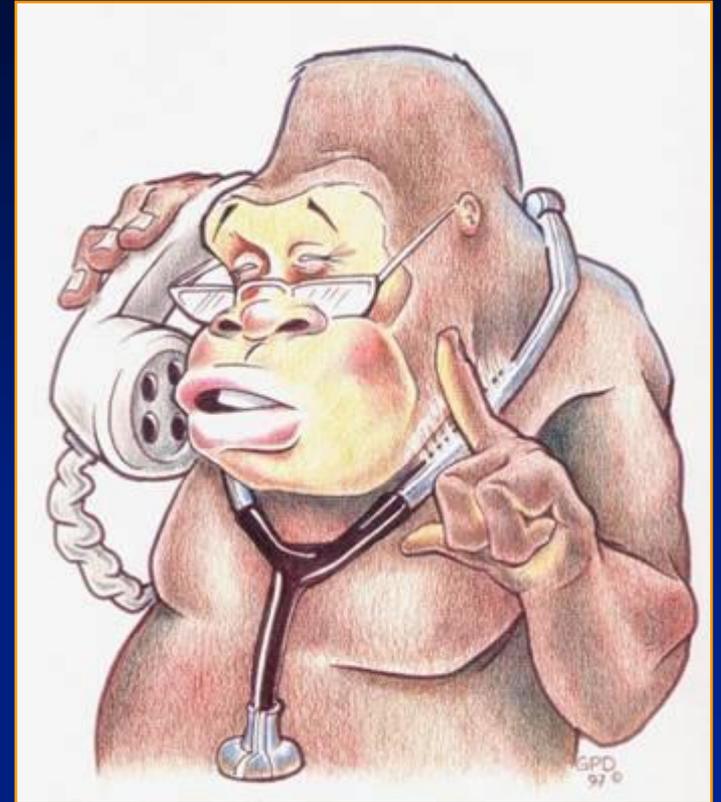
Pulse CO-oximetry





Take Home Messages

- Oxygen can hurt
- CO may help
- Empiric use is not a good practice - O₂ tx must be focused
- Use oximetry to guide care: prevent hypoxia and hyperoxia



Questions?



www.mikemcevoy.com