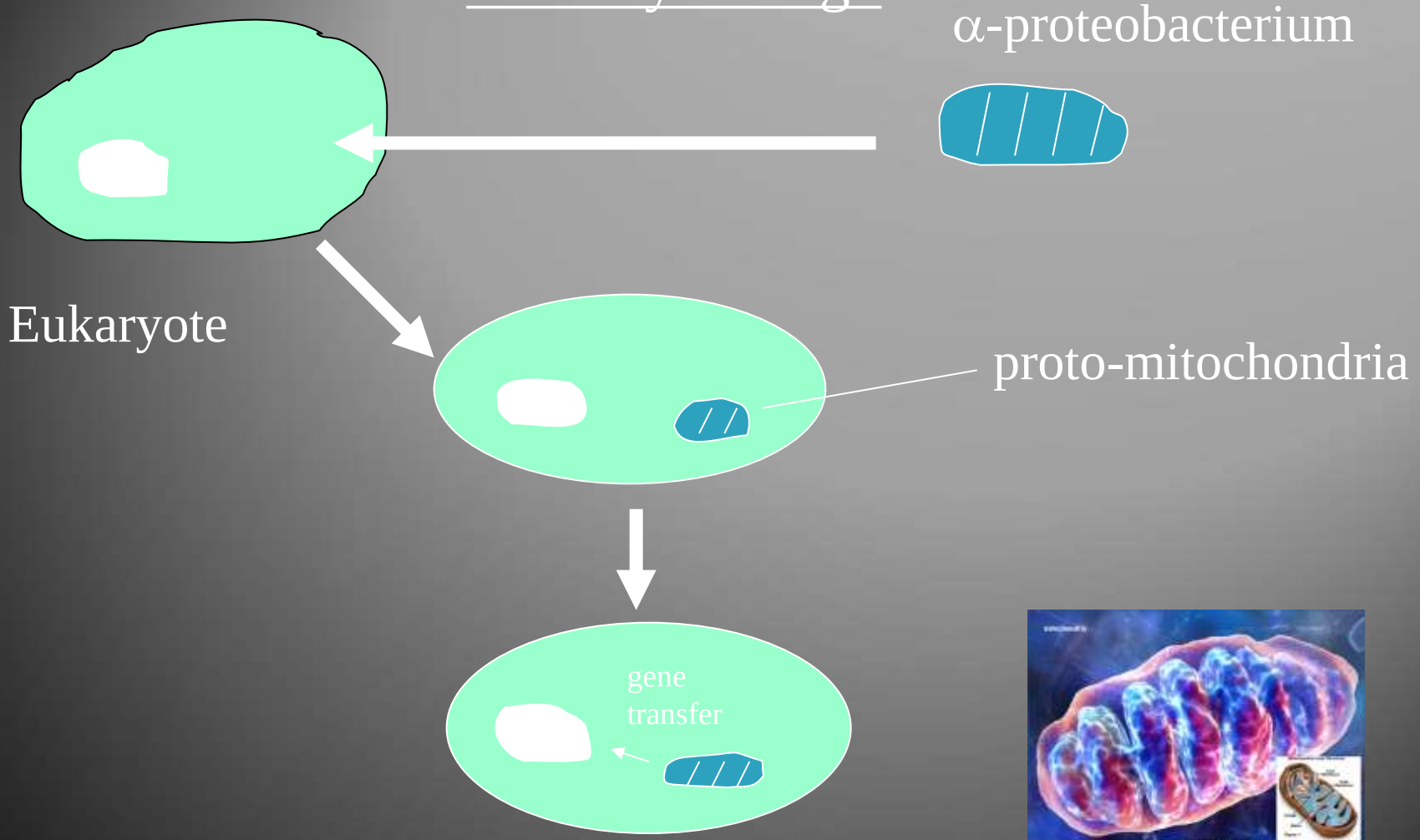
Permissive hypoxaemia – key issues

- How much oxygen do you need?
  - “natural experiments”
  - “critical care research”
- Is oxygen toxic?

Origins of mitochondria – ancient invasions > 1.5 billion years ago

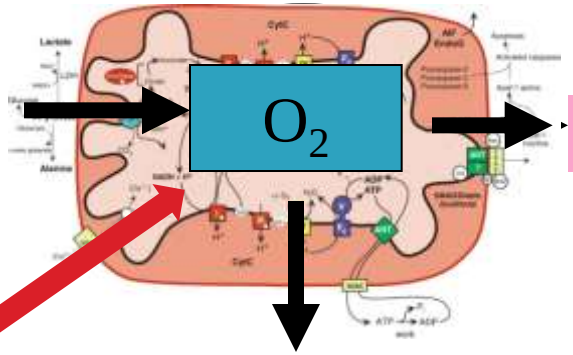


- genetic similarity to bacteria
- What drove the union
- protect anarobic host from oxygen tension

Energy production in Mitochondria

mitochondria

glucose → pyruvate → O_2 → H_2O & CO_2



2 ATP

30 ATP

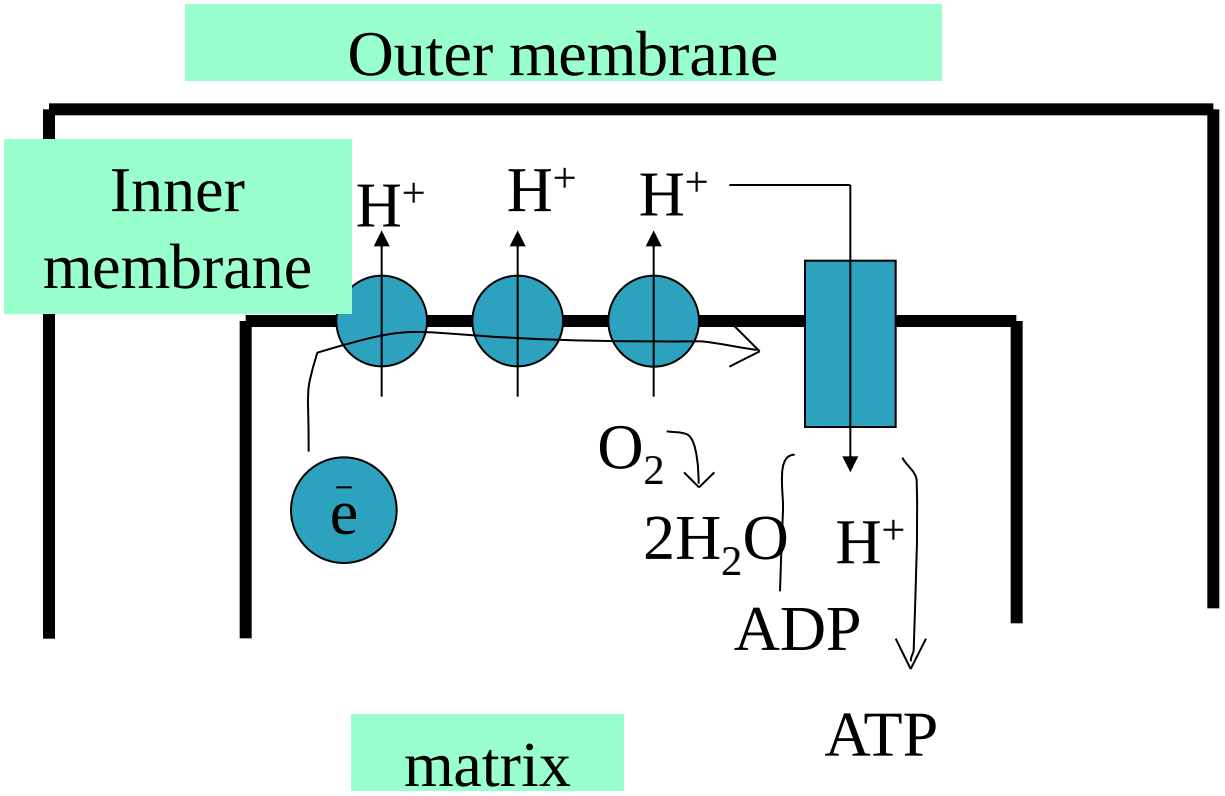
glycolysis

Oxidative phosphorylation

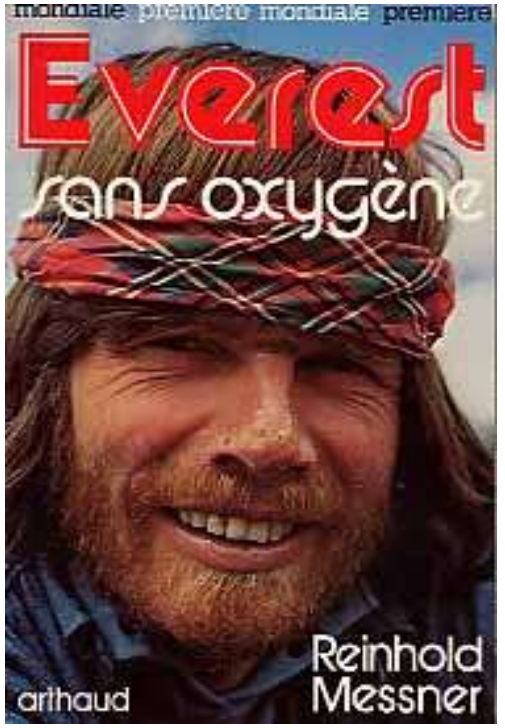
Inefficient process

Very efficient process

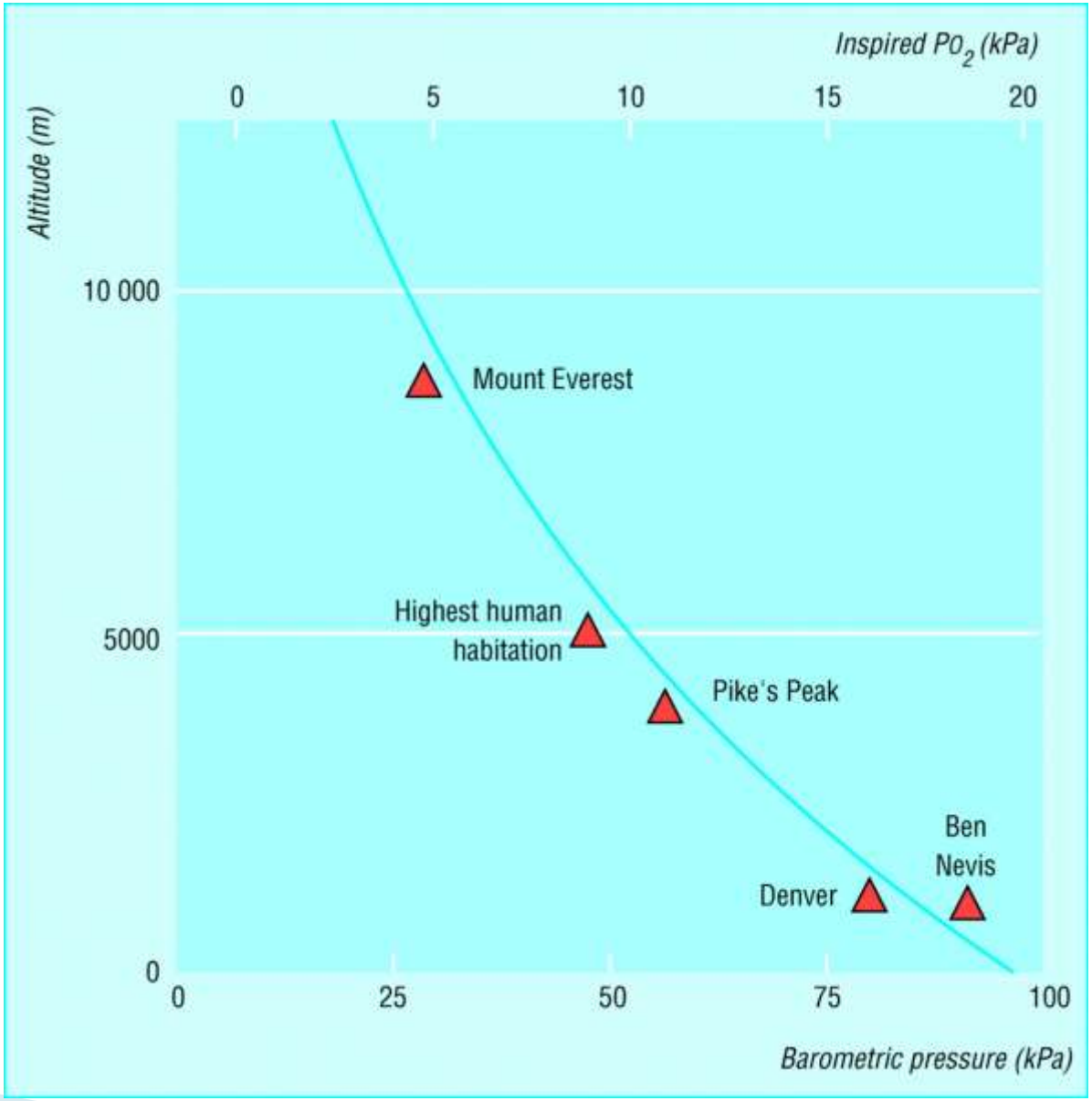
Energy production in Mitochondria



Ascent without oxygen



All 8000+ m peaks have been climbed without O_2


Inspired PO_2 (kPa)
0
5
10
15
20
Altitude (m)
10 000
5000
0
Mount Everest
Highest human habitation
Pike's Peak
Ben Nevis
Denver
0
25
50
75
100
Barometric pressure (kPa)

Altitudes

Location	Height (m)
Aircraft cabin	1800 – 2500
Mont Blanc	4800
Everest base camp	5500
Everest summit	8900

Location	Atmospheric pressure (kPa)	Inspired PO_2 (kPa)
Sea level	100	0.21X(100-6.3) = 19.6
Everest base camp	50	0.21X(50-6.3) = 9.2
Everest summit	30	0.21X(30-6.3) = 5.0

What is the alveolar PO_2 at altitude?

Alveolar $PO_2 \cong PIO_2 - PaCO_2$

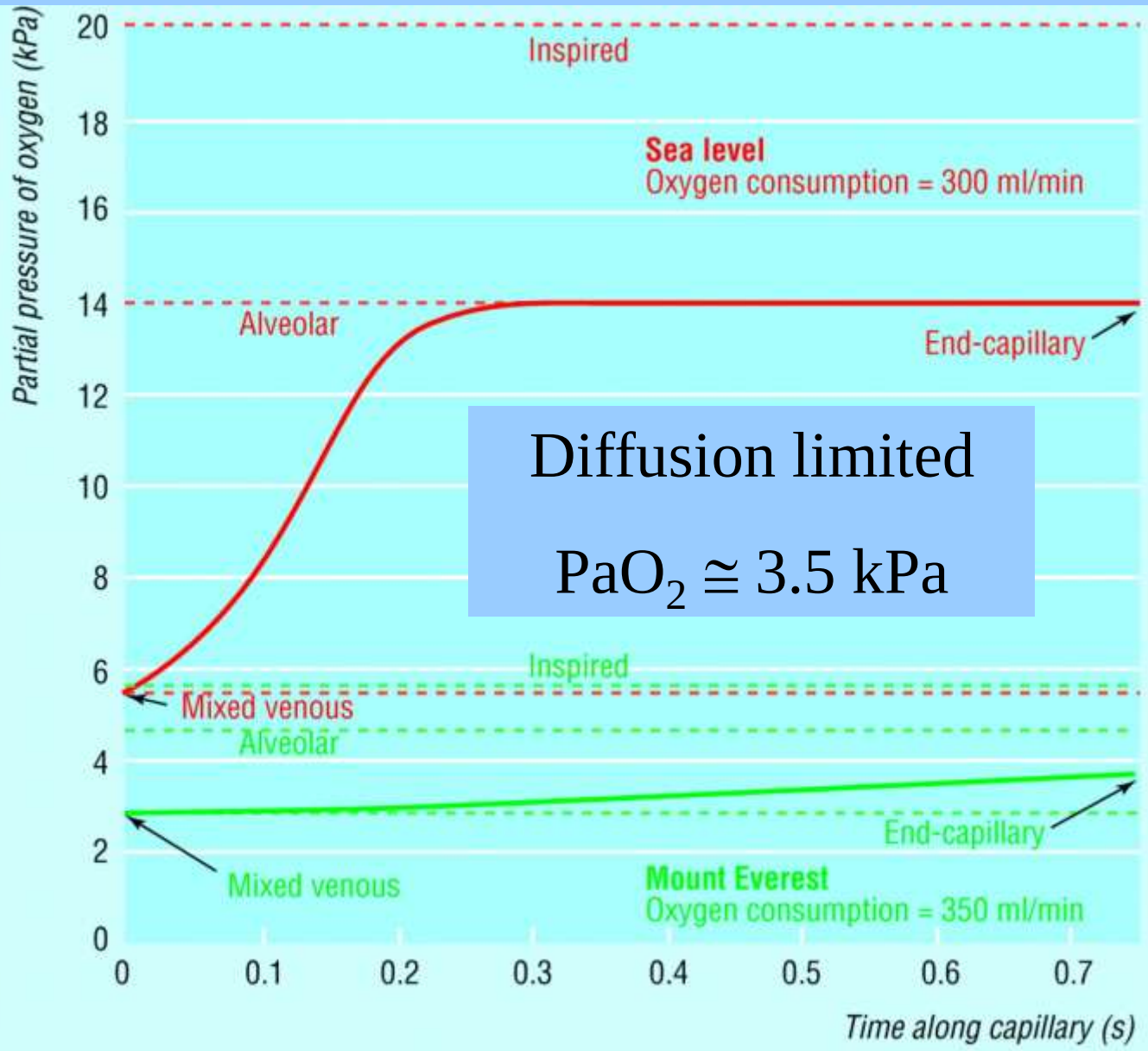
Everest summit $PAO_2 = 5.0 - 5.0 = 0$!!

What is the alveolar PCO_2 at altitude?

$PACO_2 \cong CO_2$ output/alveolar ventilation

Normal alveolar ventilation	6 L/min
Everest summit	> 40 L/min
Everest summit $PaCO_2$	1 kPa
Everest summit PAO_2	5-1 = 4 kPa

Gas transfer at altitude



What is the arterial oxygen content at altitude?

Sea Level	Hb = 14.5	96/100X14.5X1.39 = **20ml 100ml^{-1}**
5300	Hb = 18.9	75/100X18.9X1.39 = **20ml 100ml^{-1}**
Everest summit	Hb = 18.9	60/100X18.9X1.39 = **16ml 100ml^{-1}**

Oxygen delivery at altitude

VO_2 = cardiac output X arterial O_2 content

VO_2 at sea level at rest	5000 X 20 = 1000 ml/min
VO_2 at Everest summit	5000 X 15.8 = 790 ml/min
Critical oxygen delivery	= 300 ml/min

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Arterial Blood Gases and Oxygen Content in Climbers on Mount Everest

Michael P.W. Grocott, M.B., B.S., Daniel S. Martin, M.B., Ch.B., Denny Z.H. Levett, B.M., B.Ch., Roger McMorrow, M.B., B.Ch., Jeremy Windsor, M.B., Ch.B., and Hugh E. Montgomery, M.B., B.S., M.D., for the Caudwell Xtreme Everest Research Group*

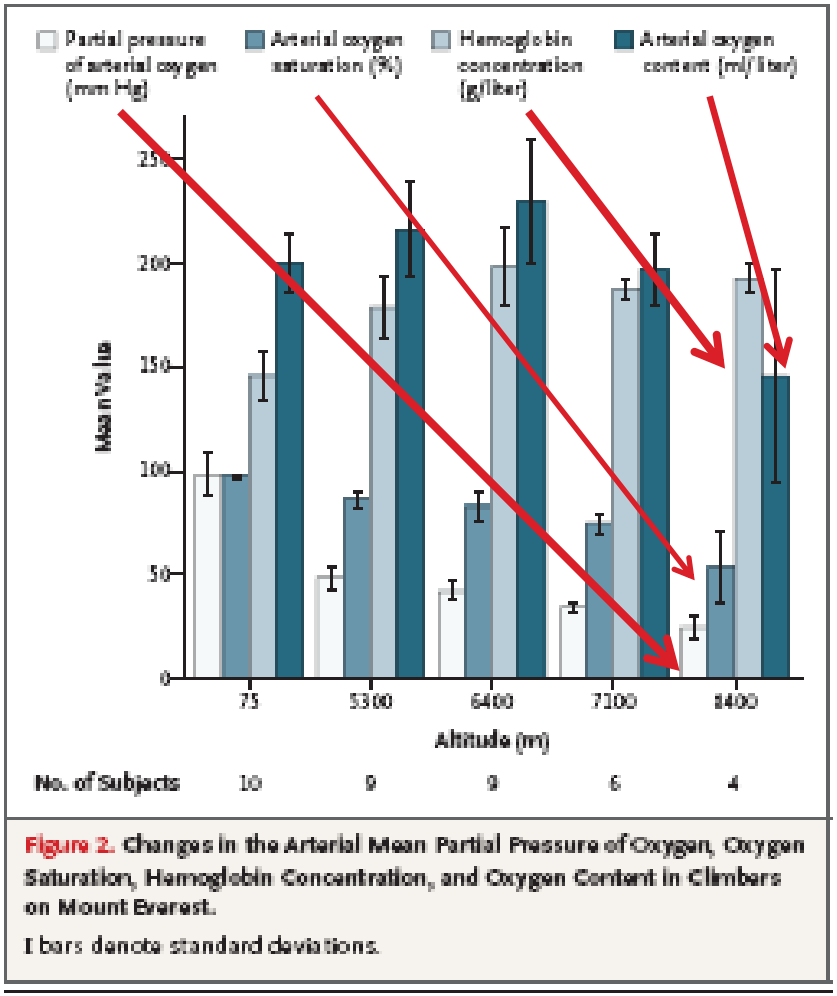


Figure 2. Changes in the Arterial Mean Partial Pressure of Oxygen, Oxygen Saturation, Hemoglobin Concentration, and Oxygen Content in Climbers on Mount Everest.

I bars denote standard deviations.

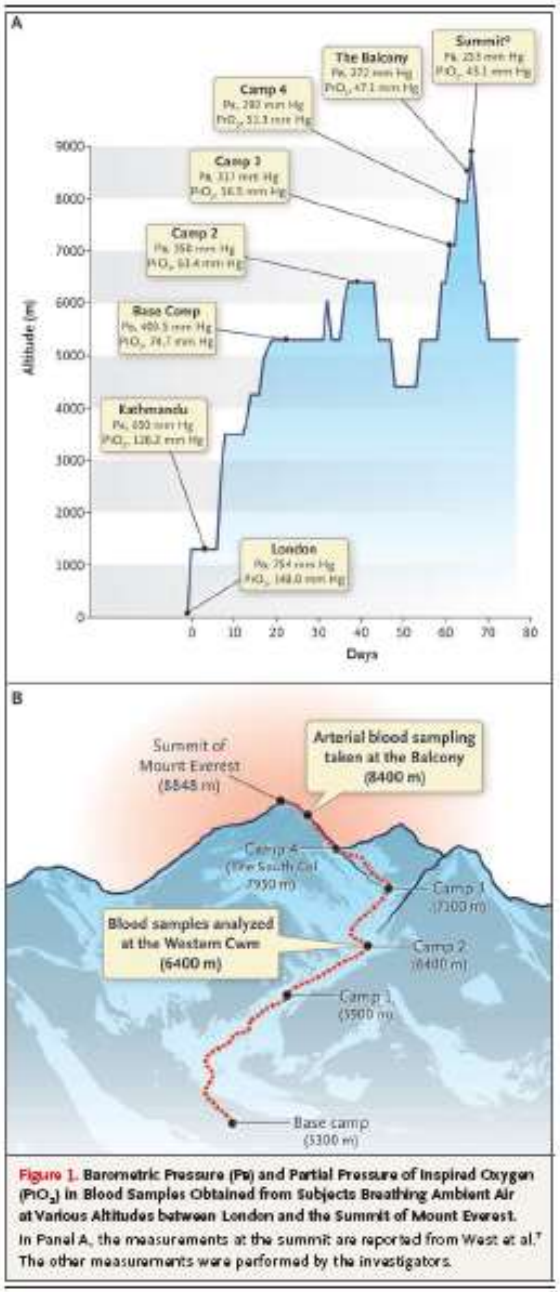


Figure 1. Barometric Pressure (Pb) and Partial Pressure of Inspired Oxygen (PiO_2) in Blood Samples Obtained from Subjects Breathing Ambient Air at Various Altitudes between London and the Summit of Mount Everest.

In Panel A, the measurements at the summit are reported from West et al.[7] The other measurements were performed by the investigators.

Table 2. Arterial Blood Gas Measurements and Calculated Values for Pulmonary Gas Exchange from Four Subjects at an Altitude of 8400 m, during Descent from the Summit of Mount Everest.*

Variable	Subject No.				Group Mean
	1	2	3	4	
pH	7.55	7.45	7.52	7.60	7.53
PaO_2 (mm Hg)†	29.5	19.1	21.0	28.7	24.6
$PaCO_2$ (mm Hg)†	12.3	15.7	15.0	10.3	13.3
Bicarbonate (mmol/liter)‡	10.5	10.67	11.97	9.87	10.8
Base excess of blood‡	−6.3	−9.16	−6.39	−5.71	−6.9
Lactate concentration (mmol/liter)	2.0	2.0	2.9	1.8	2.2
SaO_2 (%)‡	68.1	34.4	43.7	69.7	54.0
Hemoglobin (g/dl)§	20.2	18.7	18.8	19.4	19.3
Respiratory exchange ratio¶	0.81	0.74‖	0.72	0.70	0.74
PAO_2 — mm Hg†**	32.4	26.9	27.4	33.2	30.0
Alveolar–arterial oxygen difference — mm Hg†	2.89	7.81	6.44	4.51	5.41

Supplemental oxygen and montaineer death rates on Everest and K2 - JAMA 2000

Mountain	Individual Mountaineers†		Summit Teams‡	
	Ascents, No.	Deaths, No. (%)	Teams Summiting, No.	Teams With Death, No. (%)
Everest				
Used supplementary oxygen	1077	32 (3.0)	93	8 (8.6)
No supplementary oxygen	96	8 (8.3)	28	4 (14.3)
K2				
Used supplementary oxygen	47	0 (0)	12	0 (0)
No supplementary oxygen	117	22 (18.8)	36	12 (33.3)

*Summit-team analyses for Everest restricted to 1978-1992, see "Methods" section.
†For comparison by exact logistic regression, stratified by mountain, $P<.001$.
‡For comparison by exact logistic regression, stratified by mountain and with number of summiters per team as a covariate (included because the probability of a death should increase with the number of climbers exposed to risk, all else being equal), $P = .03$.

How high can you go?

- Two theories of the "vertical limit"
  - Oxygen delivery limit
  - Oxygen diffusion limit from capillary to mitochondria

Adaptation to prolonged hypoxaemia

- Cardiac output
- Respiratory rate and MV
- Haemoglobin
- Skeletal muscle
- ? Capillary/endothelial
- ? Mitochondrial/OXPHOS

Hypoxaemia & Metabolism

Hypoxia Inducible factor
Transduction factor
> 100 genes
Erythropoietin
Metabolism
Angiogenesis
Cell differentiation

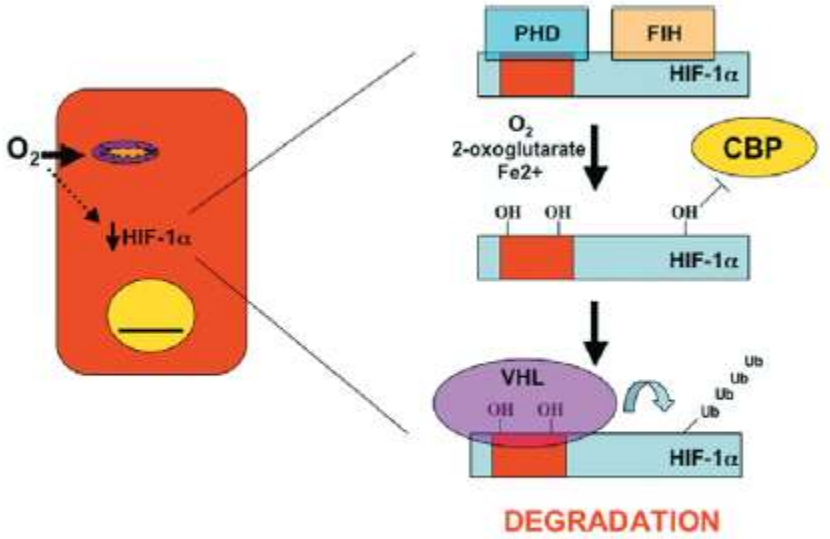


Figure 2 The HIF pathway

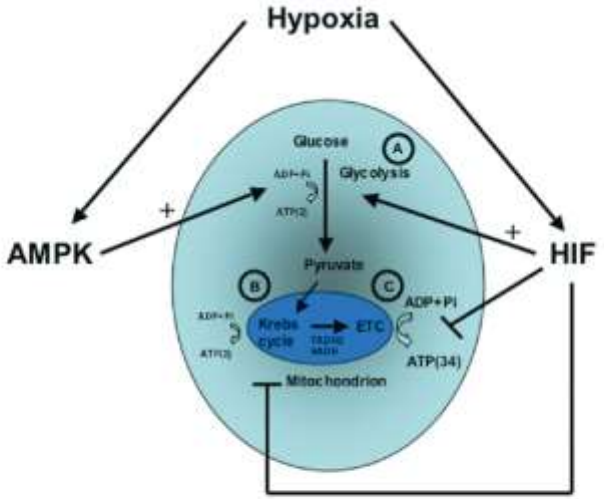


Figure 3 Regulation of metabolism by HIF

(A) Glucose is metabolized to two molecules of pyruvate during glycolysis in the cell cytoplasm generating two molecules of ATP. (B) Each pyruvate molecule generated during glycolysis is converted into acetyl CoA which enters the TCA cycle (Krebs cycle), each cycle of which generates one molecule of ATP, six molecules of NADH and two molecules of $FADH_2$. (C) NADH and $FADH_2$ generated by glycolysis and the TCA cycle function as reducing equivalents for the electron transport chain (ETC) which utilizes molecular oxygen to generate 34 molecules of ATP which fuels most active cell processes. All three phases of the aerobic metabolism of glucose can be controlled by the HIF pathway which promotes glycolysis while actively repressing the TCA cycle and oxidative phosphorylation. A further degree of regulation of glycolysis can occur through hypoxia-dependent activation of AMPK.

Genetics & hypoxia

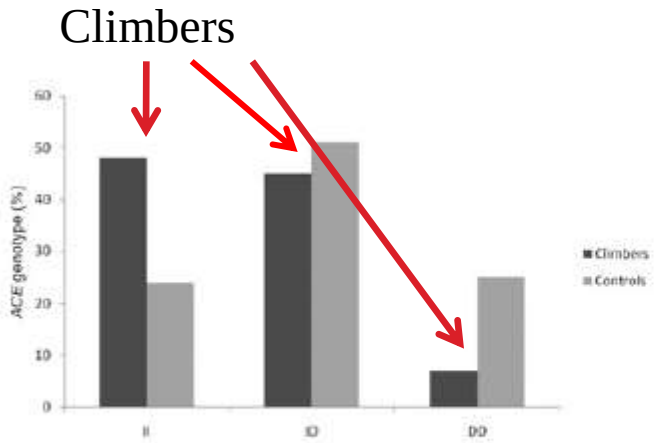


Figure 1. The *ACE* genotype distribution (as a percentage of the sample group) amongst 25 elite UK mountaineers, compared with 1906 population controls

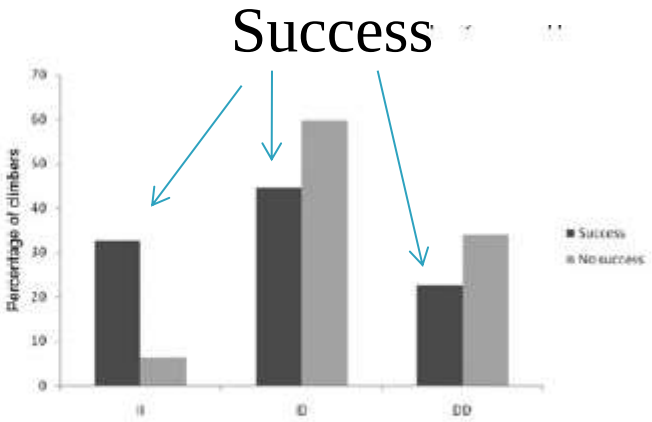


Figure 3. Percentage of 139 mountaineers attempting to climb beyond 8000 m who had been successful, by genotype

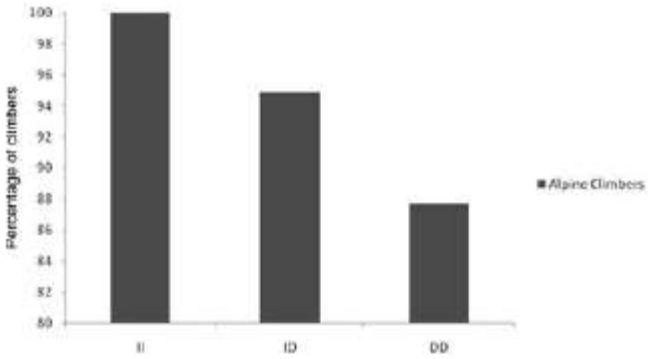
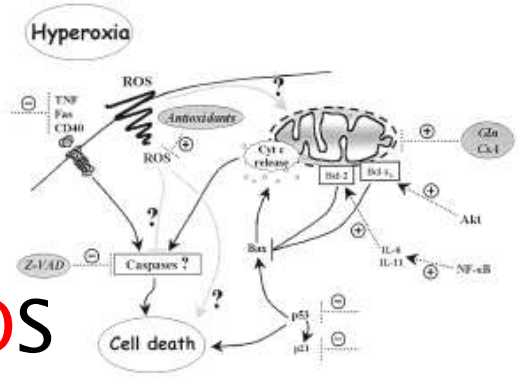


Figure 2. Percentage of 284 climbers attempting to climb Mt Blanc (4810 m) who successfully reached the summit

Oxygen toxicity



- Oxygen is bad for you!
- Oxidative phosphorylation vs. ROS
- Ubiquitous cellular defences against ROS
- Marked depletion of these in critically ill
- Many trials of “anti-oxidants”
- No RCTs of limiting oxygen

Augmented lung injury due to interaction between hyperoxia and mechanical ventilation*

(Crit Care Med 2004; 32:2496 –2501)

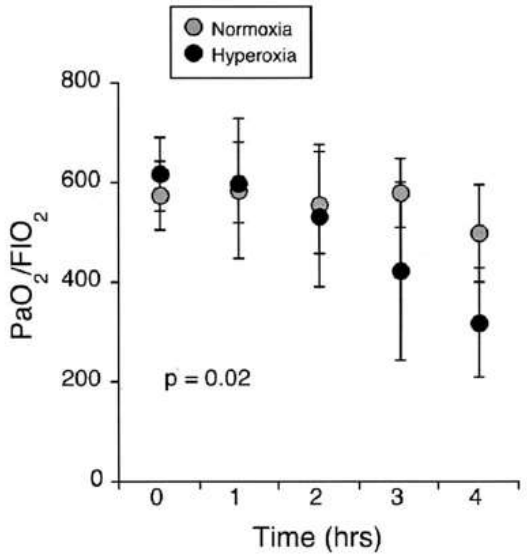
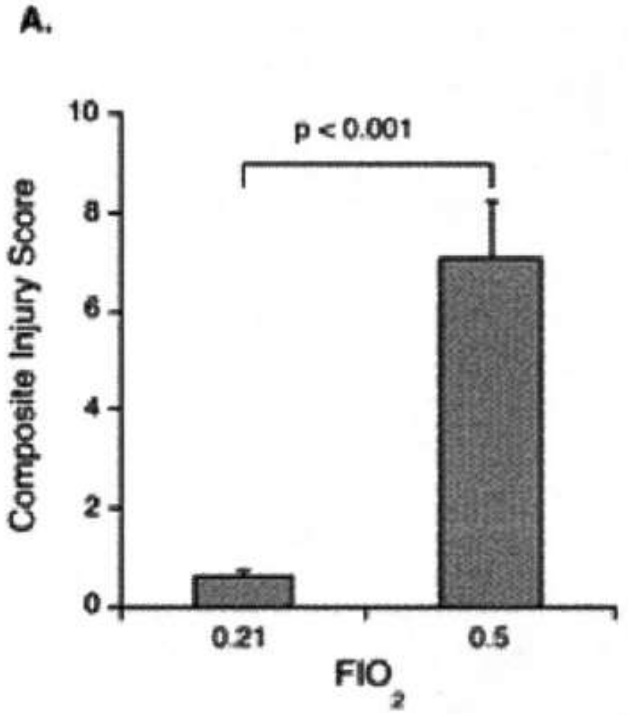


Figure 1. Mean ± SD of Pao_2/Fio_2 over time for animals mechanically ventilated for 4 hrs with tidal volumes of 25 mL/kg and an Fio_2 of either 0.21 or 0.5 (experiment 1). A significant difference over time was observed between the two groups ($p = .02$).



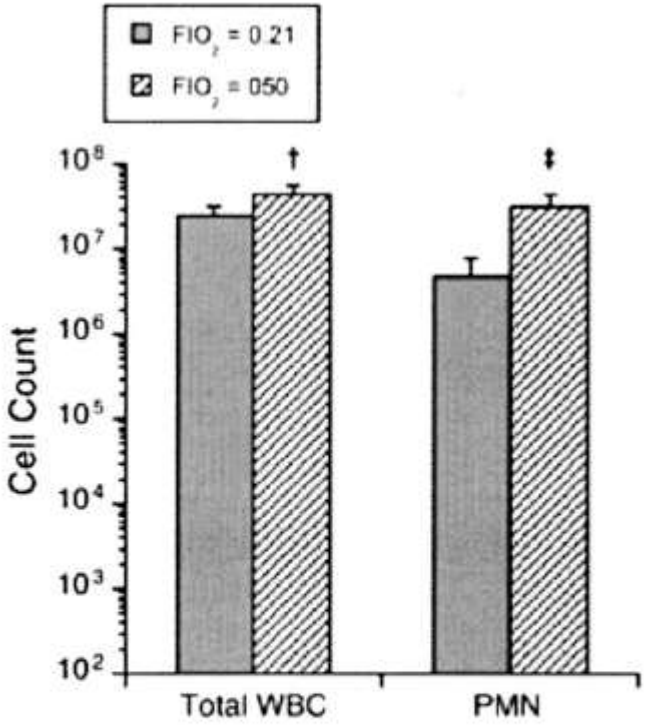


Figure 3. Mean ± SD of total leukocyte counts and polymorphonuclear (*PMN*) cell counts from bronchoalveolar lavage fluid of rabbits mechanically ventilated for 4 hrs with an FIO_2 of either 0.21 or 0.5. †$p = .003$; ‡$p = .001$. *WBC*, white blood cells.

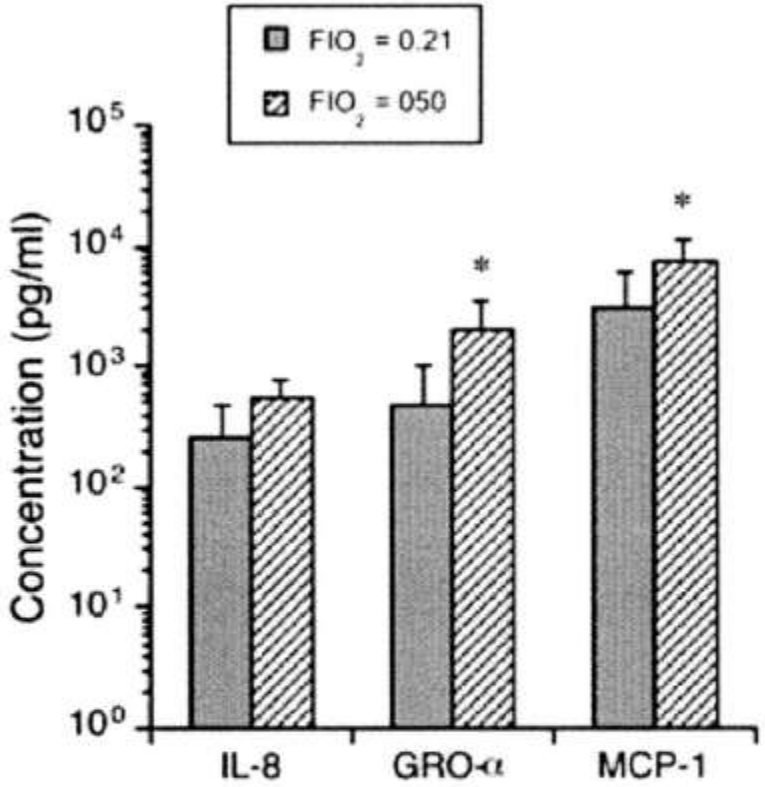
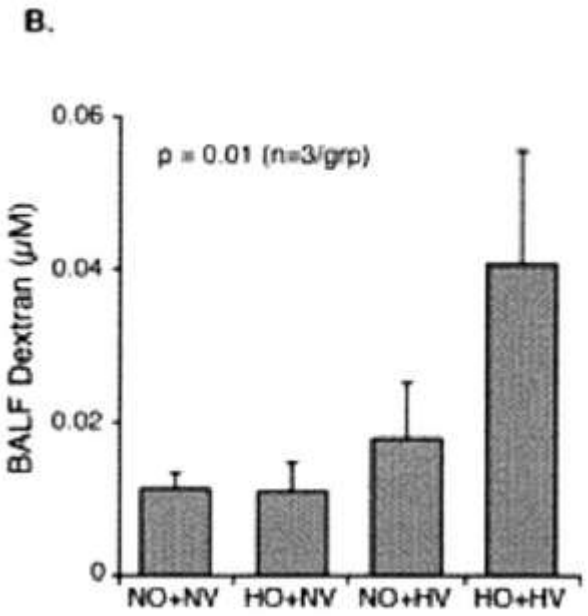
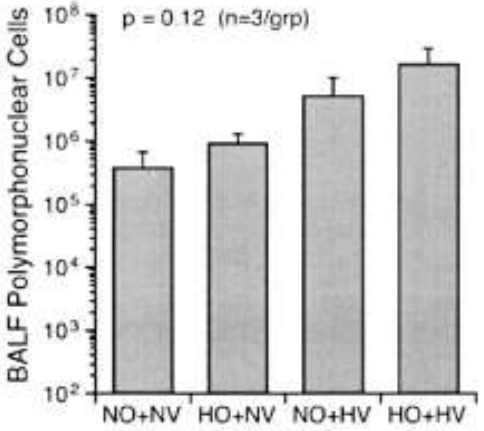


Figure 4. Mean ± SD of bronchoalveolar lavage fluid concentrations for interleukin (*IL*)-8, growth-related oncogene (*GRO*)-α, and monocyte chemotactic protein (*MCP*)-1 from rabbits mechanically ventilated for 4 hrs with an FIO_2 of either 0.21 or 0.5. *$p \leq .05$.

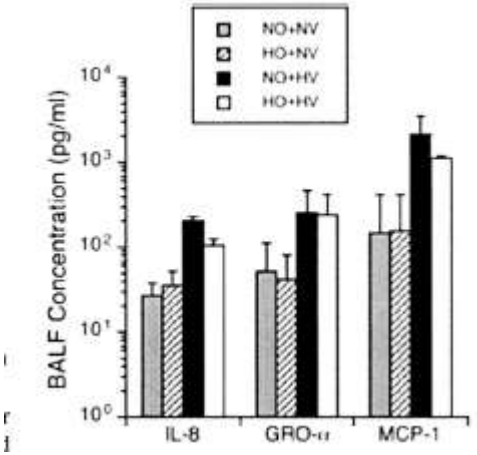
Additive effects of high TV and high oxygen



permeability



Inflammatory cells



cytokines

Oxygen toxicity in adult man

- FIO_2 75 – 100%
  - Tracheobronchitis
  - Loss of VC
  - Time & dose dependent
- Single volunteer FIO2 100% for 100 hrs
  - Deteriorating respiratory function
  - Acute respiratory failure
    - Winter PA Anaesthesiology 1972;37:210

O_2 toxicity in healthy man

Number of volunteers	FIO_2 (%)	Duration (hrs)	Outcome
1	100	100	Respiratory failure !
9	100	6–12	No change
4	100	6–60	Fall VC fall Kco
6	100	17	No change
14	95	18	BAL + albumin + transferrin

O_2 toxicity in adult ventilated patients

- "Irreversible coma"
  - 100% O_2 for a few days
  - Patchy pulmonary infiltrates & reduced gas exchange
    - *Barber New Engl J Med 1970; 283:1478-84*
- Five patients with neuromuscular disease
  - 85-100 % FIO2 for a few days
  - Patch chest radiology changes
  - Fever
  - Raised wbc
  - No infection
    - *Hyde Ann Intern Med 1969;71;517-31*

High v lower PEEP in patients with ARDS NEJM 2004

Table 3. Respiratory Values during the First Seven Days of Treatment.*

Variable	Day 1		Day 3		Day 7	
	Lower-PEEP Group	Higher-PEEP Group	Lower-PEEP Group	Higher-PEEP Group	Lower-PEEP Group	Higher-PEEP Group
Tidal volume (ml/kg of predicted body weight)	6.1±0.8	6.0±0.9†	6.1±1.1	5.8±1.0†	6.2±1.3	5.8±1.2
No. of patients	236	258	171	160	83	97
Plateau pressure (cm of water)	24±7	27±6†	24±6	26±7†	26±8	26±6
No. of patients	230	252	165	155	78	96
Mean airway pressure (cm of water)	15±5	20±5†	15±5	18±5†	15±7	19±6†
No. of patients	233	261	167	164	82	94
Respiratory rate (breaths/min)	29±7	29±7	30±7	30±7	28±7	30±7
No. of patients	248	263	180	173	98	102
Minute ventilation (liters/min)	12±4	12±3	12±4	12±3	12±4	12±3
No. of patients	247	264	178	171	96	104
FiO_2	0.54±0.18	0.44±0.17†	0.52±0.18	0.40±0.14†	0.52±0.20	0.40±0.11†
No. of patients	249	264	179	173	98	103
PEEP (cm of water)						
All patients	8.9±3.5	14.7±3.5‡	8.5±3.7	12.9±4.5‡	8.4±4.3	12.9±4.0‡
No. of patients	249	264	180	173	98	104
First 171 patients	9.1±3.3	14.2±3.2	8.7±3.6	11.3±4.6	7.6±3.0	12.0±5.0
No. of patients	76	82	60	62	40	32
Subsequent 378 patients	8.9±3.6	14.9±3.6	8.4±3.7	13.8±4.2	9.1±4.9	13.4±3.4
No. of patients	173	182	120	111	58	72
PaO_2/FiO_2	168±66	220±89‡	169±69	206±76‡	181±115	218±85†
No. of patients	230	244	159	152	87	91
Respiratory-system compliance (ml/cm of water)§	31±15	39±34‡	29±16	32±34	28±16	32±22
No. of patients	227	251	165	152	77	94
PaO_2 (mm Hg)	78±22	85±28‡	77±22	74±20	77±27	78±26
No. of patients	230	244	159	152	87	92
$PaCO_2$ (mm Hg)	41±11	41±11	43±13	43±13	48±14	47±16
No. of patients	230	244	159	152	87	92
Arterial pH	7.4±0.1	7.4±0.1	7.4±0.1	7.4±0.1	7.4±0.1	7.4±0.1
No. of patients	230	244	160	153	87	92

* Plus–minus values are means ±SD of the values recorded from 6 a.m. to 10 a.m. on days 1, 3, and 7 after enrollment in patients who were receiving mechanical ventilation in the volume-assist/control mode. PEEP denotes positive end-expiratory pressure, FiO_2 fraction of inspired oxygen, $PaCO_2$ partial pressure of arterial carbon dioxide, and PaO_2 partial pressure of arterial oxygen.

† $P<0.05$.

‡ $P<0.01$.

§ Respiratory-system compliance was calculated as the tidal volume divided by the difference between the inspiratory plateau pressure and PEEP.

Permissive hypoxaemia in prolonged Mechanical Ventilation

- Experimental evidence for O_2 toxicity in the lung
- Evidence for additive effect of hyperoxia on VILI
- No evidence that survival is determined by oxygenation alone

Hypothesis

- Ventilation at a reduced FIO_2 (accepting lower SaO_2) will improve outcome in patients receiving prolonged (4+ day mechanical ventilation) in General ITUs

Conclusions

- We do not know how low we can allow oxygen delivery to fall
- Our patients are not Mountaineers!
  - Increase CO
  - Increase RR
  - Increase Hb
  - Adapt by complex changes in gene expression
  - Good genes

Conclusions

- Oxygen toxicity occurs in small animals and neonates
- Some but controversial evidence in healthy man
- Little or no evidence in the critically ill
- Shouldn't assume that oxygen is harmless (= a drug at $FIO_2 > 21\%$)
- Need for more research