Hyperoxia a poškodenie respiračného systému - mýtus alebo skutočnosť?

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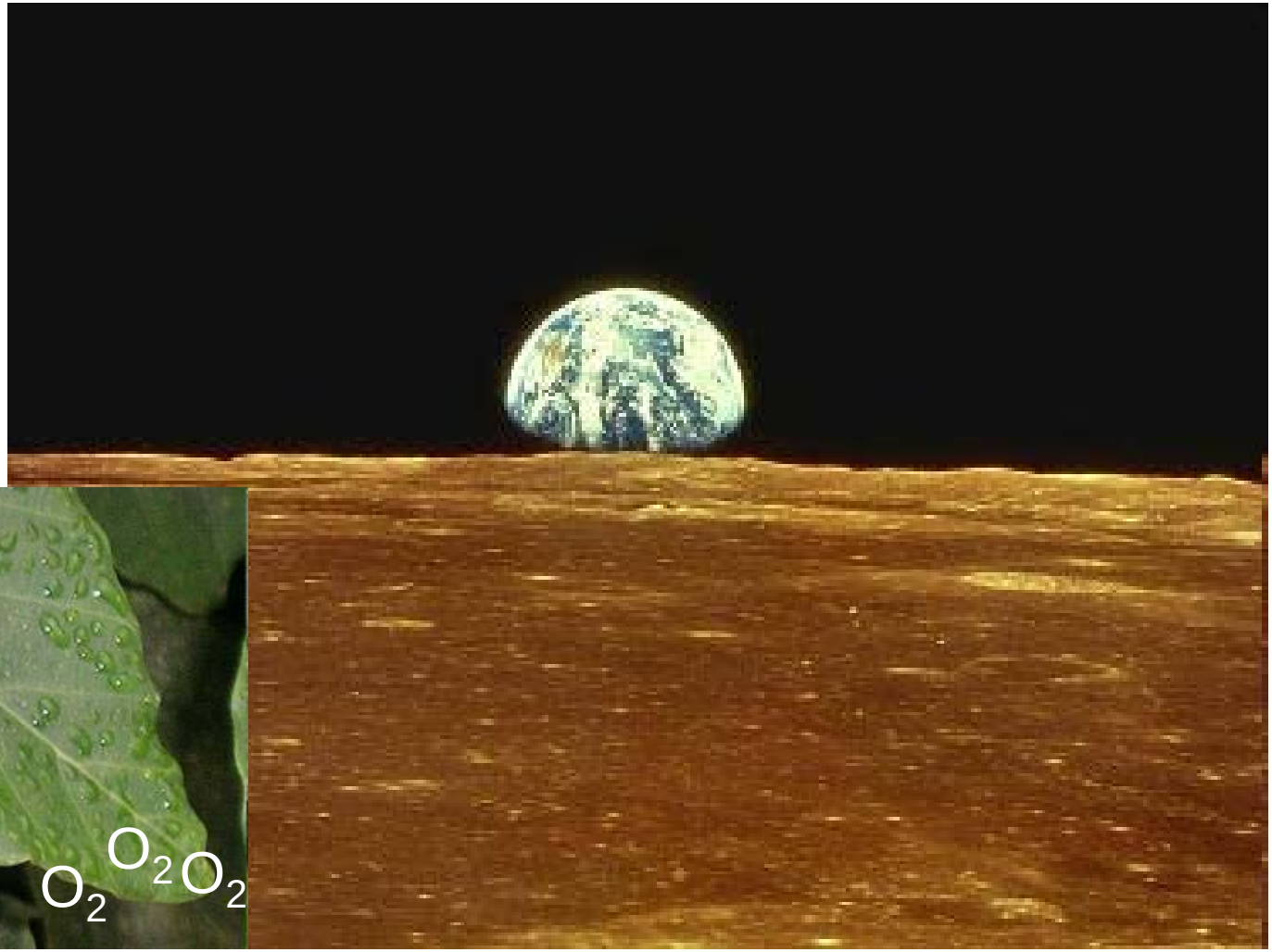
Kongres, ČSIM, Ostrava 12.6.2014

Kyslík – nevyhnutný na prežitie



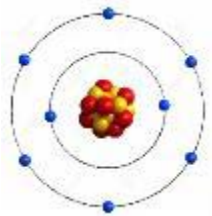
Objavitelia

Carl Wilhelm Scheele
1773

Joseph Priestley
1774

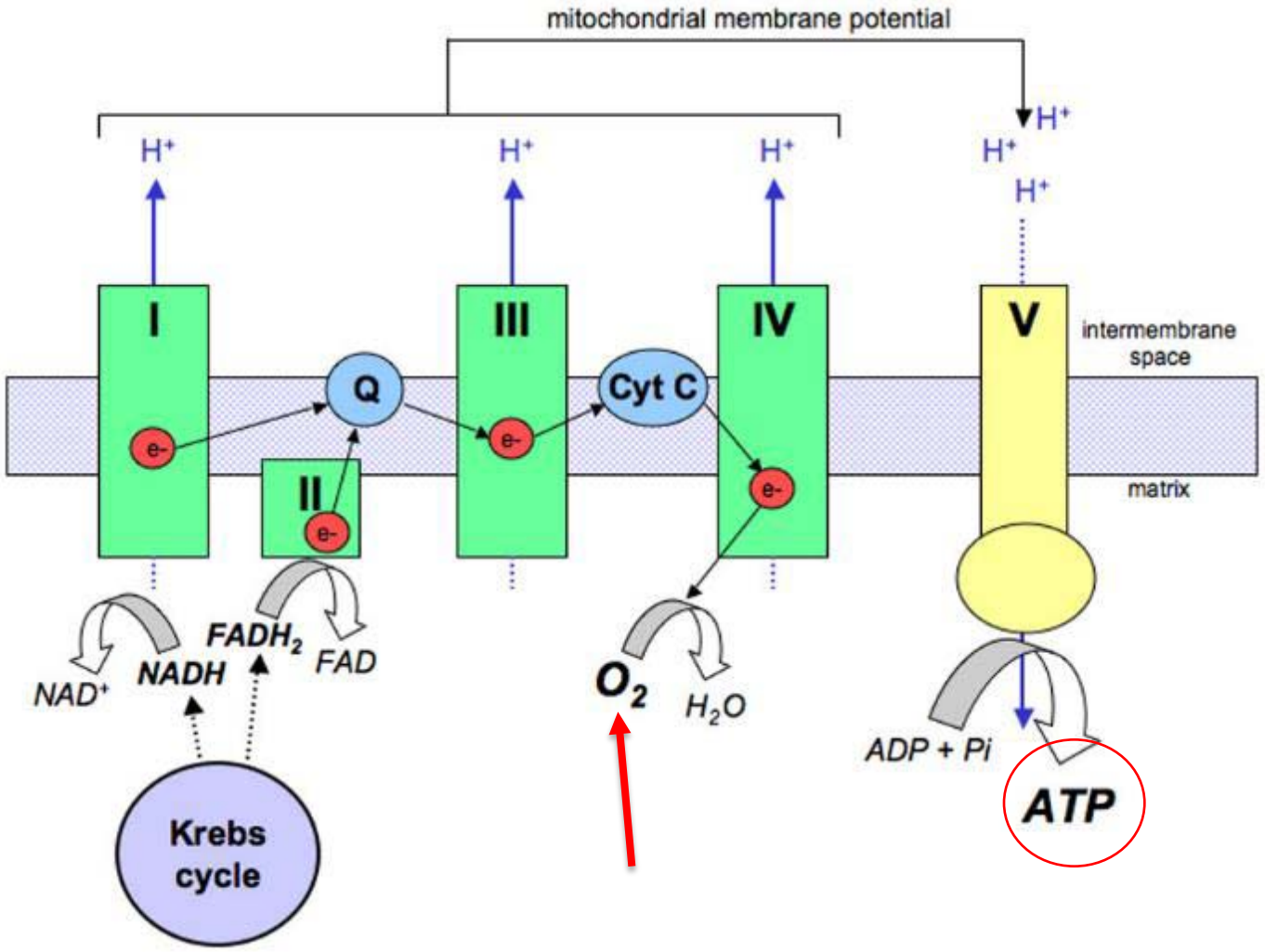
Antoine Lavoisier
1778

Objavitelia



- J. Priestley 1774: mohol by byť vhodný pri ochoreniach pľúc .... Ale nie u zdravých.
- A. Lavoisier 1778: Všetky prasiatka dýchajúce čistý oxygén uhynuli; červené pľúca
- Becker + Clamann 1939: 65 hod 90% kyslík; parestézie, dyspnoe, leukocytóza, horúčka, pokles VC

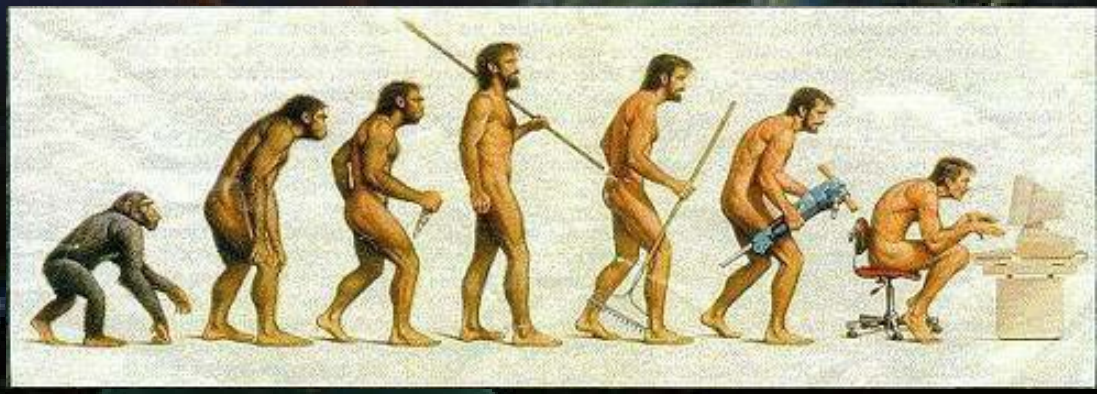
Kyslík v mitochondriách



Veľký tresk

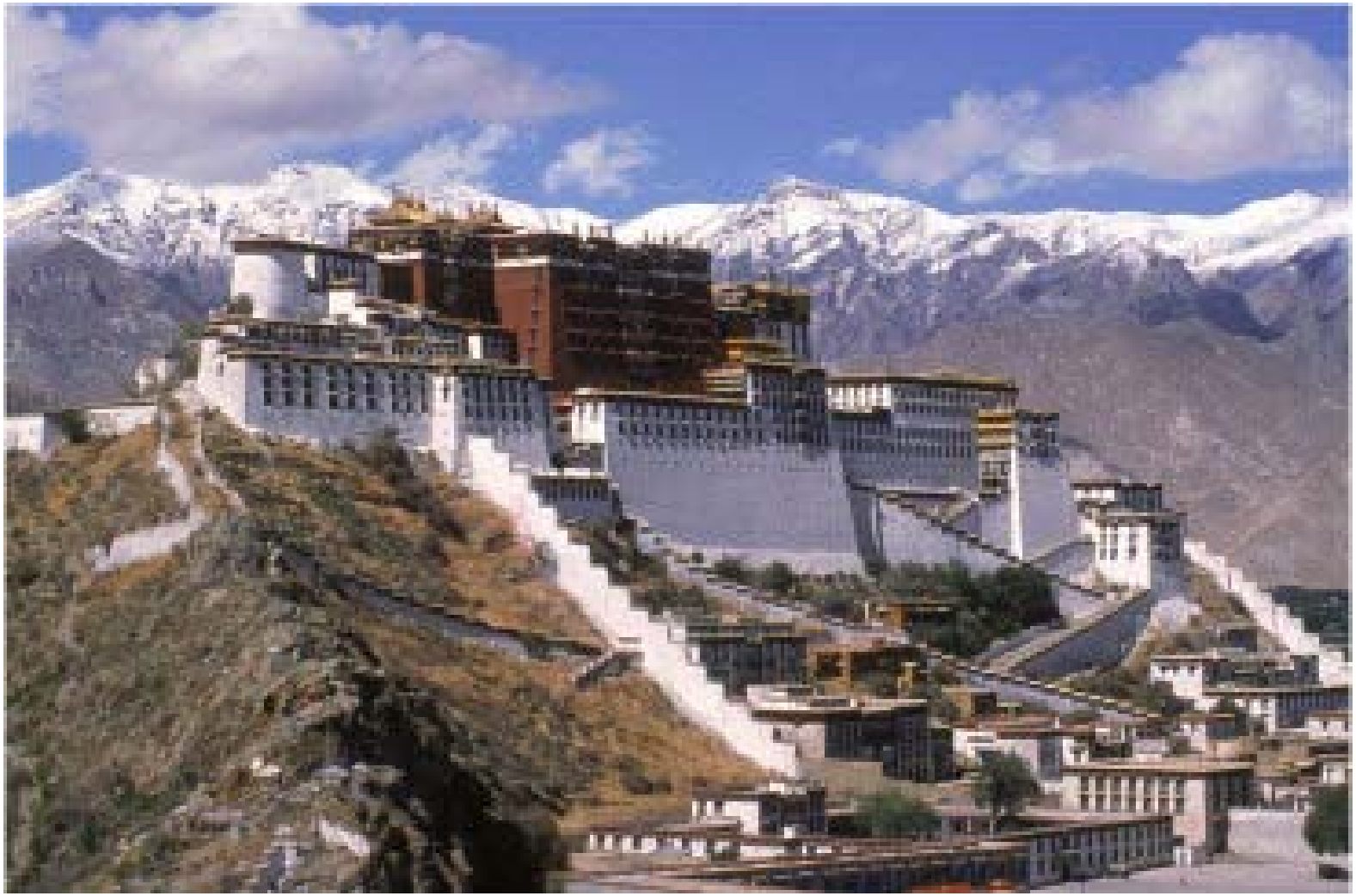
	3 000 000 000		350 000 000	
< 1 % O_2	→	21 % O_2	→	21 % O_2

700 000 rokov 21 % O_2



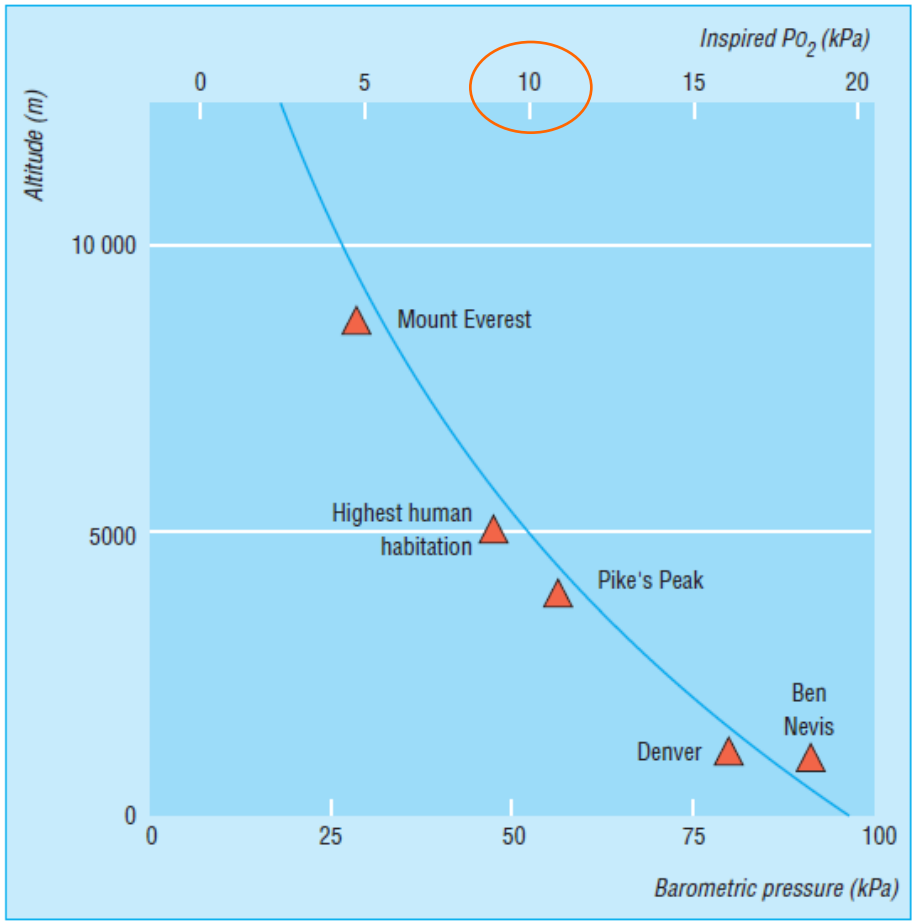
Kyslík v prírode. 21 % stačí?

Lhasa, Tibet; 3600 metrov/morom

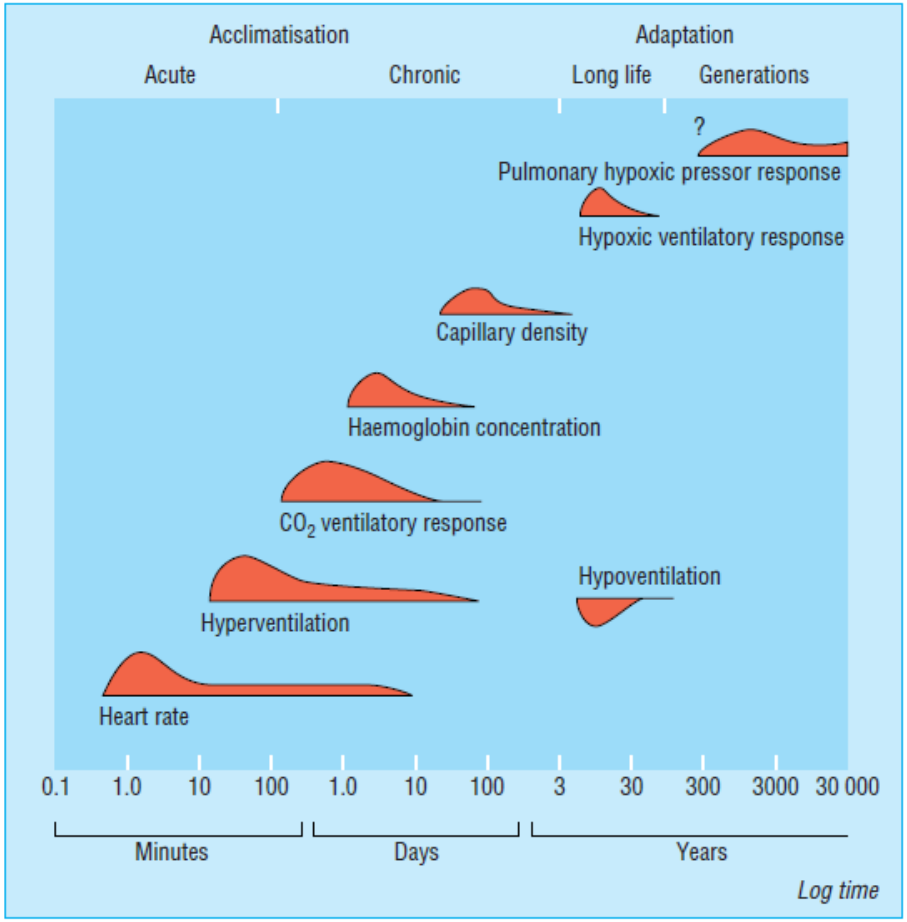


BMJ 1998

Hypoxia z výšky

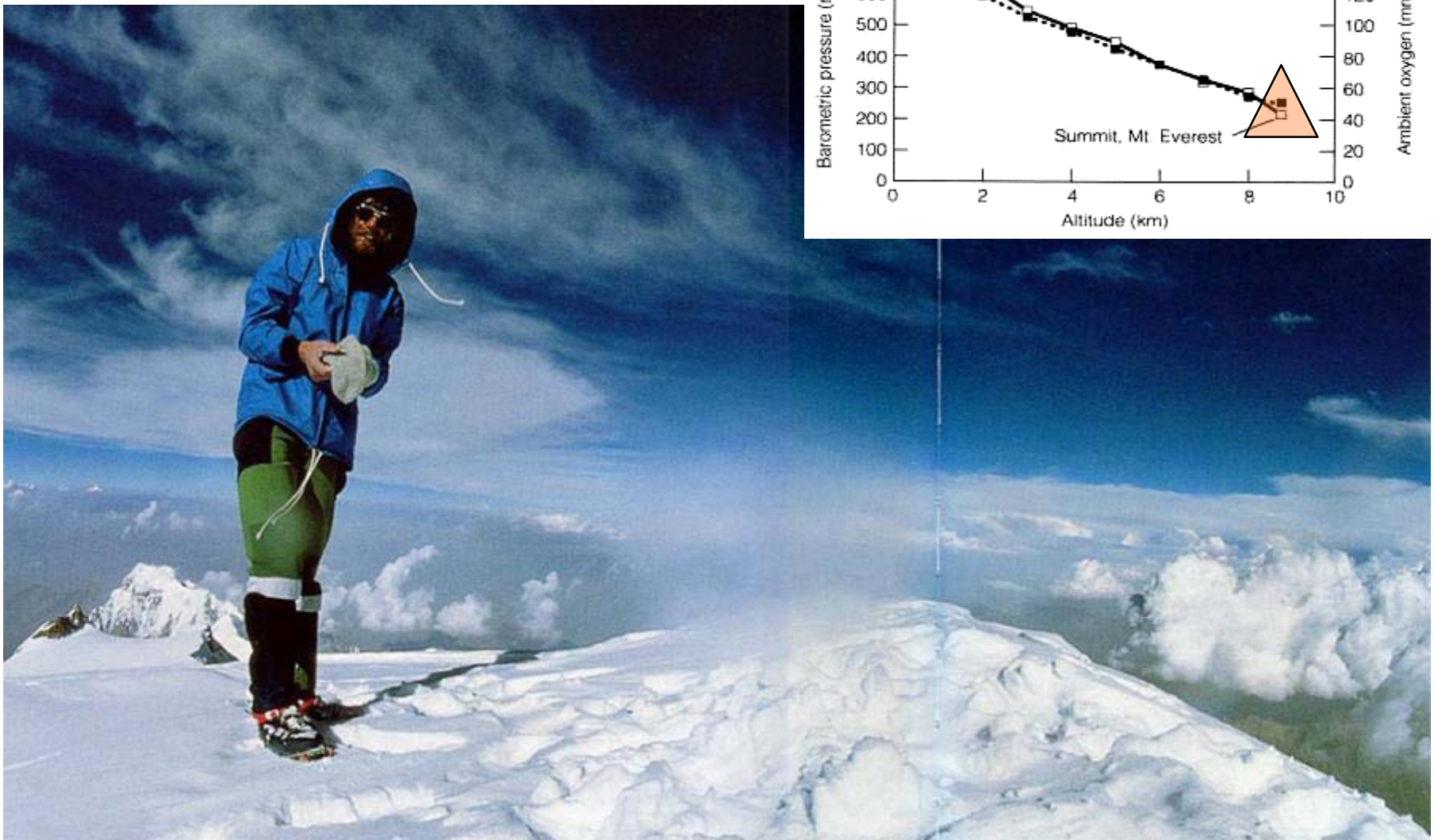


Relation between altitude and inspired oxygen pressure



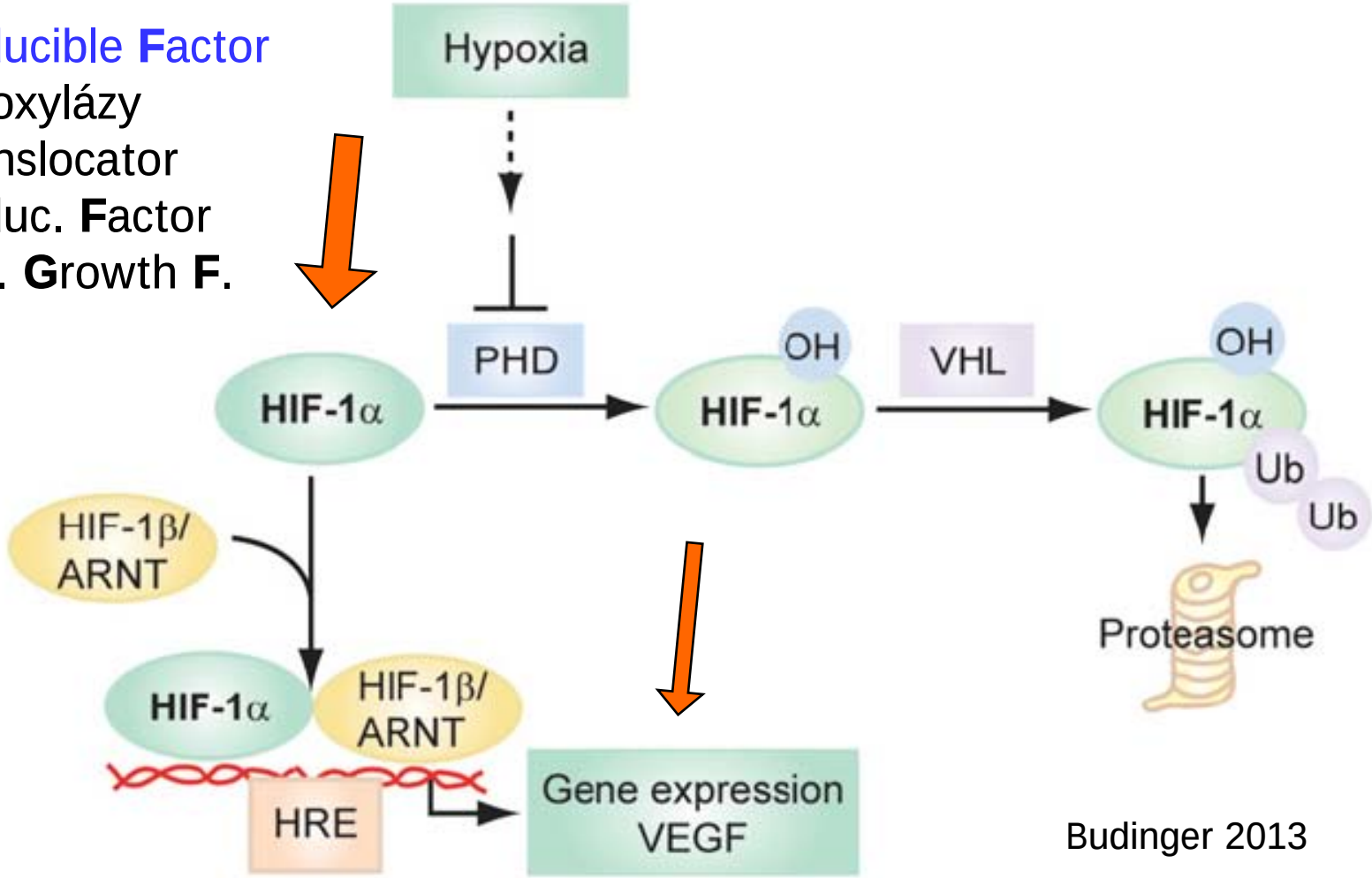
Time course of acclimatisation and adaptive changes plotted on log time scale. The curve of each response denotes the rate of change

R. Messner. Mt. Everest 1978



Tolerancia hypoxie

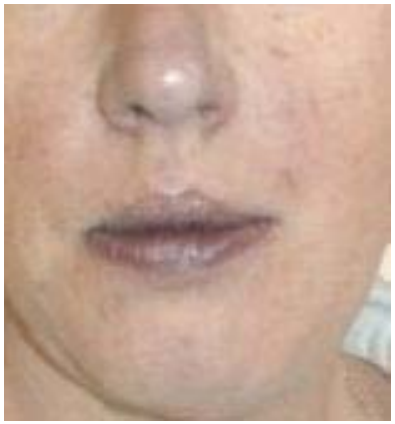
Hypoxia **I**nducible **F**actor
Prolyl **H**y**D**roxylázy
Nuclear **T**ranslocator
Hypoxia **I**nduc. **F**actor
Vasc. **E**ndot. **G**rowth **F**.

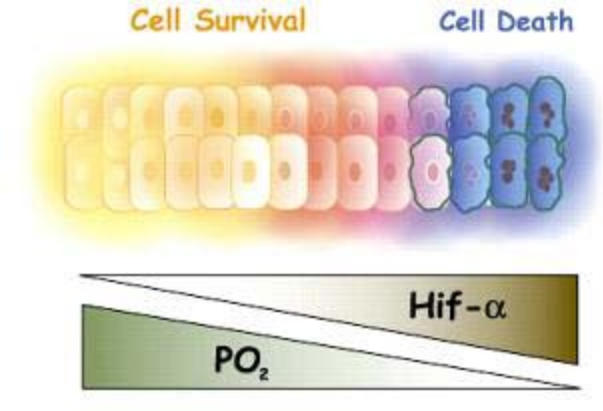


Budinger 2013

Akútna hypoxia

- Hypoxémia, hypoxia
- Anaerobný metabolizmus
- Vznik laktátu, acidózy
- Deficit ATP
- Smrť organizmu





Liečba hypoxie – kyslík!

- Najčastejšie predpisovaný liek
- Dostupný
- Jednoduchá aplikácia
- Merateľný efekt
- Dávka?

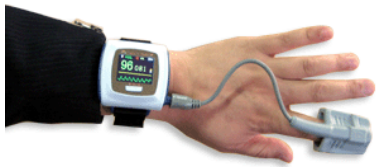
PREDávkovanie kyslíka?

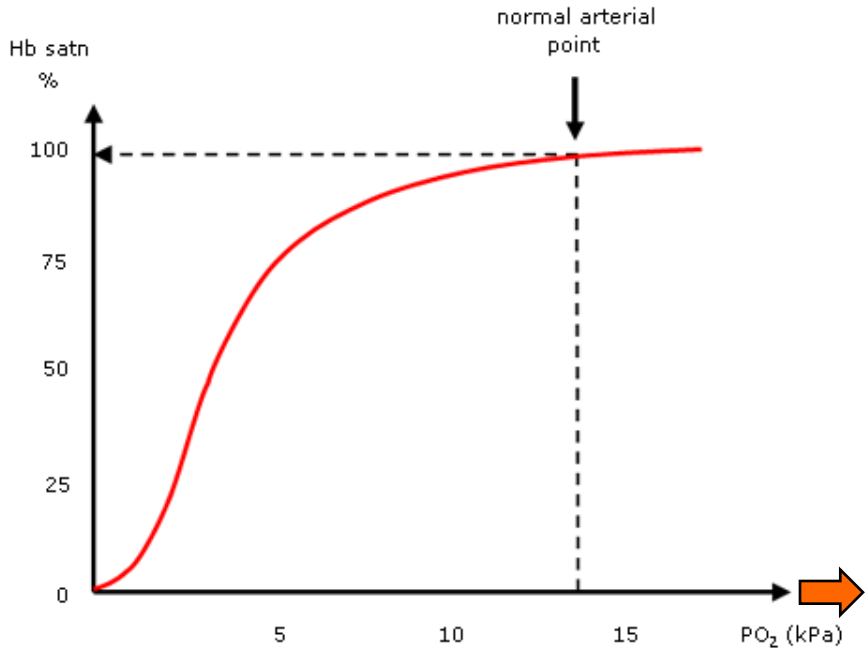
- FiO_2 21-100 %

  PaO_2 10-100 KPa
- Hyperbaroxia (1,1-3 atm)

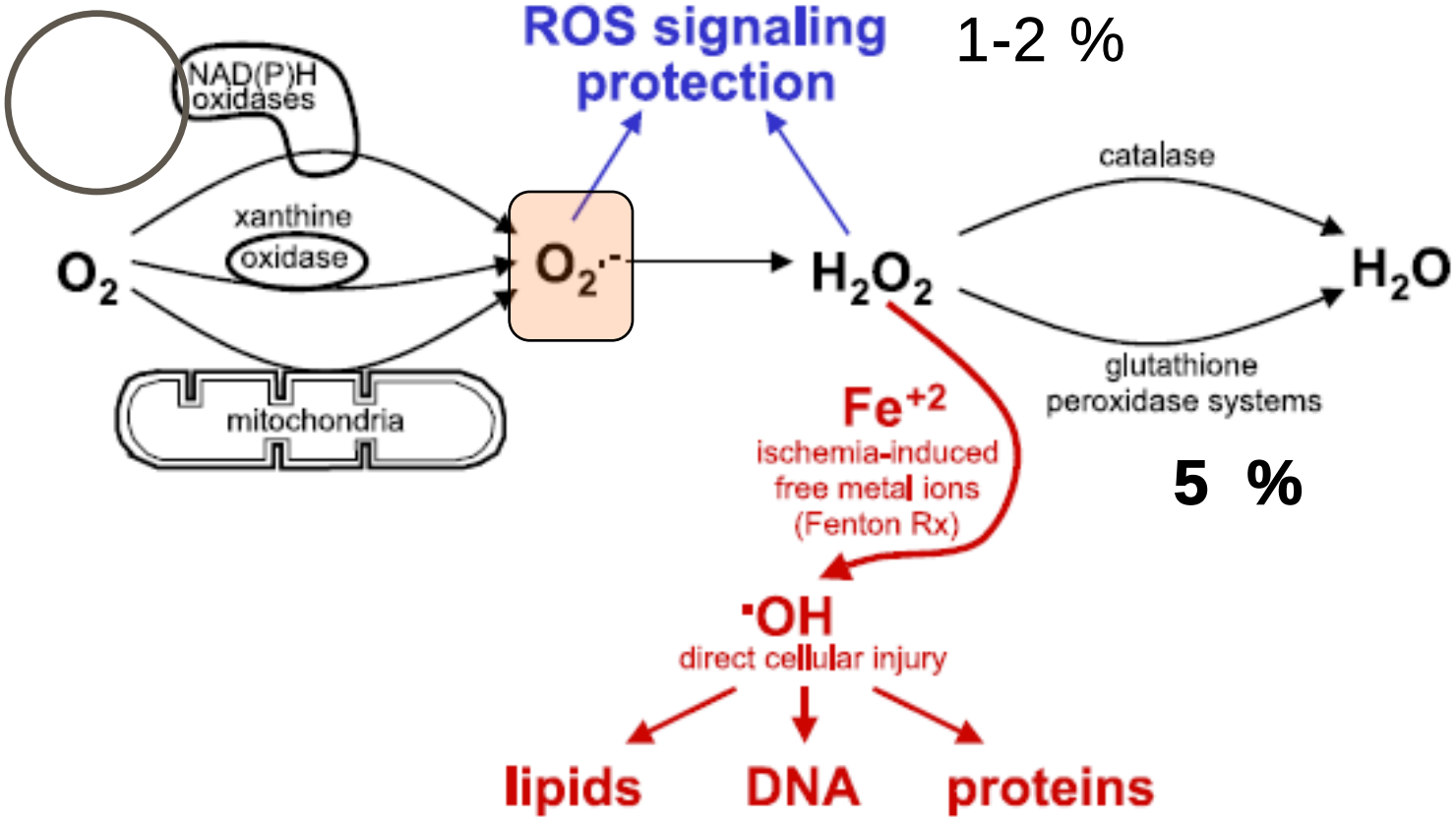
  PaO_2 100-300 kPa

- $SpO_2 \leq 100$ %





Čo sa ešte deje v mitochondriách?

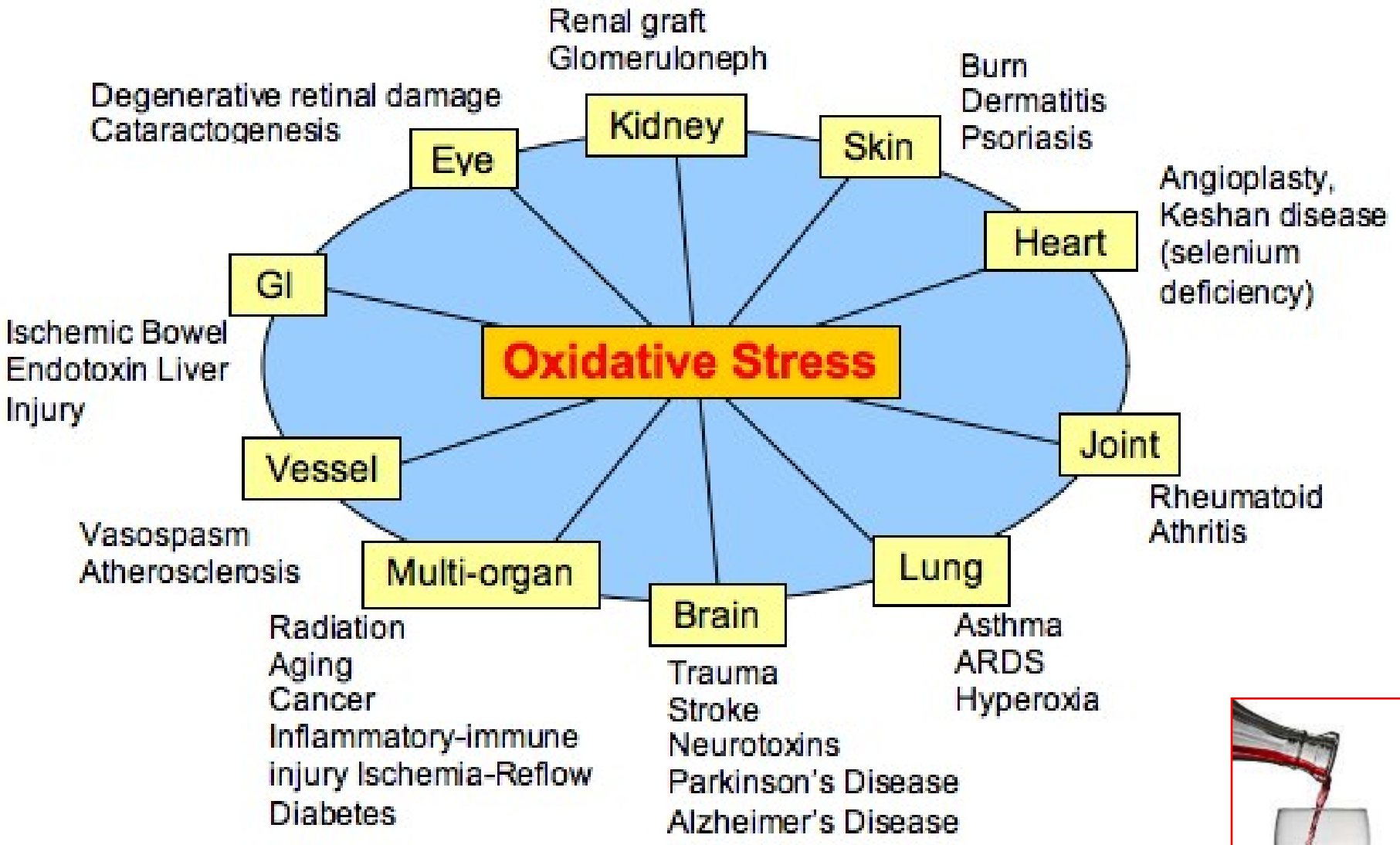


ROS – reactive oxygen species
(reaktívne formy kyslíka)

Oxidačný stres

- Hyperoxia

- Sepsa
- Reperfúzia (ischemicko-reperfúzne poškodenie)
- ....

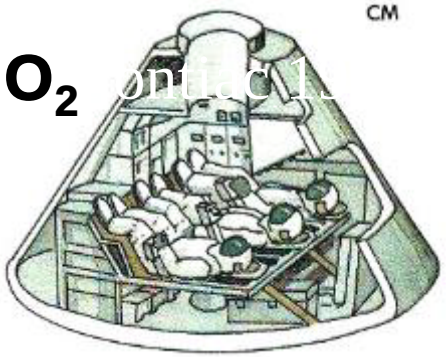

Renal graft
Glomeruloneph
Degenerative retinal damage
Cataractogenesis
Kidney
Eye
Skin
Burn
Dermatitis
Psoriasis
Angioplasty,
Keshan disease
(selenium
deficiency)
Heart
GI
Ischemic Bowel
Endotoxin Liver
Injury
Oxidative Stress
Joint
Rheumatoid
Athritis
Vessel
Vasospasm
Atherosclerosis
Multi-organ
Brain
Lung
Radiation
Aging
Cancer
Inflammatory-immune
injury Ischemia-Reflow
Diabetes
Trauma
Stroke
Neurotoxins
Parkinson's Disease
Alzheimer's Disease
Asthma
ARDS
Hyperoxia

Kyslík v prírode. 21 % dosť?

100 % prive'a?

27.1.1967 skúška Apollo 1
V. Grissom, E. White, R. Chaffee

100 % O_2 pri 0,1



História hyperoxie

Paul Bert (1833-1886), francúzsky fyziológ
V roku 1878 popísal škodlivosť kyslíka pre **CNS**
Paul-Bertov efekt (kŕče ak >3 ATA)

James Lorrain Smith (1862-1931), Škót
V roku 1899 popísal škodlivosť kyslíka pre **pľúca**
Lorrain-Smithov effect

Smith, J.L. The Pathological Effects Due to Increase of Oxygen Tension in the Air Breathed.
J. Physiol 1899;24:19-35.

História

- Kistler 1967; hyperoxia 6-72 hod, potkany
  - tekutina v interstíciu
  - deštrukcia endotelu
- Freeman a Capo, 1981, potkany
  - produkcia ROS
  - oxidatívny stres
- Budinger 2011: potvrdené na myšiach

Paradigma: Hyperoxia – tvorba ROS na molekulárnej úrovni z mitochondrií a iných zdrojov

J Biol Chem 1981
A j Resp Crit Med 2011

Oči:
Strata poľa
Katarakta
Krvácanie
Fibróza

Svaly:
Zášklby

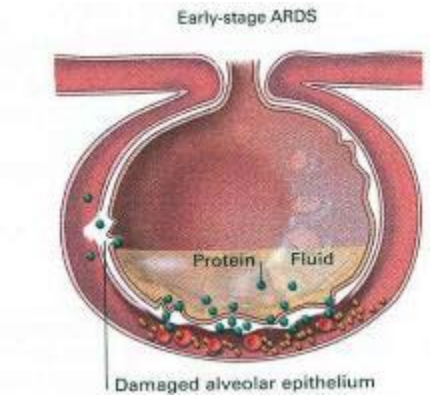
CNS:
Kŕče

Pľúca:
Tracheobronchitis

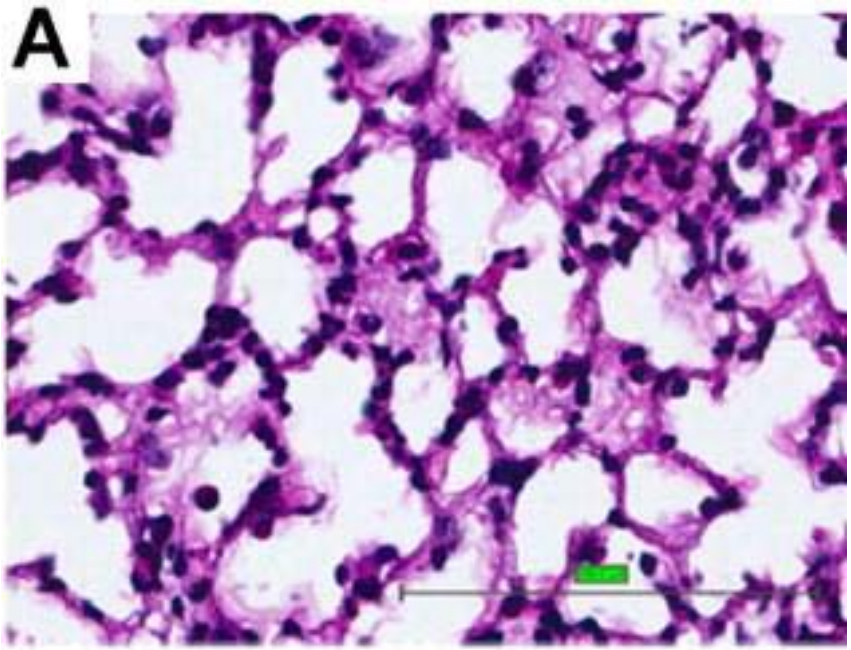
Aphrodita, Rhodos

Hyperoxia a pľúca

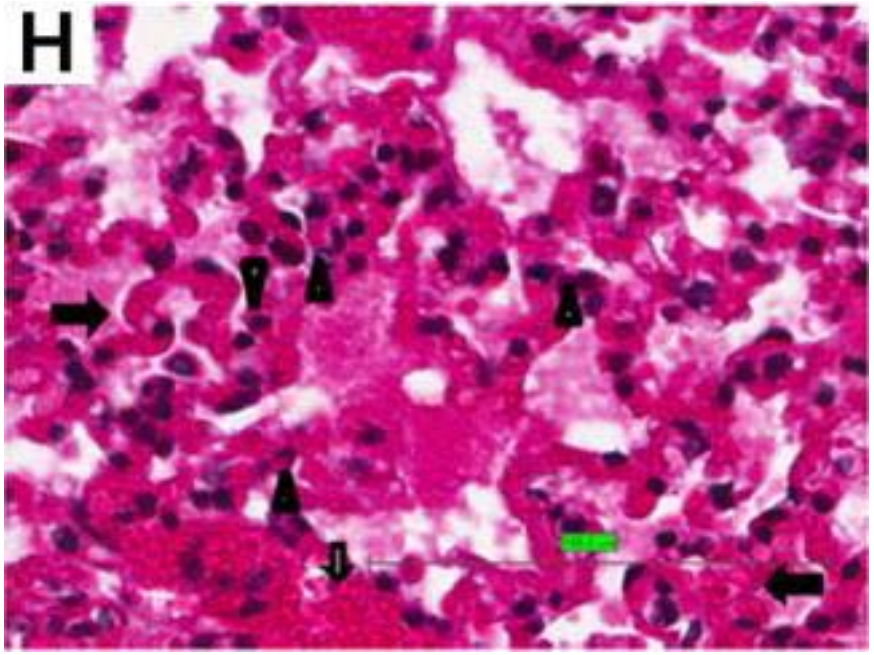
- Anatomicky:
  deštrukcia endotelu, alv. buniek (zhrubnutie), hyalinné membrány, edém alveolov, ťažké, červené pľúca
- Fyziologicky:
  pokles VC, atelektázy, pokles difúzie, mierna obštrukcia, zvýšená permeabilita
- Klinicky:
  tracheobronchitis, kašeľ, bolesť, dýchavica
- **ARDS**



Hyperoxia a pľúca



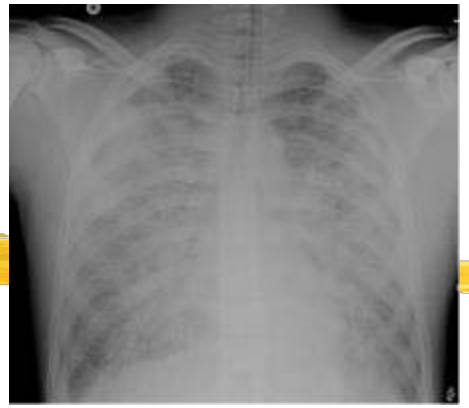
Normálne pľúca



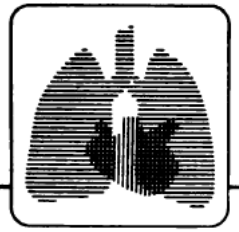
Hyperoxia

Patrudu 2010

ARDS a kyslíková liečba



- Ashbaugh D et al: Acute respiratory distress in adults. *Lancet* 1967;7511:319-23
- Hypoxémia: skrat pre edém alveolov (kardiogénny, ARDS, krvácanie do alveolov)
- Nedá sa zvýšiť saturácia hemoglobínu
- Fyzikálne rozpustený kyslík
- Zvýšenie obsahu – **vysoké FiO_2**
- PEEP



review

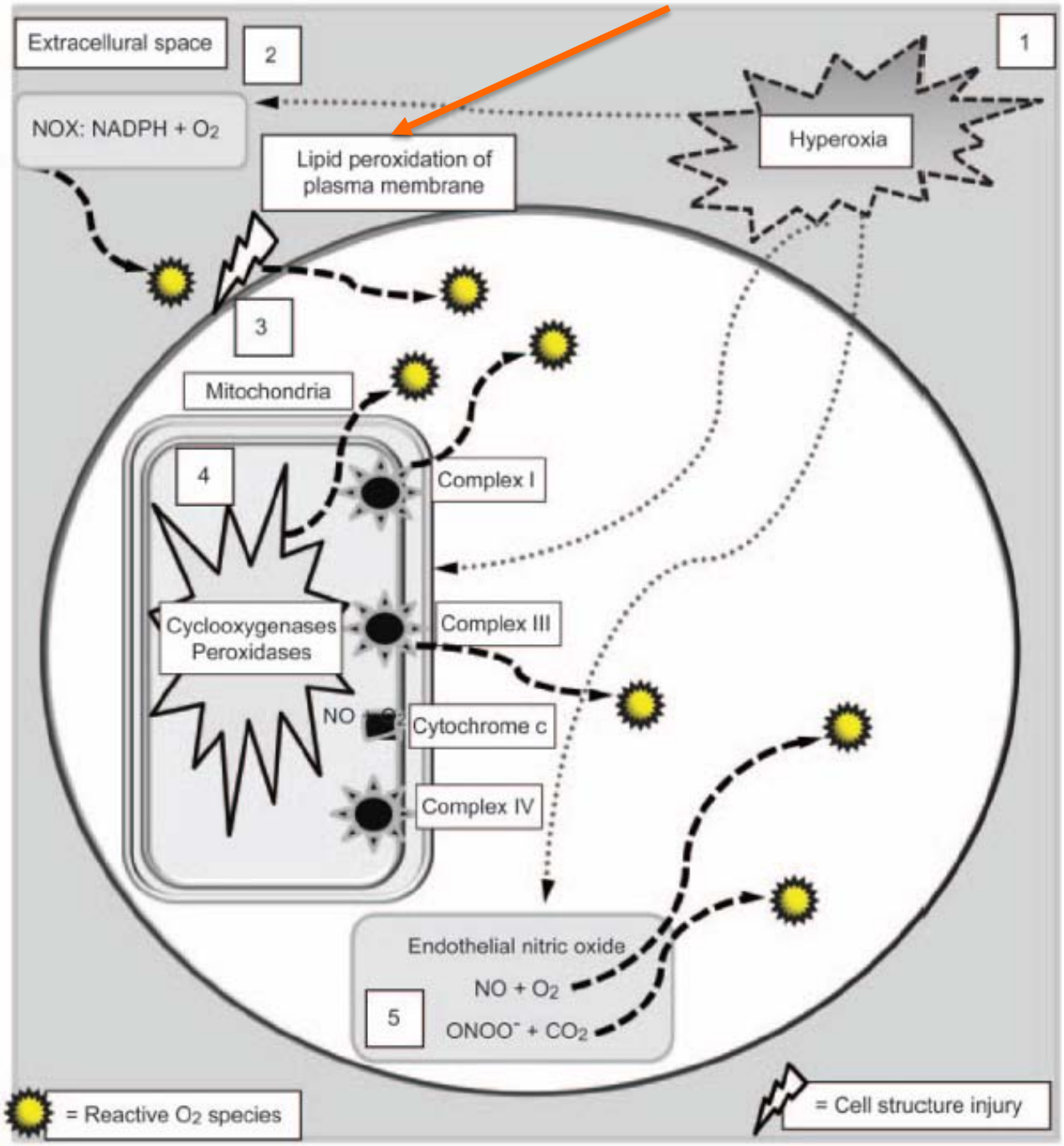
Pulmonary Oxygen Toxicity*

Robert M. Jackson, M.D., F.C.C.P.†

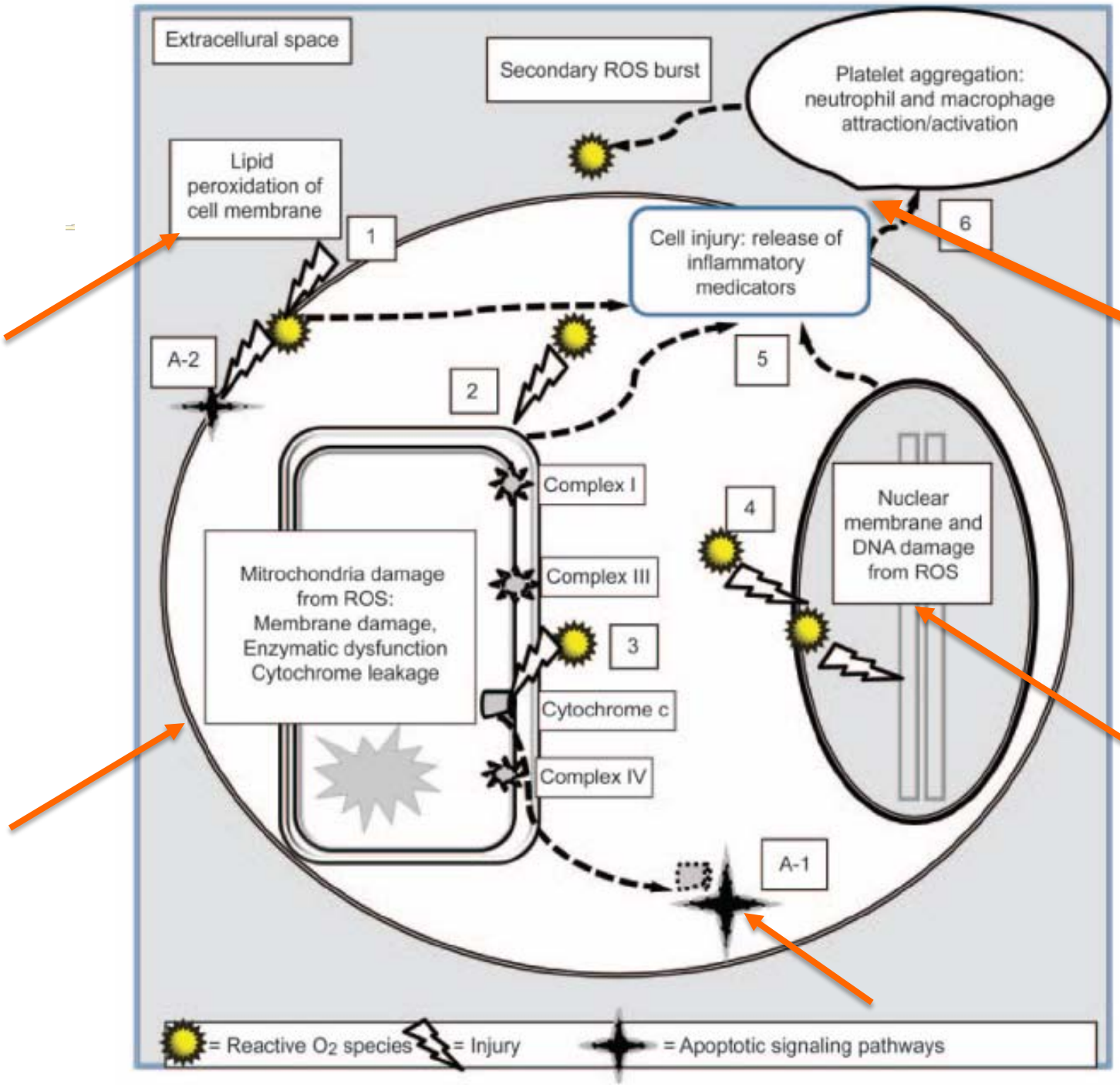
Although oxygen therapy has been used in the care of critically ill patients for many years, the recognition of pulmonary oxygen toxicity as an important clinical problem is relatively recent. The biochemical basis of oxygen toxicity is increased production of highly reactive, partially reduced metabolites of oxygen, including hydrogen peroxide and free radicals, by cells in hyperoxia. Enzymatic intracellular defense mechanisms exist which protect cells from the toxic effects of oxygen free radicals. The physiologic manifestations of oxygen toxicity include decreases in vital capacity, diffusing capacity, and lung compliance. The pathologic changes of oxygen toxicity are not specific and resemble those of the adult respiratory distress syndrome. Many drugs used in the care of patients, including bleomycin, nitrofurantoin, and corticosteroids, may exacerbate oxygen-induced lung injury. No effective pharmacologic means exist for lessening pulmonary oxygen toxicity in humans.

Podobnosť pľúcnej patológie...
1. Toxicita kyslíka
2. Šok, trauma, sepsa .....

The parallels in lung pathology in oxygen toxicity and lung injury associated with a variety of disease states including shock, sepsis, trauma, drug overdose, and cardiac arrest have led investigators to consider oxygen-induced lung injury a prototype of diffuse alveolar damage.[43] Bachofen and Weibel[44] found pathologic changes resembling oxygen toxicity in patients who died with ARDS but who had not received high concentrations of inspired oxygen. The basic pathologic findings consisting of transformation of the alveolar epithelium into cuboidal cells, interstitial edema, and apparent deposition of connective tissue were present regardless of the cause of ARDS. This



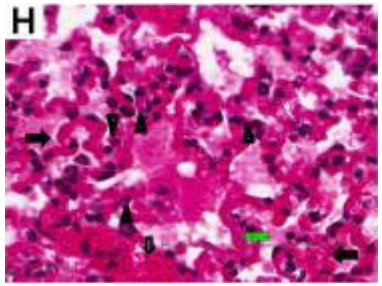
Resp Care 2013



Resp Care 2013

Účinky hyperoxie v pľúcach

- Kontinuálna produkcia ROS
- Zabraňuje inhibícii PHD = degradácia HIF
- Strata rastových faktorov, zvlášť VDGF
- Apoptóza + nekróza
- Porucha endotelu ⇨ alv. epitelu
- Permeabilizácia alveolo-kapilárnej membrány; alveolárny edém
- Hypoxické respiračné zlyhanie ....
- **H**yperoxic **A**cute **L**ung **I**njury (HALI)



J Physiol (2003), **552.2**, *pp.* 335–344
© The Physiological Society 2003
DOI: 10.1113/jphysiol.2003.049478
www.jphysiol.org

Topical Review

Mitochondrial formation of reactive oxygen species

Julio F. Turrens

Department of Biomedical Sciences, University of South Alabama, Mobile, AL 36688, USA

$$\frac{d[O_2]}{dt} = k\,[O_2]\,[R\bullet].$$

As oxygen concentration increases, the rate of mitochondrial $O_2^{-}\bullet$ production increases linearly (Turrens *et al.* 1982). However, the release of H_2O_2 from mitochondria is biphasic, increasing at a faster rate above 60 % O_2 (Turrens *et al.* 1985). The slower release of H_2O_2 at lower P_{O_2} suggests that the mitochondrial antioxidant defences can compensate for sudden increases in the concentration of this peroxide. Apparently these defences become overwhelmed at higher P_{O_2}, which explains the mitochondrial alterations observed in the lungs of animals exposed to oxygen concentrations around 60 % or higher (Crapo *et al.* 1983).

$FiO_2 < 0{,}6$

Lethality of Hyperoxia in Primate Studies

First Author	Year	Primate	*n*	F_{IO_2}	Days to Onset of Distress	Days to Death	Average Days to Death	Mortality (%)	Study Length (d)
Friedrich[7]									
Protocol 1	1944	Rhesus	4	> 0.90	ND	16,18	17	50	20
Protocol 2	1944	Rhesus	8	> 0.90	5	6–10	8	75	10
Weir[41]	1965	Sooty Mangabey	2	0.98	3	6, 9	7.5	100	9
Robinson[13]									
Protocol 1	1967	Rhesus	8	0.85–0.90	2–3	12–16	14	38	16
Protocol 2	1967	Rhesus	15	1.0	2.3	4–7	ND	60	7
Kaplan[8]	1969	Rhesus	16	1.0	3–8	2–7	4	44	12
Robinson[42]	1969	Rhesus	6	0.95	ND	4–9	6.5	33	14
		Baboon	7	0.95	ND	4–8	6.3	57	14
		Squirrel Monkey	12	0.95	ND	8–13	10	25	14
de los Santos[15]	1985	Baboon	4	1.0	ND	6	6	25	14
Protocol 1									
de los Santos[31]	1987	Baboon	8	1.0	ND	5–7	6	50	8
Fracica[39]	1991	Baboon	8	1.0	ND	3–5	ND	63	5
Protocol 3									
Huang[12]	1994	Baboon	5	1.0	ND	3	3	25	4
Protocol 1									
Total *N* and overall averages			103				8.0	51	11.5

ND = no data reported

Resp Care 2013

Clinical Case Studies Describing Potential Oxygen Toxicity in Adults

First Author	Year	*n*	Oxygen Exposure	Potential ALI/VILI Risk Factors Type (*n*)
Pratt[47]	1958	32	O_2 catheters at 4–7 L/min for 1–19 d	Intra-cerebral hemorrhage (3)
Capers[49]	1961	37	13 patients treated with unspecified F_{IO_2} prior to death	One patient treated with MV without specific data Aspiration (6) Interstitial pneumonitis (1) Pancreatitis (1) Blood transfusions of 1–7 units (18)
Cederberg[50]	1965	14	F_{IO_2} 0.4–0.8 for 0.75 h to 6 d Average F_{IO_2} 0.53 for 22 h Highest F_{IO_2} 0.7–0.8 for 0.75 h to 5 h	Aspiration, sepsis, large bone fractures, and CPB in some patients
Pratt[23]	1965	47	< 1 d: 9 1–4 d: 19 > 4 d: 6 F_{IO_2} not specified	Infection (15) Trauma (7)
Nash[53]	1967	70	4 groups analyzed according to duration of MV (< 10 d or > 10 d) and F_{IO_2} (<0.9 or > 0.9	Bronchopneumonia (22) Presumed CPB (17)* Other potential factors not described
Pratt[54]	1968	6	F_{IO_2} and MV settings not specified Some patients died within < 1 d; other cases received therapy 3–18 d	Non-thoracic trauma (6)
Barter[55]	1968	10	Pressure-cycled MV for 0.6–15 d F_{IO_2} not specified	Trauma (5) Sepsis (2) Bronchopneumonia (7)
Hyde[16]	1969	5	Highest (mean) F_{IO_2} 0.88 Mean duration of high F_{IO_2} 16.6 d Mean onset of chest radiograph changes 7.8 d	Cases not associated with major risk factors

Resp Care 2013

Table 1—*Combinations of Oxygen and PEEP for the Treatment of Patients With ARDS as Recommended by the ARDS Network*

Lower PEEP/Higher FIO_2		Higher PEEP/Lower FIO_2	
PEEP	FIO_2	PEEP	FIO_2
5	0.3	5	0.3
5	0.4	8	0.3
8	0.4	10	0.3
8	0.5	12	0.3
10	0.5	14	0.3
10	0.6	14	0.4
10	0.7	16	0.4
12	0.7	16	0.5
14	0.7	18	0.5
14	0.8	20	0.5-0.8
14	0.9	22	0.8
16	0.9	22	0.9
18	0.9	22	1.0
18-24	1.0	24	1.0

The combination of PEEP and FIO_2 should be increased if the PaO_2 is <55 torr or the SpO_2 is $<88\%$ and decreased if the PaO_2 is >55 or the SpO_2 is $>95\%$. PEEP = positive end-expiratory pressure. (Adapted with permission from The Acute Respiratory Distress Syndrome Network,[61] Wiedemann et al,[62] and Brower et al.[63])

NEJM 2000

Ako znížiť FiO_2

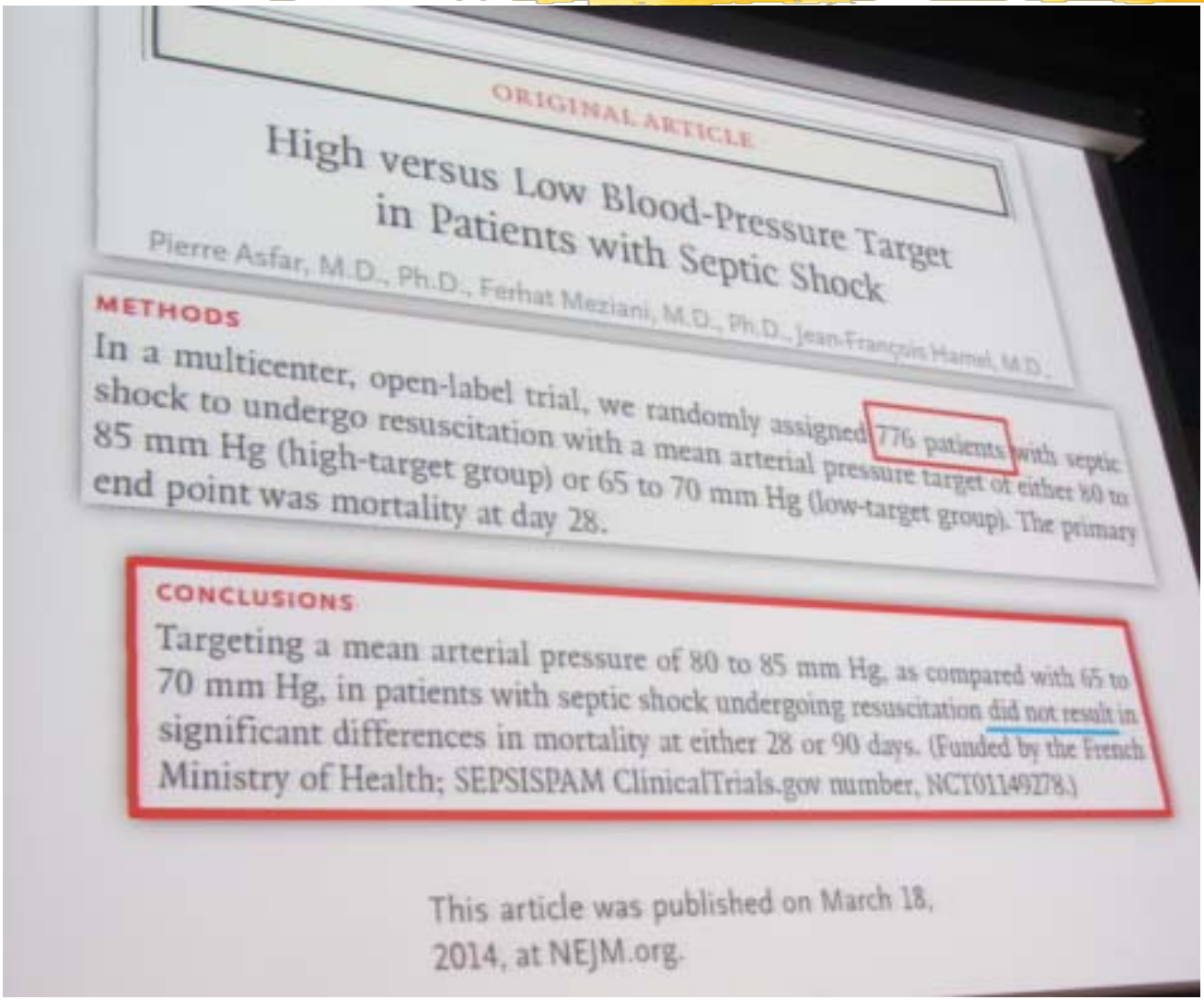
Table 2—*Strategies to Improve Oxygenation in Patients With ARDS*

Objective/Study	Strategy	Improved Oxygenation	Improved Mortality
Reduce shunt fraction			
Gattinoni et al,[73] Guerin et al,[74] Voggenreiter et al,[75] Taccone et al,[76] Mancebo et al,[77] and Fernandez et al[78]	Prone positioning	Yes	No[a]
Wiedemann et al[62]	Conservative fluid management strategy	Yes	
Troncy et al,[79] Michael et al,[80] Cuthbertson et al,[81] Dellinger et al,[82] Gerlach et al,[83] and Lundin et al[84]	Inhaled nitric oxide	Yes	
Anzueto et al[85] and Spragg et al[86]	Inh[illegible]		
Kacmarek et al[87]			No
Increase mean airway pressure			
Brower et al,[63] Meade		Yes	No[c]
Derdak	[illegible] ventilation	Yes	No
Brower e and Pe	[illegible]uitment maneuvers	Yes	No
Putensen	Airway pressure release ventilation	Yes	No
Increase Cvo			
Papazian et al[88]	Paralysis	Yes	Yes
Fernandes et al[93] and Parsons et al[94]	RBC transfusion	Unknown	Unknown
Peek et al,[90] Zapol et al,[91] and Morris et al[92]	Extracorporeal oxygenation	Yes	Conflicting results

Aké je miesto korekcie hypoxémie?

Chest 2013

I. Novák, 8. kongres ČSIM, Ostrava 2014



ORIGINAL ARTICLE

High versus Low Blood-Pressure Target in Patients with Septic Shock

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D.,

METHODS

In a multicenter, open-label trial, we randomly assigned 776 patients with septic shock to undergo resuscitation with a mean arterial pressure target of either 80 to 85 mm Hg (high-target group) or 65 to 70 mm Hg (low-target group). The primary end point was mortality at day 28.

CONCLUSIONS

Targeting a mean arterial pressure of 80 to 85 mm Hg, as compared with 65 to 70 mm Hg, in patients with septic shock undergoing resuscitation did not result in significant differences in mortality at either 28 or 90 days. (Funded by the French Ministry of Health; SEPSISPAM ClinicalTrials.gov number, NCT01149278.)

This article was published on March 18, 2014, at NEJM.org.

CHEST Postgraduate Education Corner

CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Balancing the Risks and Benefits of Oxygen Therapy in Critically Ill Adults

G. R. Scott Budinger, MD; and Gökhan M. Mutlu, MD

Oxygen therapy is an integral part of the treatment of critically ill patients. Maintenance of adequate oxygen delivery to vital organs often requires the administration of supplemental oxygen, sometimes at high concentrations. Although oxygen therapy is lifesaving, it may be associated with deleterious effects when administered for prolonged periods at high concentrations. Here, we review the recent advances in our understanding of the molecular responses to hypoxia and high levels of oxygen and review the current guidelines for oxygen therapy in critically ill patients.

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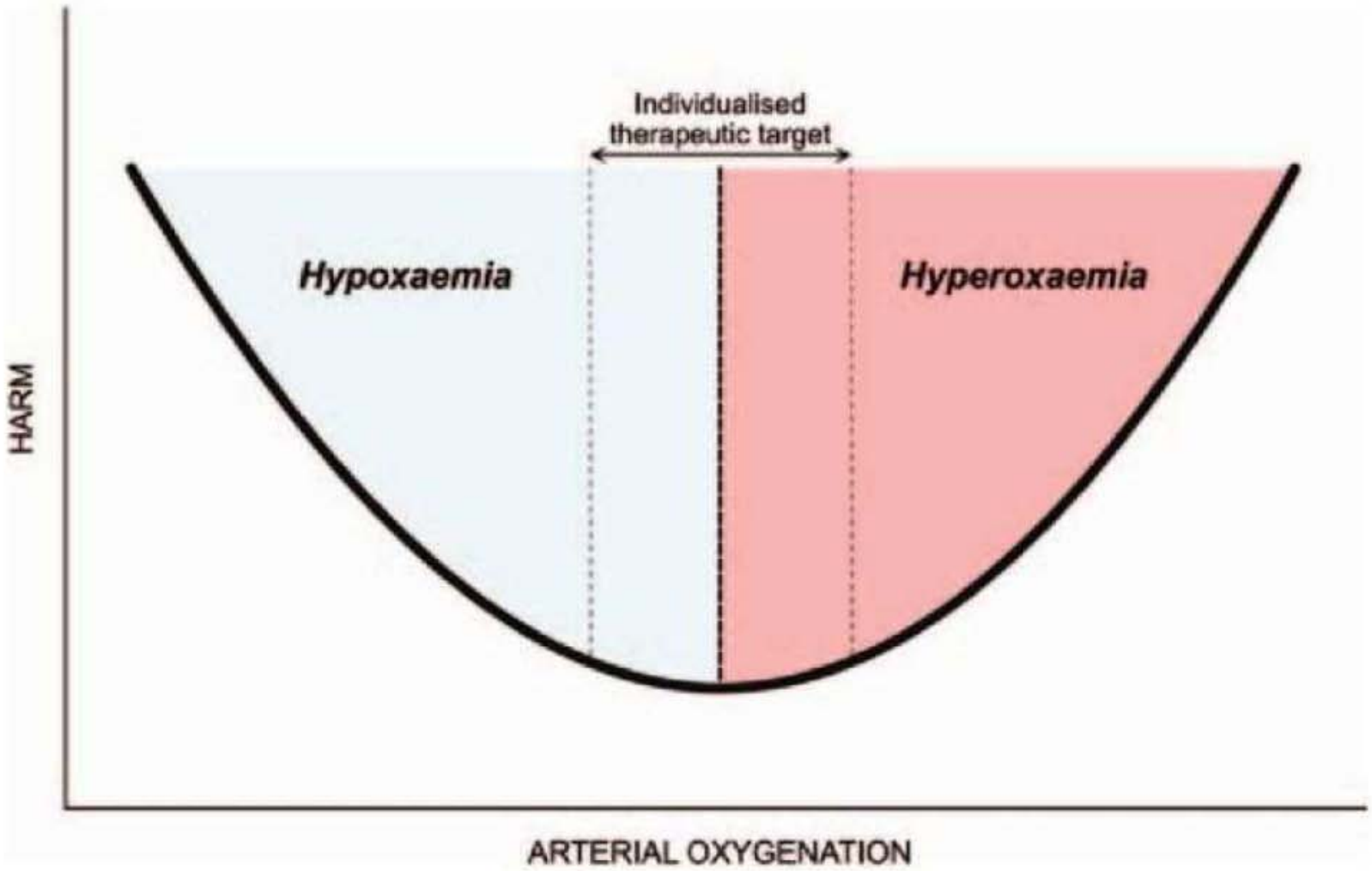
Abbreviations: HIF = hypoxia inducible factor; H_2O_2 = hydrogen peroxide; PEEP = positive end-expiratory pressure; PHD = prolyl hydroxylase; ROS = reactive oxygen species; VEGF = vascular endothelial growth factor

Precise control of arterial oxygenation

Target PaO_2 (goal directed?)

CCM 2013



Permissive hypoxemia

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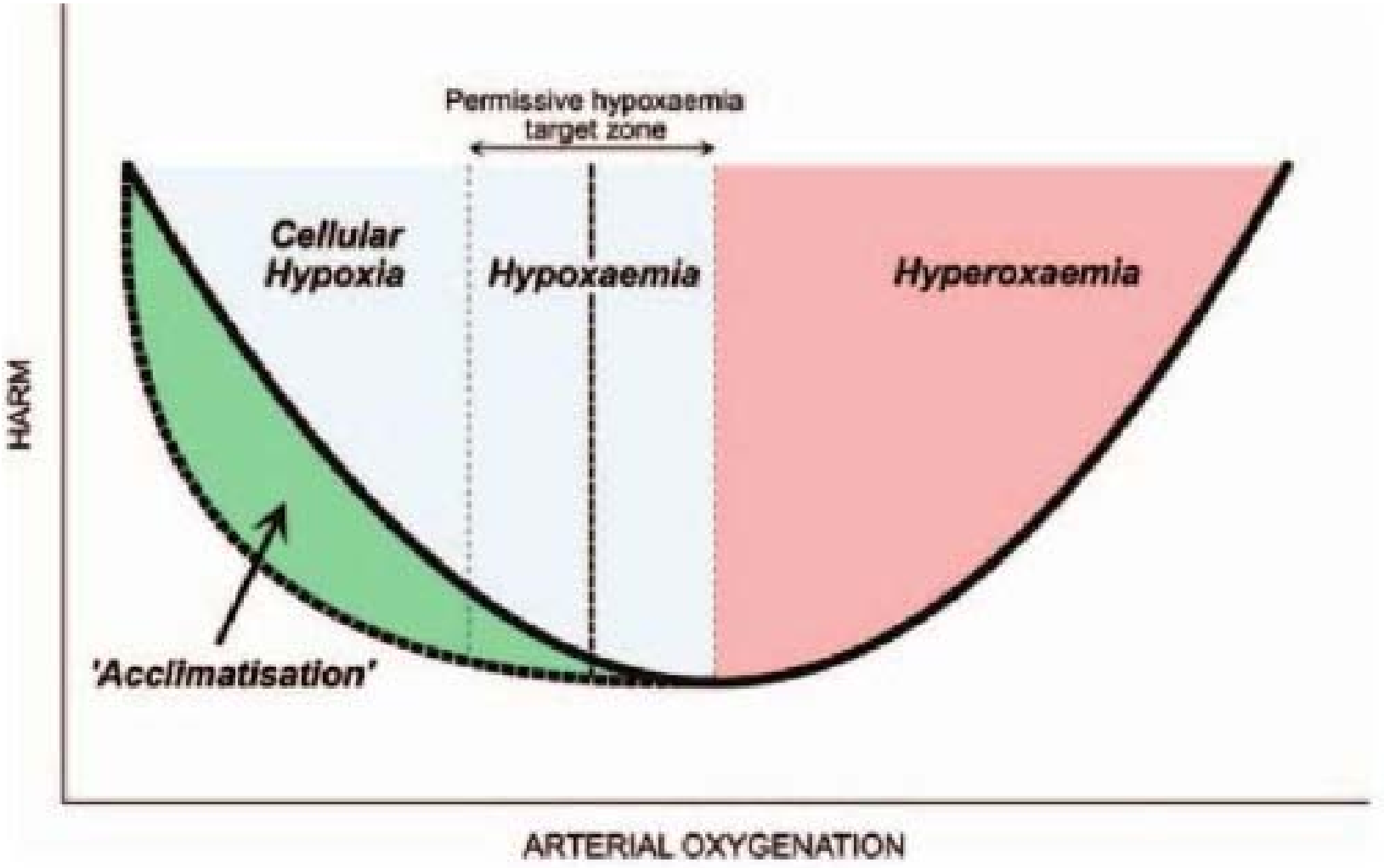


Hyperbaroxia - Cochrane

1. Kranke P et al. Cochrane Database Syst Rev. 2004

   Hyperbaric oxygen therapy for *chronic wounds.*

   Foot ulcers due to diabetes improve healing at 1 year

2. Bennett M et a. Cochrane Database Syst Rev. 2005

   Hyperbaric oxygen therapy for *acute coronary syndrome*.

3. Bennett M et al. Cochrane Database Syst Rev. 2012

   Hyperbaric oxygen therapy for the adjunctive treatment of *TBI.*

Obecné závery

Rutinná aplikácia HBO sa neodporúča.

Vzhľadom na malý počet pacientov, metodologické chyby a nedostatočný reporting treba výsledky interpretovať opatrne.

Sú potrebné RCT.

Životný cyklus hyperoxie

- **Resuscitácia novorodenca:** 100% O_2

  Odporúčané desaťročia

  Súčasnosť (ERC 2010): *vzduch*

- **Nekomplikovaný AIM** 100% O_2

  Odporúčané desaťročia

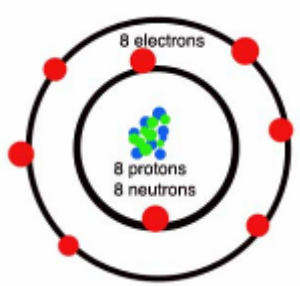
  Súčasnosť: (ERC/AHA 2010) *vzduch*

- **Rutinná liečba NCMP** 100% O_2

  Odporúčané desaťročia

  Súčasnosť (Stroke foundation, ASA 2013): *vzduch*

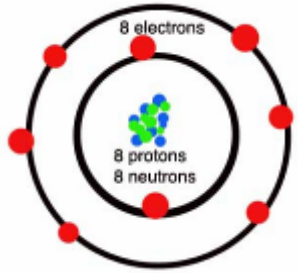
Súhrn



- HALI existuje (FiO_2>0,9) so smrteľnými následkami pre primáty
- Hraničné hodnoty u ľudí (FiO_2, trvanie) nie sú jasné; variabilita!
- Riziko: - nízke pri (protektívnej ventilácii) $FiO_2 \leq 0,6$
  - vyššie pri $FiO_2 > 0,7$
  - vysoké pri (prolongovanom) $FiO_2 > 0,8$
- Závažný ARDS + prolongované vysoké FiO_2 = riziko prítomné

  Potenciovanie: vírusové ochorenia, hypermetabolický stav (sepsa, trauma ...)
- Prevencia: PEEP, protektívna ventilácia, presná kontrola FiO_2, adjuvantné postupy ...

Čo robiť?



- Kyslík zachraňuje životy
- Považovať za LIEK – indikácie, kontraindikácie, dávkovanie
- Najnižšia vhodná koncentrácia v danom okamžiku
- Cielená liečba v úzkom rozmedzí podľa typu ARI
- Tolerancia hypoxémie?
- Ďalšie adjuvantné manévre
- Balansovať prínos riziko

Budúcnosť?

- Markery včasného postihnutia
- Cielená farmakologická liečba (HIF), transkripčné gény
- Antioxidancia

Ďakujem za pozornosť

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