

Using altitude in the prevention or treatment of some diseases

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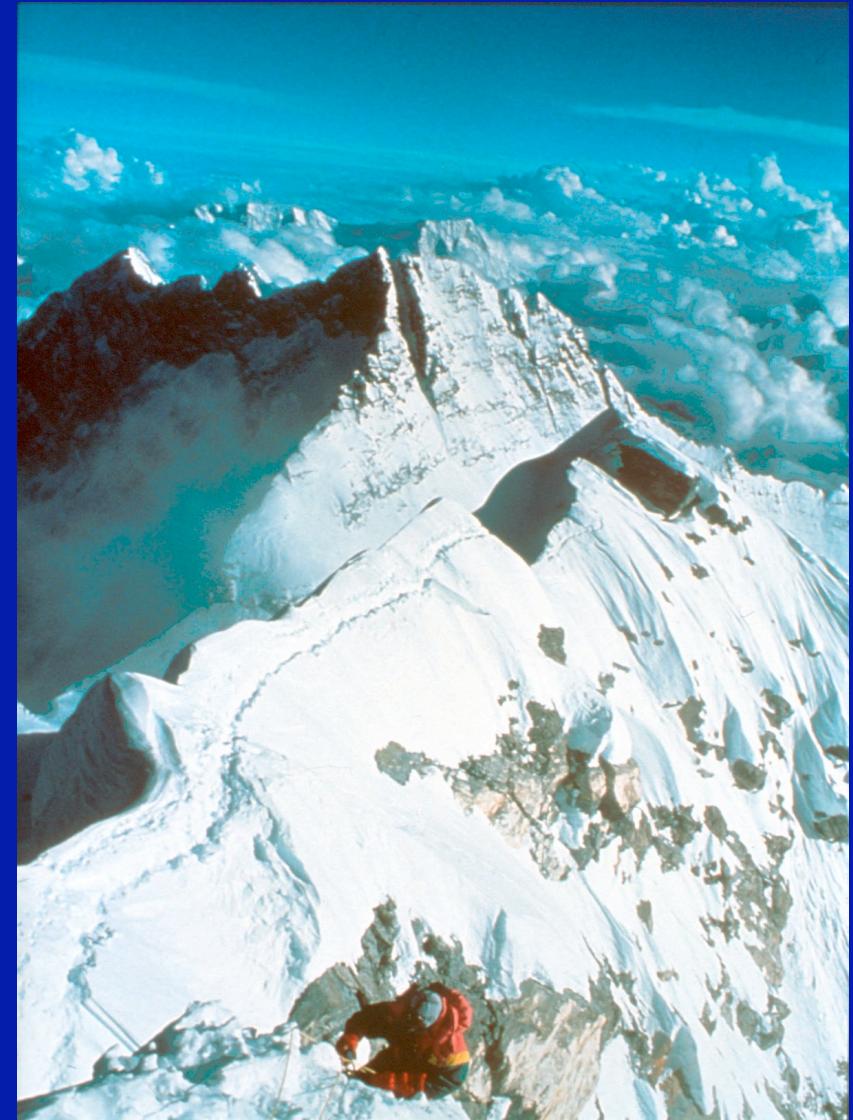
EA 2363 « Réponses cellulaires et fonctionnelles à l'hypoxie »
Bobigny, Université Paris 13, France

La Serena, 2009

Ambiente de altura



Everest cara norte



Arista terminal del Everest

Trekking Tour des Annapurnas



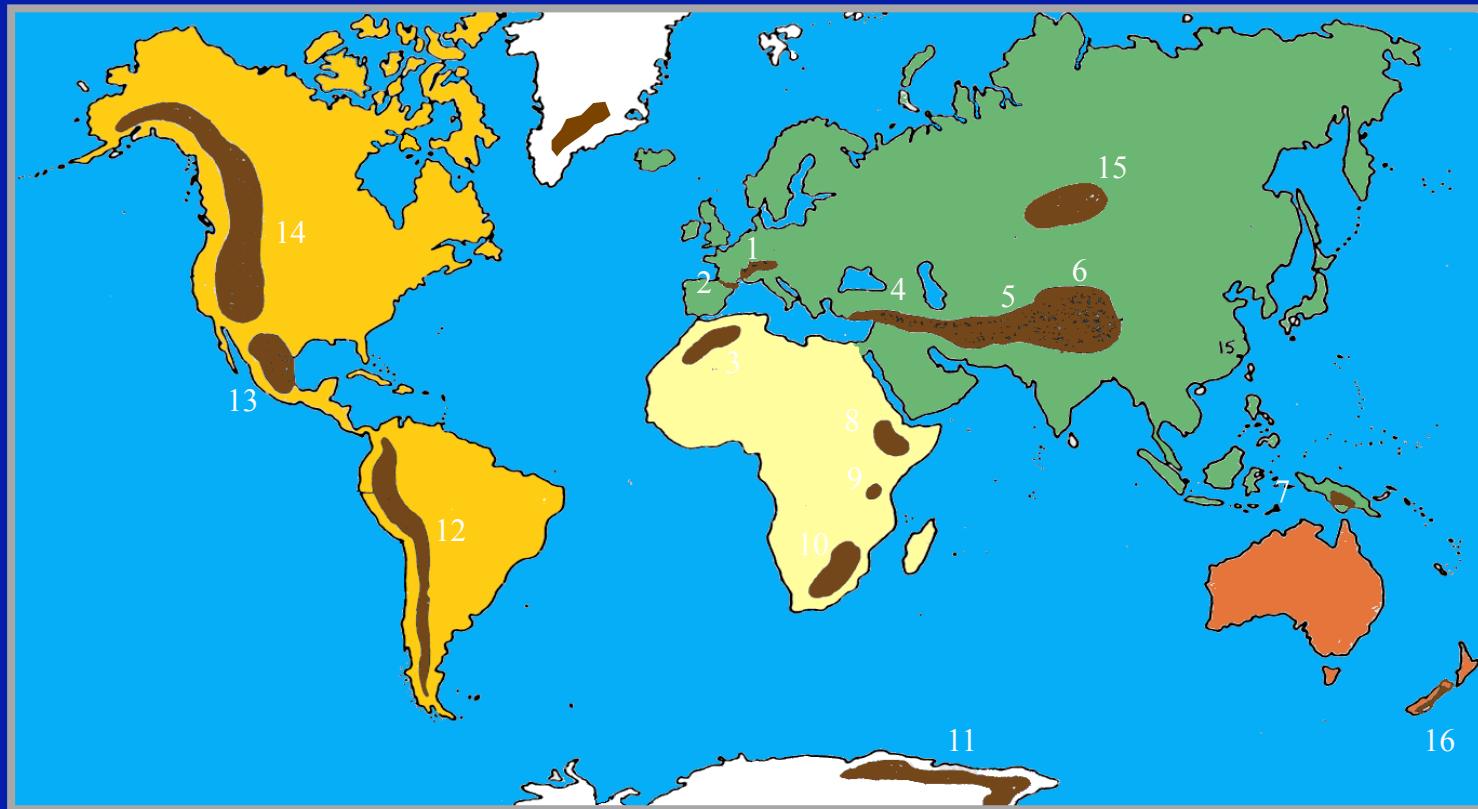
Raid deportista en altura



Turismo a Lhassa



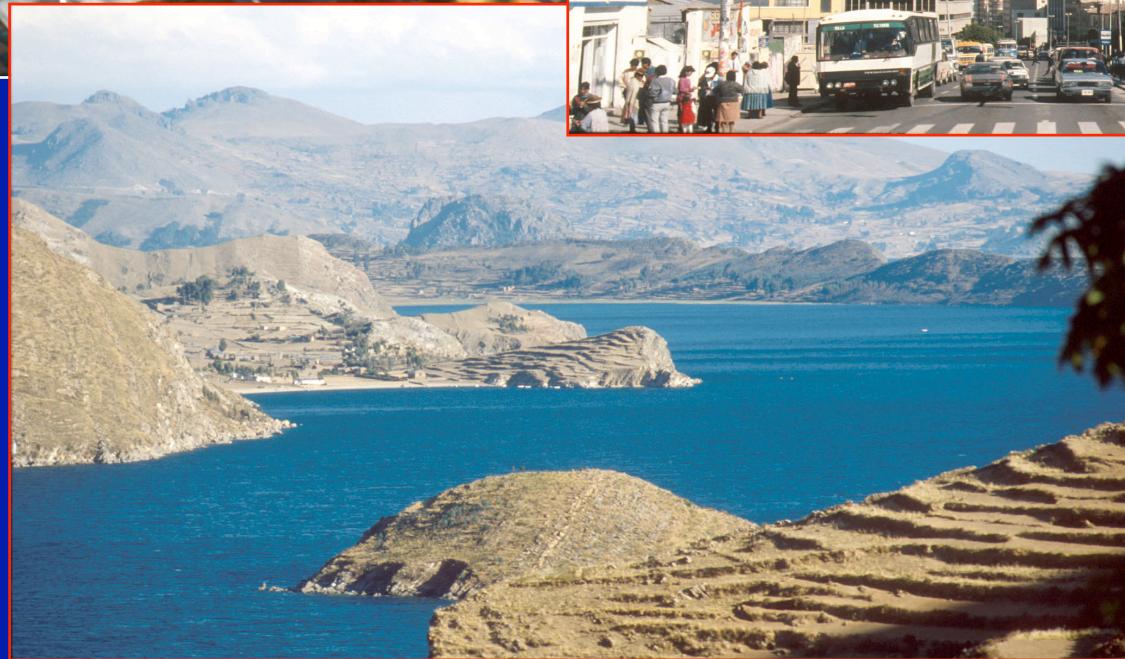
Regions of high altitude



In brown : regions where altitude is higher than 3000 m

1. Alpes
2. Pyrénées
3. Atlas
4. Caucase, Iran, Afghanistan
5. Himalaya
6. Plateau tibétain
7. Nouvelle Guinée, Bornéo, Indonésie
8. Ethiopie
9. Kenya, Tanzanie
10. Drakensberg
11. Antarctique
12. Andes
13. Haut plateau mexicain
14. Montagnes rocheuses
15. Altaï
16. Nouvelle-Zélande
17. Groenland

Poblaciones de altura - Altiplano



Trabajo en altura

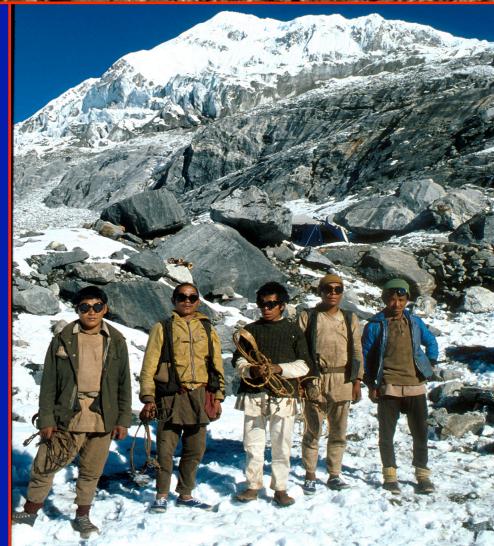
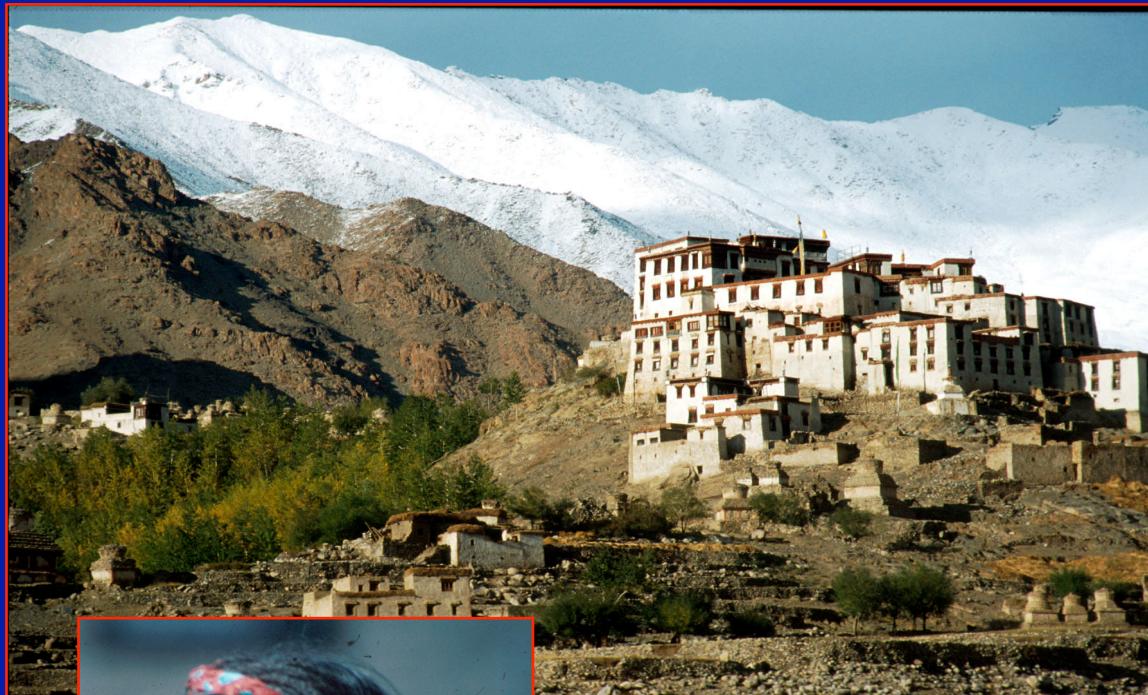


Cerro de Pasco, 4350m
Peru



Collahuasi, 4500m
Chile

Poblaciones de altura - Himalaya Karakoram



Acceso facil a la altura



Peru
Carretera transversal
central

La Paz
aeropuerto 4050m
ciudad 4000 a 3200m



Is altitude good or bad
for health ?

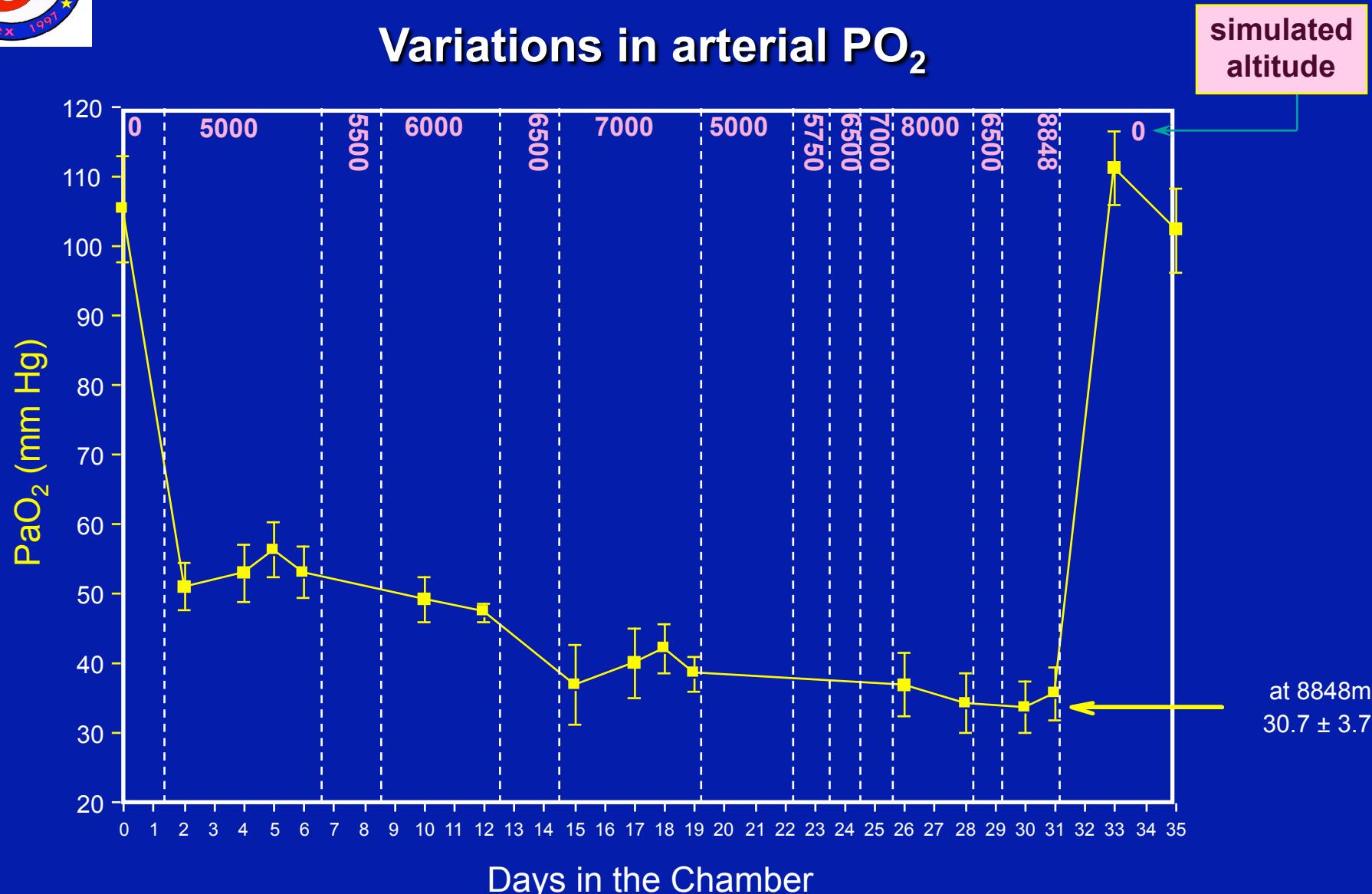
Depending on the intensity of
hypoxia...

DEFINICION BIOLOGICA DE ALTURA





Operation EVEREST III (COMEX 97)



Depending on the modality of exposure to hypoxia...

Tres modelos de exposición a la hipoxia

Hipoxia aguda



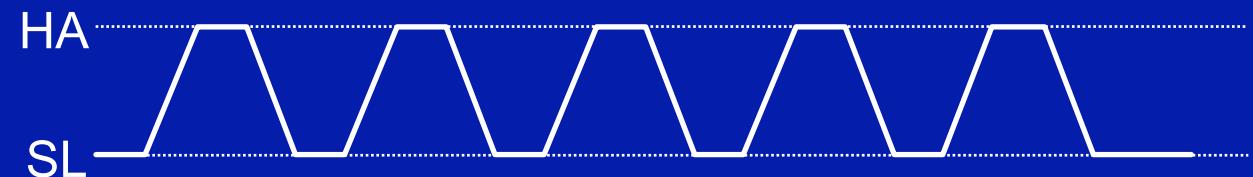
Alpes,
Himalayas

Hipoxia cronica



Peru,
Bolivia

Hipoxia
intermittente
cronica



Norte
Chile

Altitude can be bad...

MAM – edema localizado de altura





Ladakh, J+0



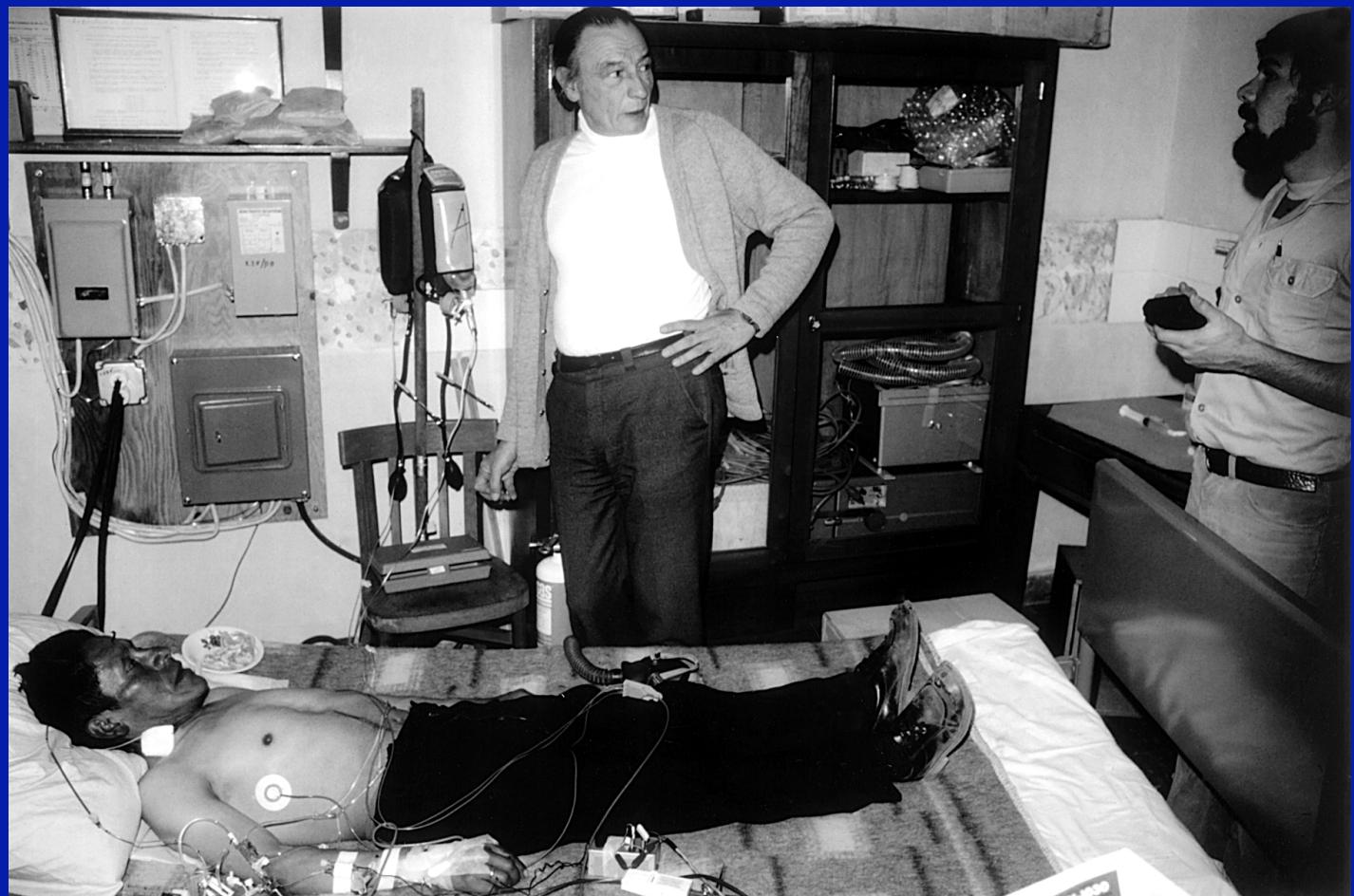
Ladakh, J+2



Ladakh, J+4

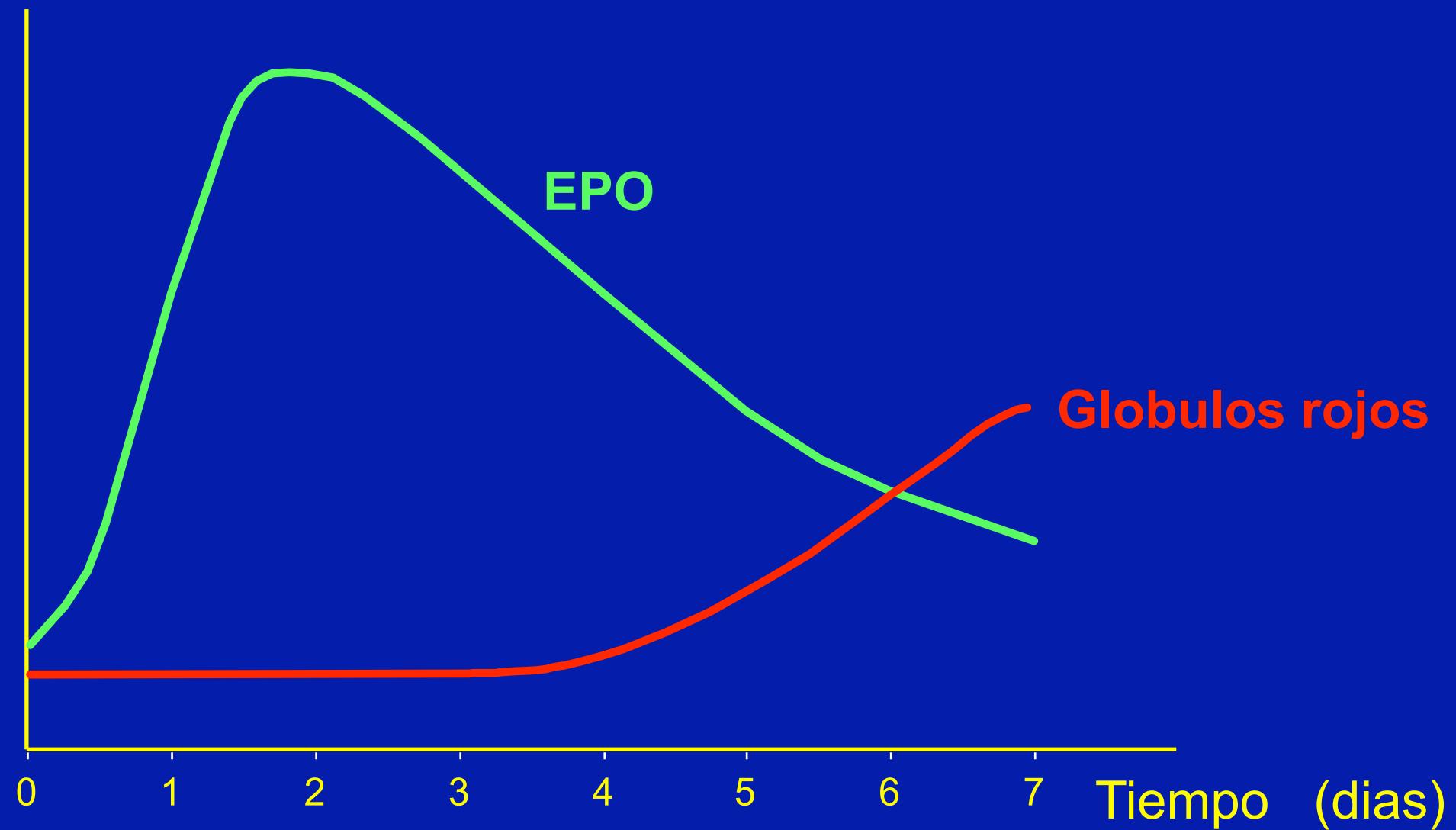
Edema pulmonar de altura

Mal de montaña crónico



Altitude can be good...

Evolución de la concentración de EPO y del numero de globulos rojos durante una exposición de una semana a 4350 m.



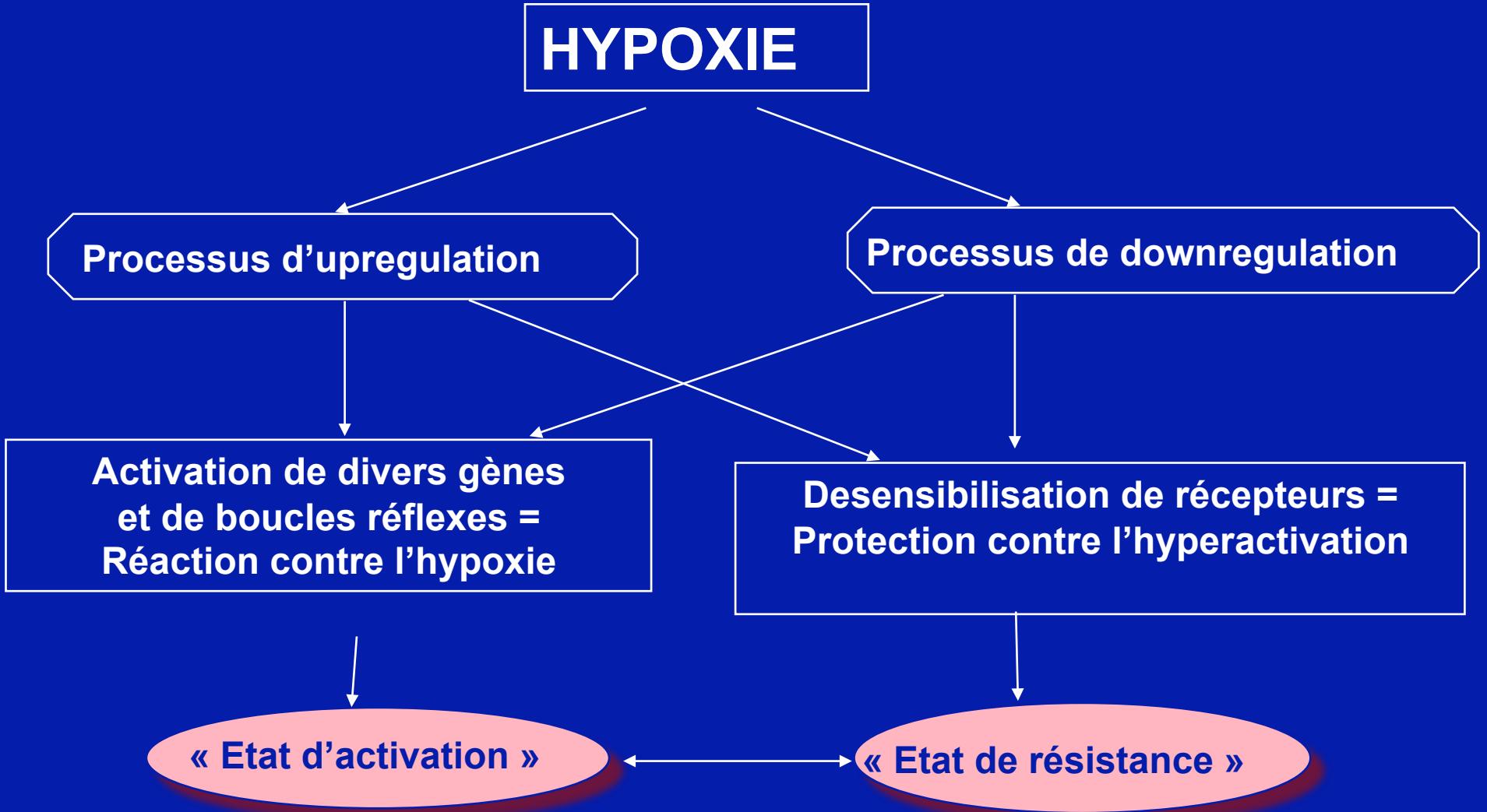
Intermittent hypoxic exposure



Hypoxic hotels

- The **Barcelo Pueblo Park** is the first hotel to include hypoxia equipment in the rooms to allow elite sportspeople, and particularly cyclists, to improve their output before competing.
- What hypoxia does is to activate the production of red blood cells, thus increasing maximum oxygen consumption and aerobic resistance.





Can some diseases benefit from
acute, chronic or intermittent
exposure to hypoxia ?

HYPOXIA

Detection of hypoxia

Genes with a “Hypoxia responsive element”
HIF-1a, EPO, VEGF, NFkB, NOS, PDGF, ET-1, etc...

Chemoreceptors

Erythropoietin producing cells

Skeletal muscle cells

Pneumocytes PII

Smooth muscle cells

Endothelial cells

Secreting cells with/without O₂ sensitive enzyme

Central

Peripheral

Ventilatory muscles

Erythropoietin

Myoglobin

Alveolar hypophase

pulmonary vasoactivity systemic

Respiratory system

mediators
vasomotricity hemostasis cell proliferation cap. permeability

Cardiovascular system

Water / electrolytes

PO₄/Ca metabolism

Autonomous nervous system

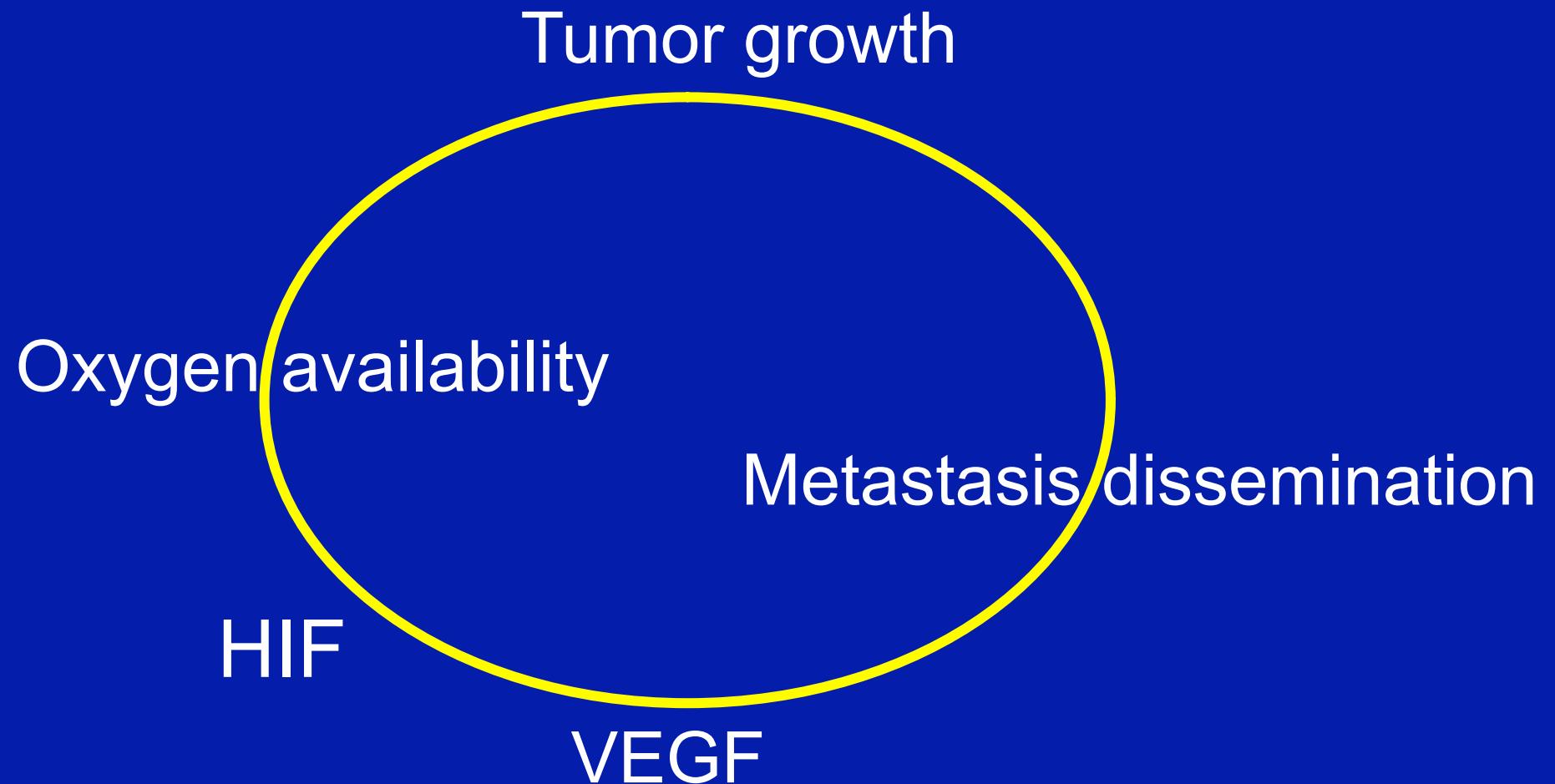
Respiratory system

Cardiovascular system

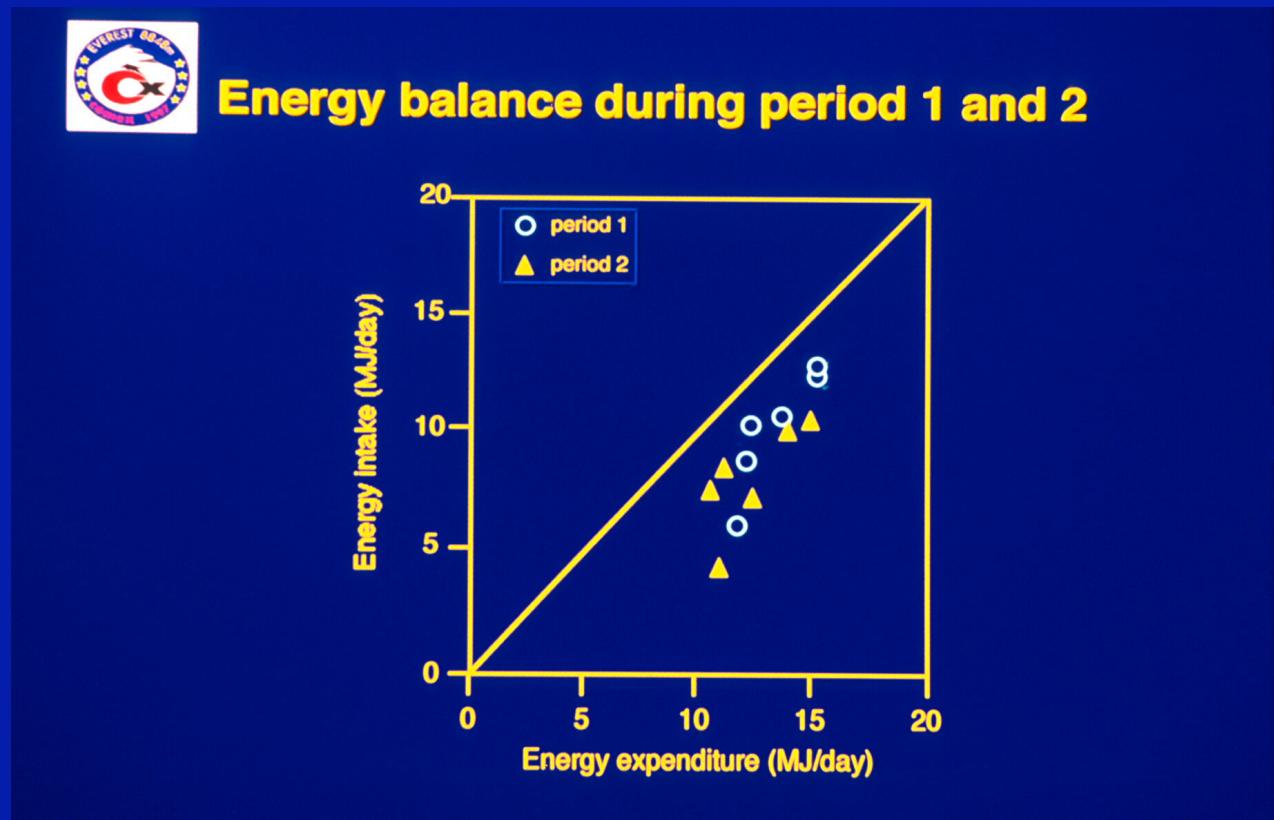
Hypoxia and Cancer

- In solid tumours, the interdependent relationship between **tumour and endothelial cells** modulates tumour development and metastasis dissemination.
- The tumour microenvironment (PO_2) plays an important role in this cell interplay, and changes in PO_2 have a major impact on **tumour growth** as well as on anticancer therapy responsiveness.
- Different studies have shown irregular blood flow in tumours, which is responsible for hypoxia and reoxygenation phases: **intermittent hypoxia**.
- The accumulation of HIF-1 α during intermittent hypoxia accounts for the higher resistance of endothelial cells.
- Recent *in vitro* and *in vivo* studies have shown that intermittent hypoxia could induce **tumour development, angiogenic processes, chemoresistance, and radioresistance**.

Hypoxia and Cancer

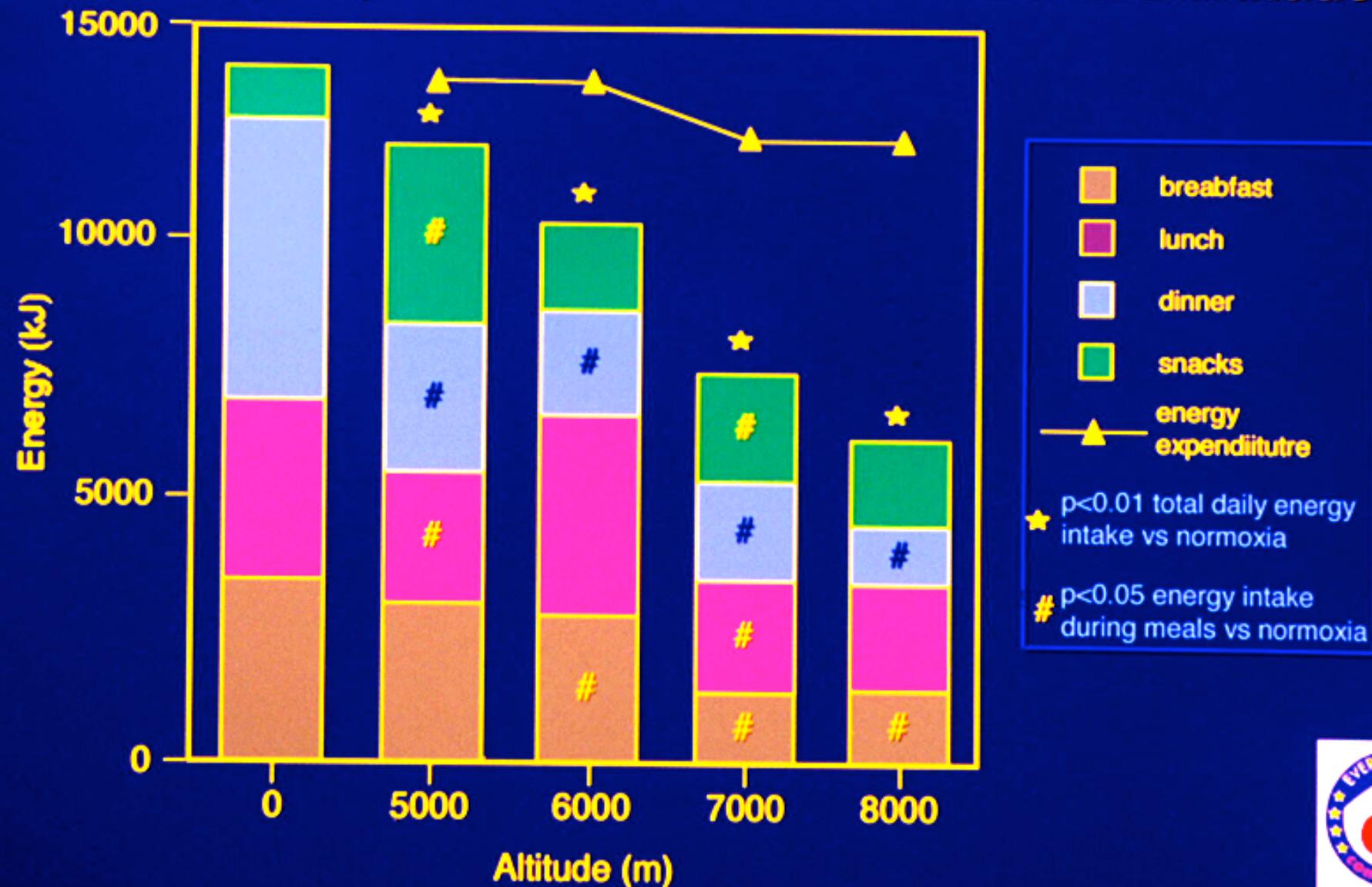


Hypoxia and obesity



Body weight loss after 4 weeks
at the top of Sajama (6542m): 7 kg

Energy intake at different eating occasions and energy expenditure at different simulated altitudes



Hypoxia and obesity

Comparing training in hypoxia (15% O₂) and training in normoxia (3 times/week during 4 weeks at 65% maxVO₂) in 24 + 21 subjects:

- Body composition, QR, lactate at ventilatory threshold: better in the hypoxic group
- Training load lower in the hypoxic group: good for obese patients with orthopedic comorbidity

Wiesner et al., 2009

Hypoxia and obesity

Comparing training in hypoxia (16% O₂) and training in normoxia (3 times/week during 4 weeks at 70-85 % maxHR) in 18 + 14 subjects:

- Lean body mass : +1.4 kg in Hyp group,
- Systolic blood pressure : - 10 mmHg in Hyp group
- VO₂max : + 0.46 l/min in Hyp group

“The stimulus of IHT invoked additive cardioprotective effects”

Bailey et al. MSSE, 2000

Hypoxia and bronchial asthma

- In 93 patients with BA, after IHT (16-12%) during 3-10 min, 5-10 times/day, 15-20 days:
 - 58% very good effects
 - 38% satisfactory effects
 - 4% no effect
 - 6% intolerant
- In 200 children with BA vs sham group:
 - Positive effects in 85% hyp group vs 25% in sham group
 - Effect persisted for 4 months

*Serebrovskaya et al., J Physiol Pharmacol, 2003
Anokhin et al., 1992*

Hypoxia and COPD

- IHT in 550 patients with COPD:
 - Improved respiratory function
 - Improved immunological reactivity
 - Improved VO₂max
 - Normalization of “electrobiological activity of cerebral cortex”

Borukaeva et al., 2007; 2009

Mechanisms evoked to explain the benefit of IHT in respiratory diseases

1. Regulation of respiration: improved chemosensitivity
2. Inhibition of free radical production, improvement of anti-oxydant pathways
3. Improvement of mitochondrial respiration: increased efficiency of O₂ utilization for ATP production, via NO pathways

Serebrovskaya et al., *J Physiol Pharmacol*, 2003

Hypoxia and cardiovascular diseases

“Improvement of myocardial perfusion in coronary patients after intermittent hypobaric hypoxia.”

- Six male SL native patients (aged>53 yrs) with severe stable coronary heart disease.
- 14 sessions of exposure to intermittent hypobaric hypoxia (4200 m)
- Exercise perfusion imaging with technetium 99m
- The mean summed stress score for hypoperfusion, in arbitrary units, decreased from 9.5 to 4.5 after treatment ($P=.036$).

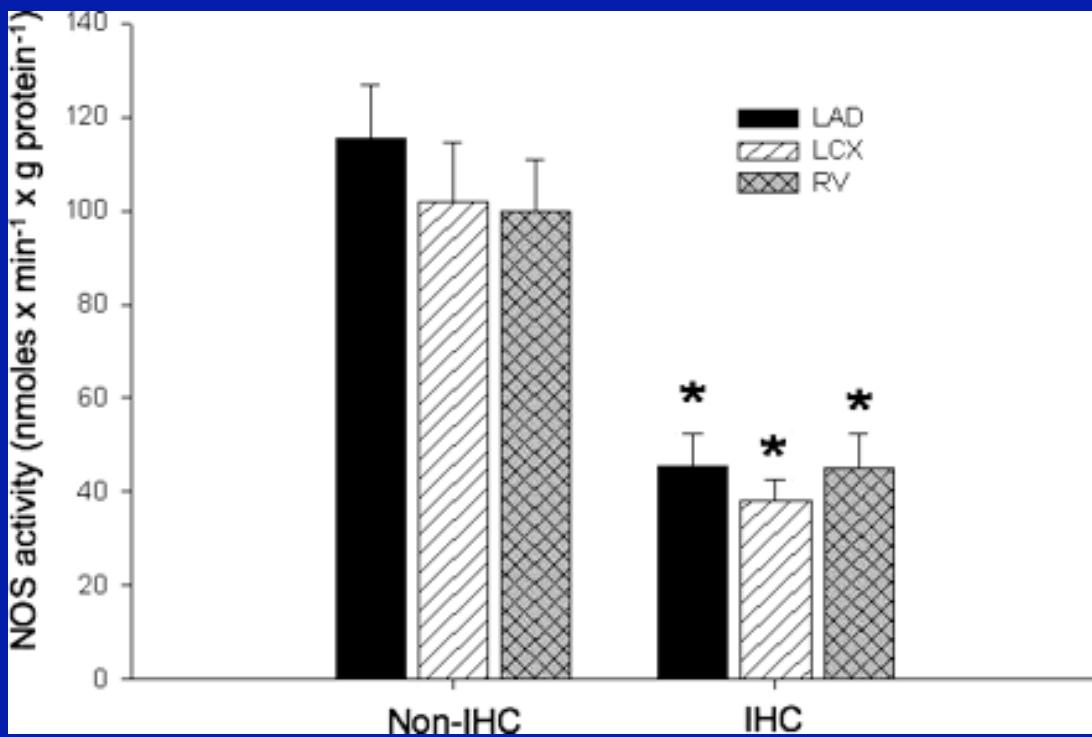
Intermittent hypoxic conditioning

- Intermittent hypoxic conditioning produces robust cardioprotection against infarction and lethal arrhythmias in a canine model of coronary occlusion-reperfusion: reduction in the myocardial infarct size (Zong et al., Exp Biol Med, 2004)
- ***NO formation:***
 - **If moderate:** beneficial, through relaxation of smooth muscle, suppression of platelet aggregation, decrease of fibrinogen formation
 - **If excessive:** activation of pro-apoptotic transcription factors, inhibition of metabolic enzymes, necrosis, apoptosis

Intermittent hypoxic conditioning

Dogs: FIO₂: 10%, 5-10 min hypoxia/cycle, 5-8 cycles/day, 20 days

Attenuation of the NOS/NO system may contribute to IHC-induced protection of myocardium from ischemia-reperfusion injury.



IHC suppressed nitric oxide synthase activities in left and right ventricular myocardium.

Ryou et al., *Exp Biol Med*, 2008

Hypoxia and chronic heart failure

- Clinical study at Montefiore Medical Center (Bronx, USA)
- Patients with chronic heart failure
- 3-4 hours/day, 3 days/week, 3 weeks
- Approved by FDA....



Conclusion

- Exposure to hypoxia might be beneficial or detrimental, depending on many factors including the modalities of exposure
- Intermittent exposure to hypoxia seems to be beneficial in some respiratory and cardiac diseases
- Further studies are needed, with control groups carefully selected, before any systematic use of hypoxia in human diseases.