

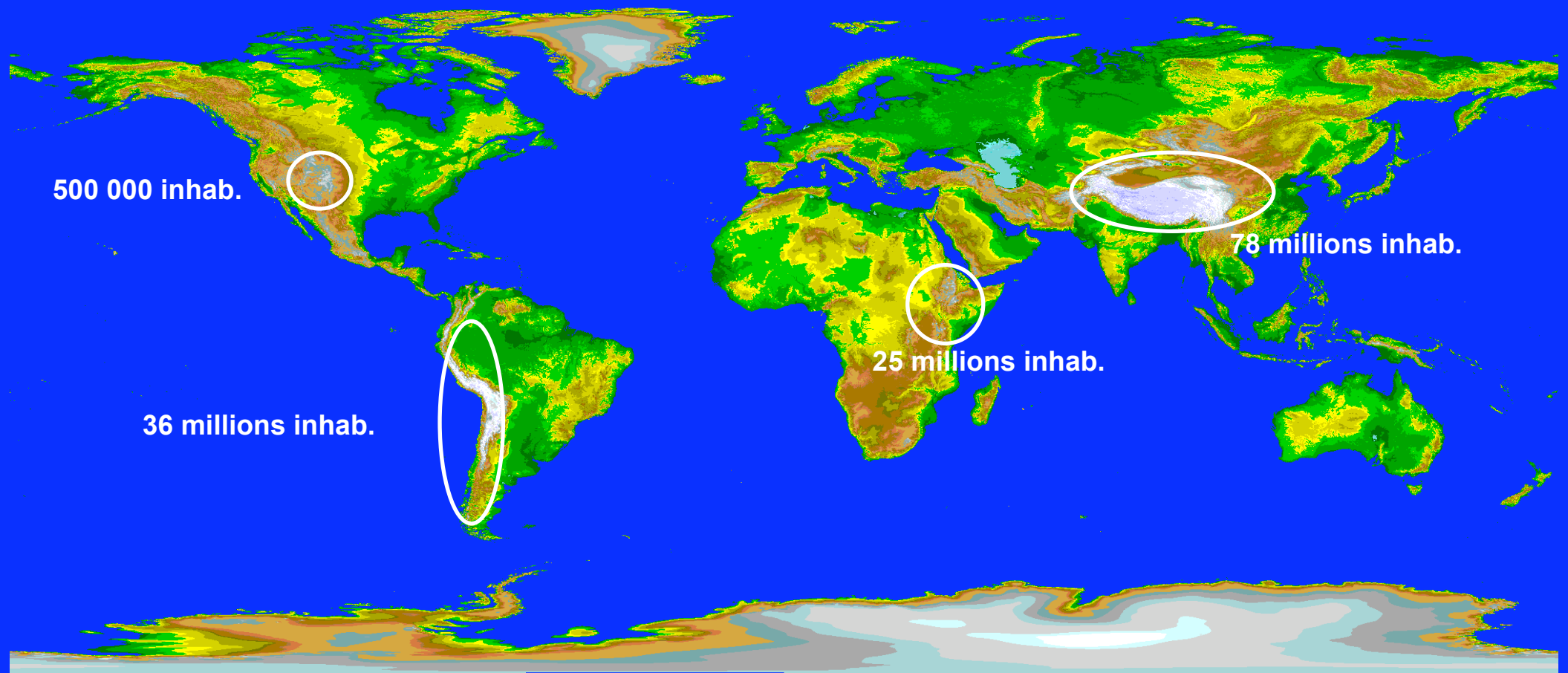


Monge's disease

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140 million persons live permanently above 2500m of altitude

Moore LG et al. 1998 and WHO

Context



Monge's disease or Chronic Mountain Sickness is an excessive **polycythemia**:

males : Hb > 21 g/dl

females: Hb > 19 g/dl

In some cases associated with **pulmonary hypertension**.

Mainly males and post-menopausal women

Hurtado, 1964; Spielvogel et al., 1981

Monge C., 1966; Monge et al., 1989

Leon Velarde, 1993

Juan tiene 27 años y MMC



CMS clinical aspects

Symptoms:

headache, dizziness, paresthesia
somnolence, fatigue, insomnia, tinnitus
difficulty in concentration, loss of mental acuity
irritability, depression
dyspnea on exertion, poor exercise tolerance
« burning feet or hands »

Signs:

cyanosis, black lips
clubbed fingers
congestion of conjunctives

The CMS score

Breathlessness and/or palpitations

- 0 No breathlessness / palpitations
- 1 Mild breathlessness / palpitations
- 2 Moderate breathlessness / palpitations
- 3 Severe breathlessness / palpitations

Sleep disturbance

- 0 Sleep as well as usual
- 1 Did not sleep as well as usual
- 2 Woke many times, poor night's sleep
- 3 Could not sleep at all

Cyanosis

- 0 No cyanosis
- 1 Mild cyanosis
- 2 Moderate cyanosis
- 3 Severe cyanosis

Dilatation of veins

- 0 No dilatation of veins
- 1 Mild dilatation of veins
- 2 Moderate dilatation of veins
- 3 Severe dilatation of veins

Paresthesia

- 0 Paresthesia
- 1 Mild paresthesia
- 2 Moderate paresthesia
- 3 Severe paresthesia

Headache

- 0 No headache
- 1 Mild headache symptoms
- 2 Moderate headache
- 3 Severe headache, incapacitating

Tinnitus

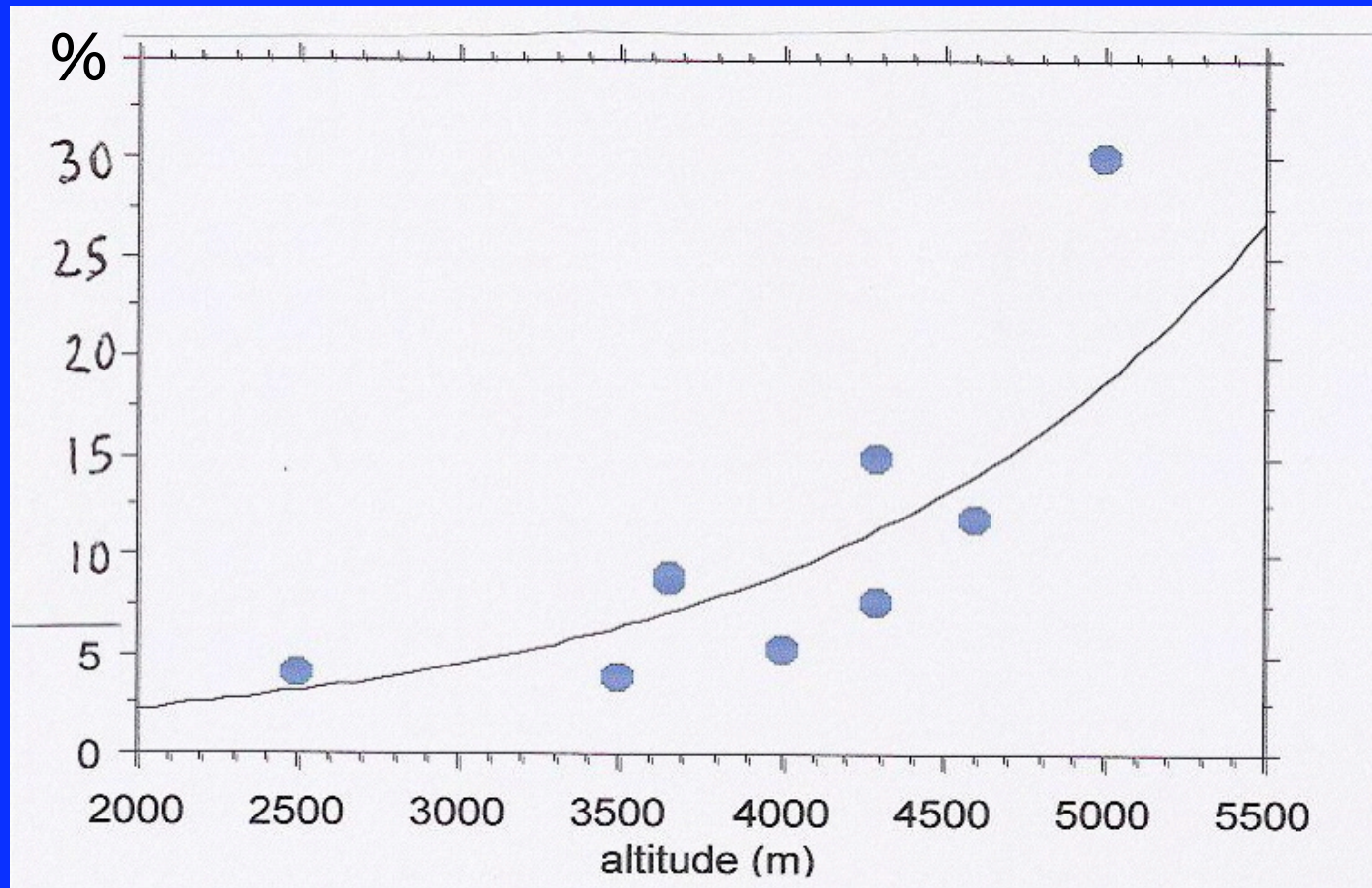
- 0 No tinnitus
- 1 Mild tinnitus
- 2 Moderate tinnitus
- 3 Severe tinnitus

Hb

Males:	< 21 g/dl	score = 0
	≥ 21g/dl	score = 3
Females:	< 19g/dl	score = 0
	≥19g/dl	score = 3

According to the sum of points given for each symptom and the Hb, CMS is defined as:

Absent	score = 0 – 5
Mild	score = 6 – 10
Moderate	score = 11 – 14
Severe	score > 15

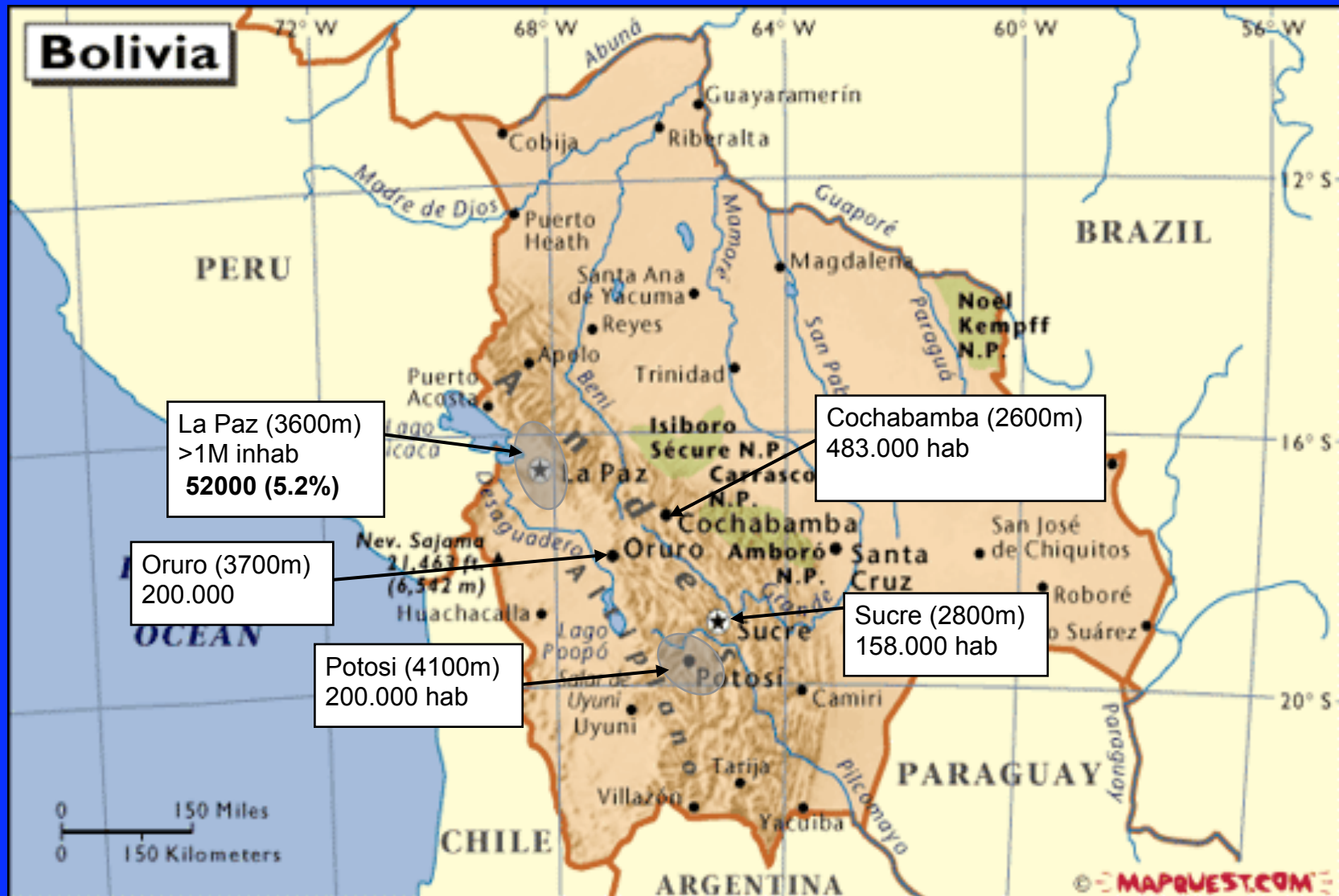


The prevalence of CMS is correlated to the altitude of residency following a hyperbolic regression $Y = e^{-0.651 + 0.001 \times X}$.
Data from Moore (1998), Léon-Velarde (1994), Spielvogel (1981), Wu (1998), Chao (1996), Pei (1989), Heath and Williams (1995).

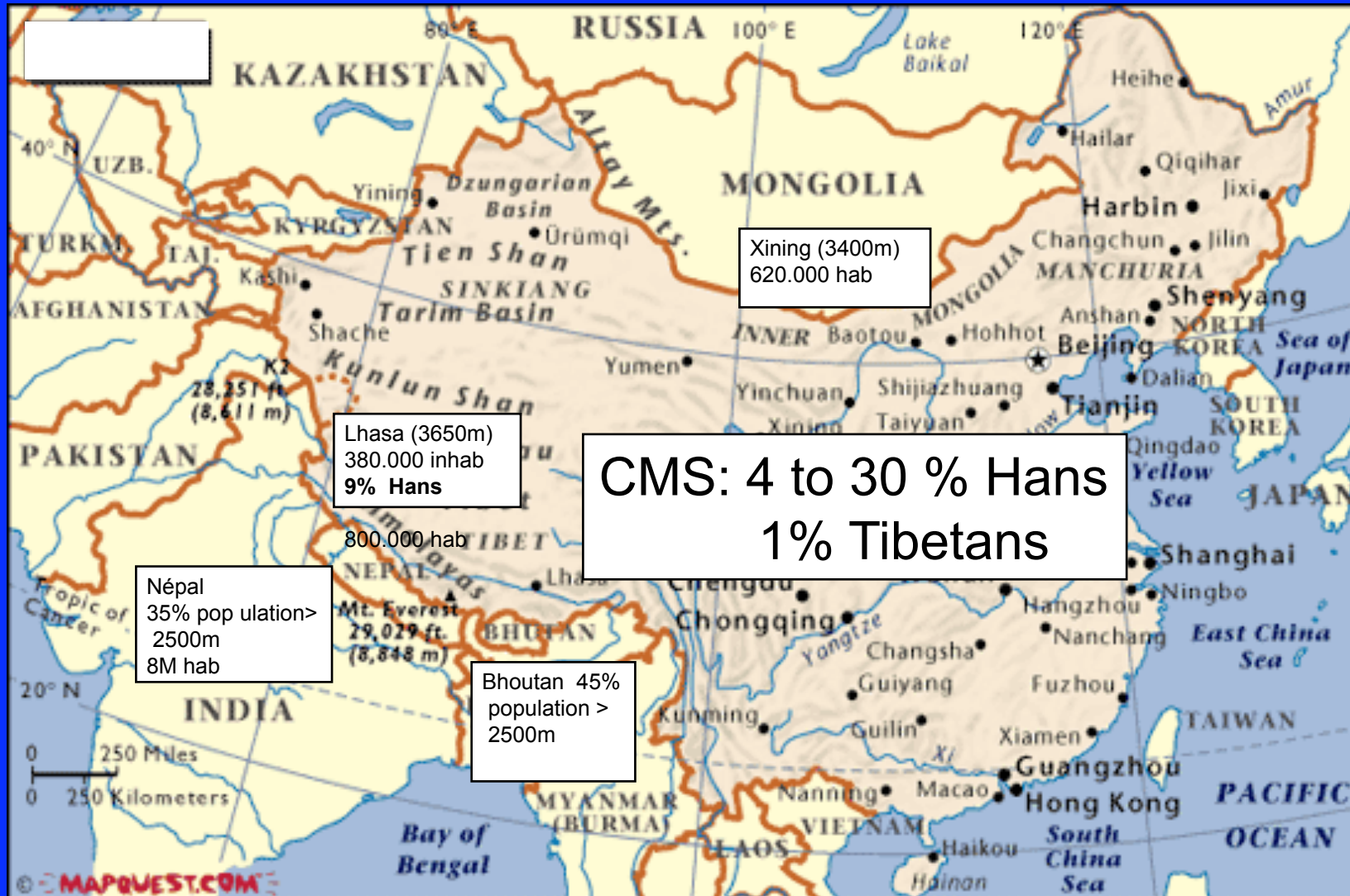
CMS in PERU



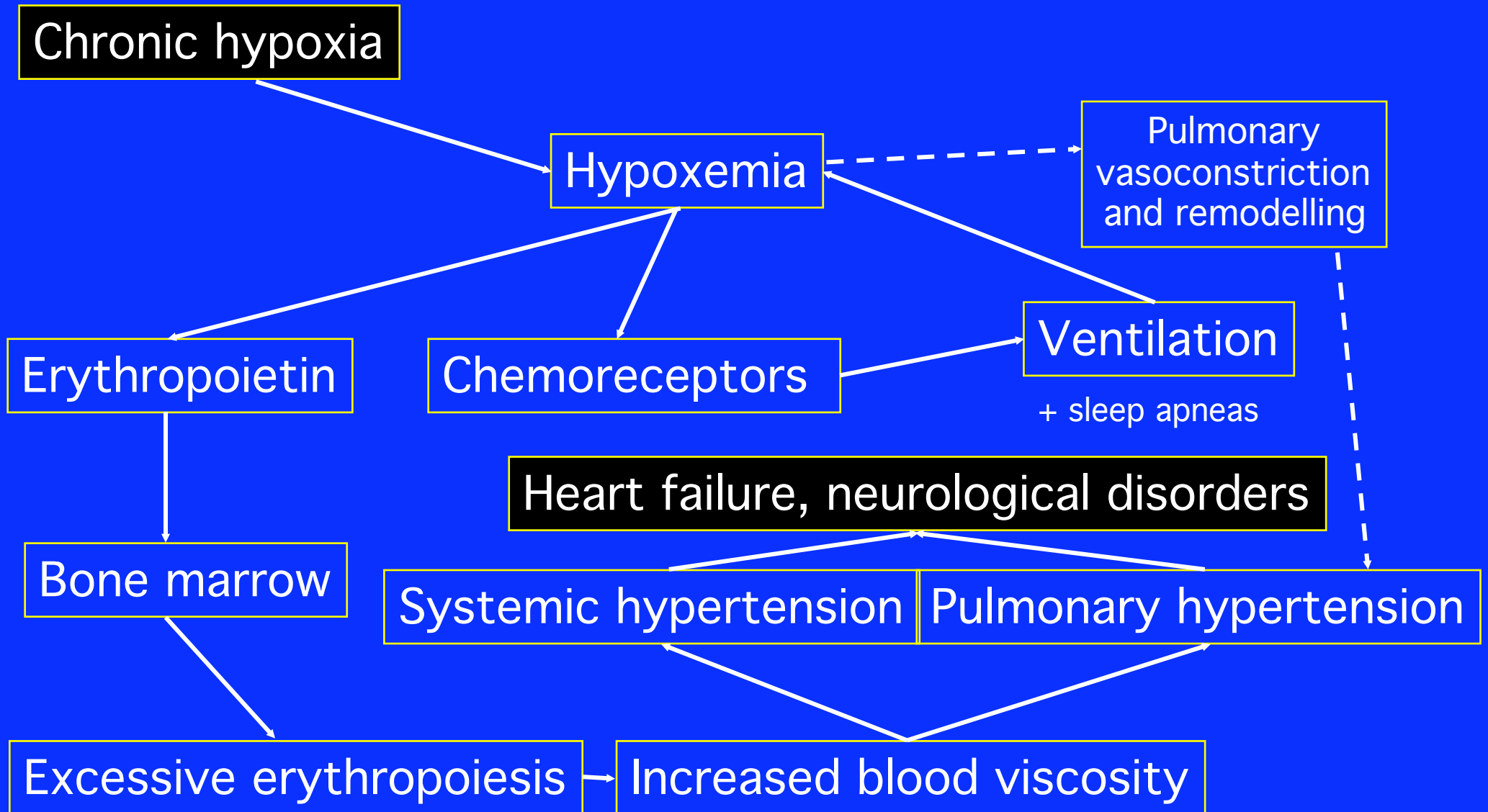
CMS in BOLIVIA



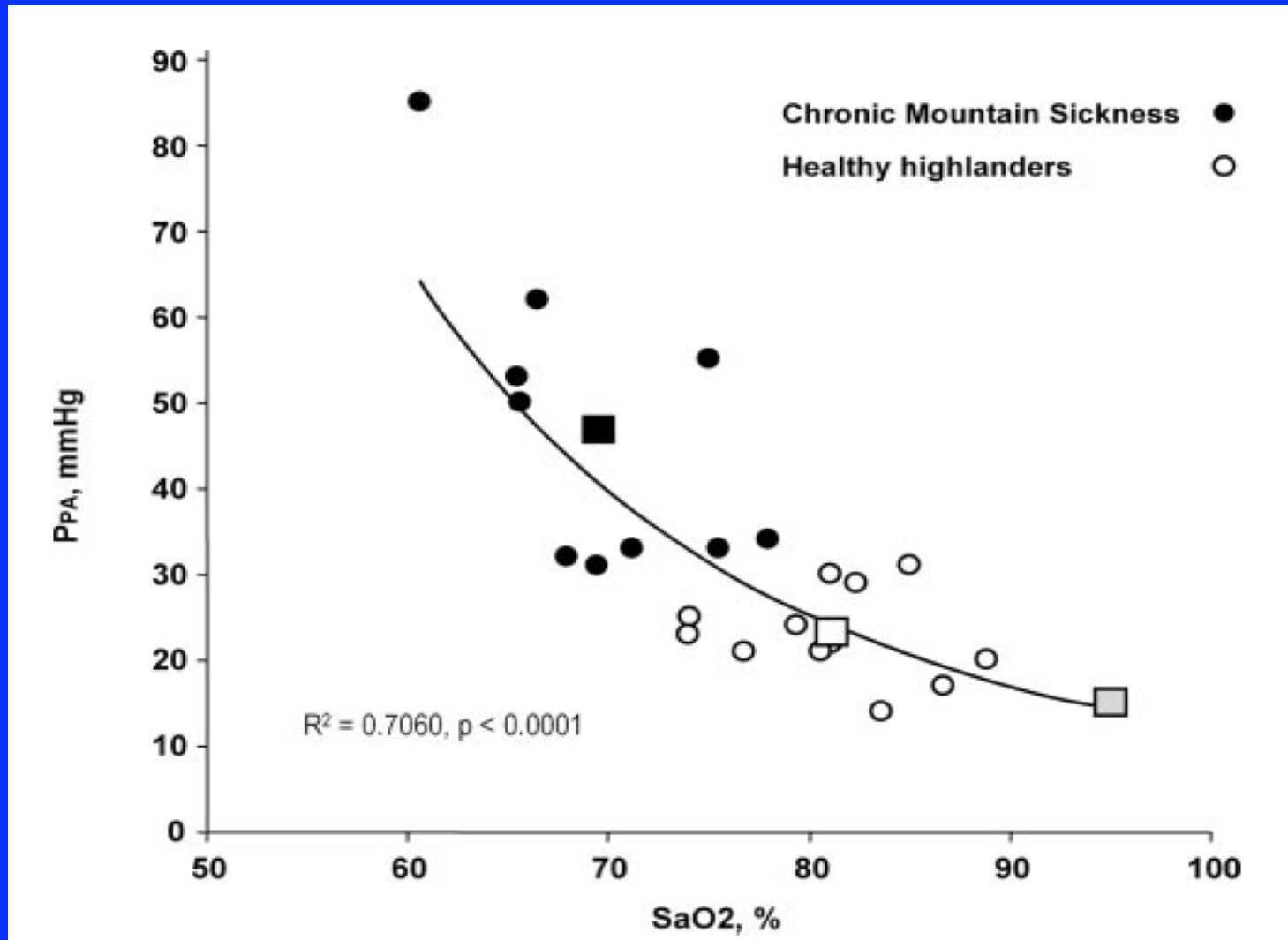
CMS in ASIA



Pathophysiology of CMS



Variation of pulmonary artery pressure with SaO₂ at altitude of residence



From Penalzoza et al., 2007

Treatments of CMS

- Displacement to lower altitudes
 - Familial and socio-economical negative consequences
- Blood letting
 - With or without isovolemic hemodilution
 - Reduces Ht, increases PaO₂
 - But transient effects (several days or weeks ?)
 - No controlled studies (Monge et al., 1966; Cruz et al., 1979; Manier et al., 1988; etc.)

Treatments of CMS

- To decrease erythropoiesis
 - ACE inhibitors (enalapril, 5mg/day for 2 years), by increasing renal blood flow and reducing renal O₂ consumption (COMGAN study, Bolivia, Lancet 2002): reduction of Ht by 6.7%
 - Methylxanthines (theophylline, pentoxifylline), by decreasing cAMP and EPO (no clinical studies)
- Traditional medicine...
 - No controlled studies, toxic effects ?

Treatments of CMS

- To increase ventilation
 - medroxyprogesterone: no controlled studies, decreases Ht to normal, but side effects for males (Kryger et al., 1978)
 - almitrine (4 weeks, 1 mg/kg/day): decreases Ht by 3.5%, no effect on PaO₂ (Villena et al., 1985)
 - dopamine inhibitor, domperidone: increase HVR but no clinical study on Ht (Gamboa et al., 2003; Leon-Velarde et al., 2003):

Treatments of CMS

Acetazolamide (carbonic anhydrase inhibitor):

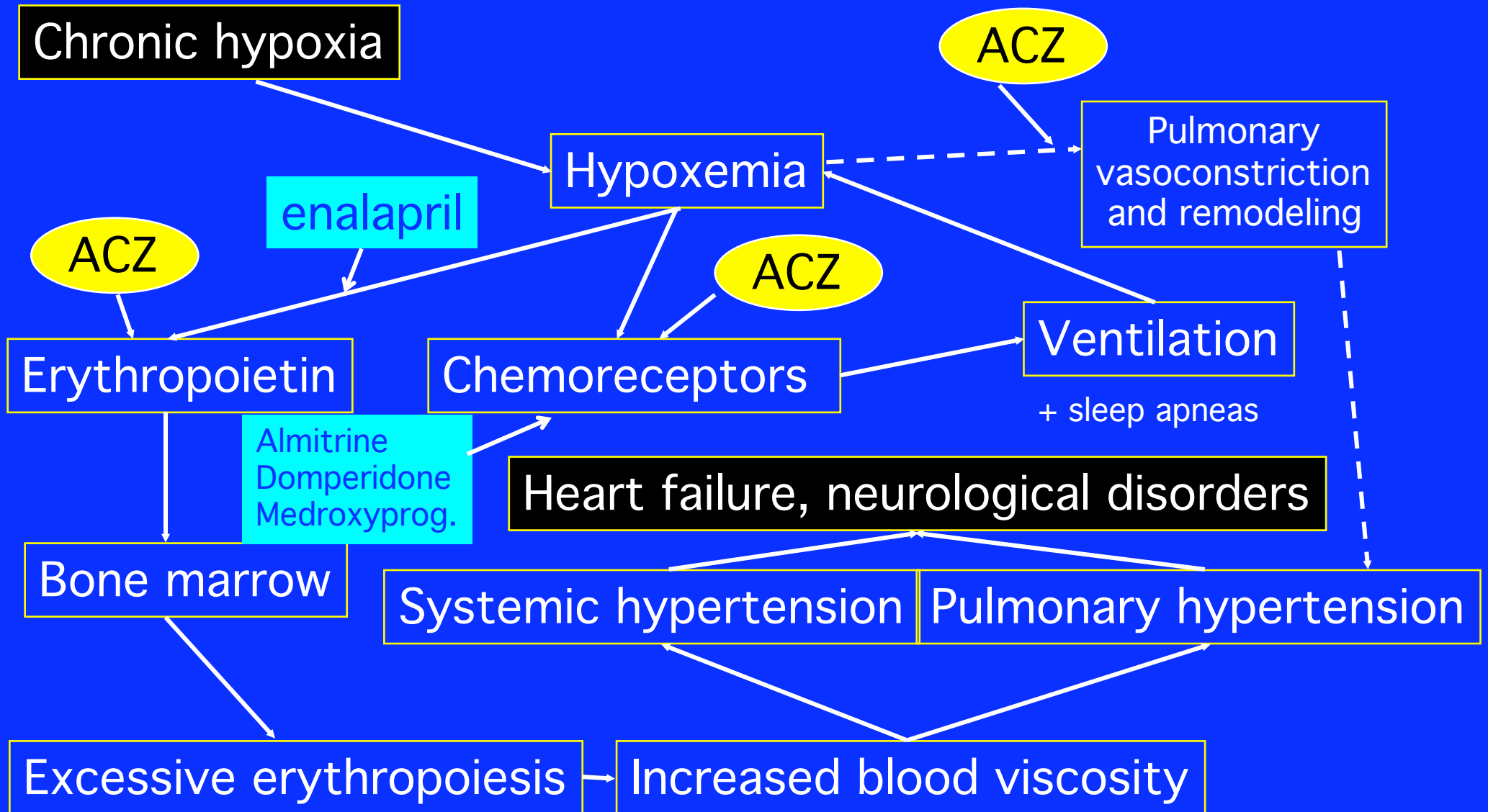
- by inducing a metabolic acidosis and increasing ventilation
- by a direct effect on Epo renal production
- by reducing pulmonary hypertension and ameliorating gas exchange

Richalet et al., *AJRCCM*, 2005; Richalet et al., *AJRCCM*, 2008

Rivera-Ch et al., *Respir Physiol Neurobiol* 2008

Maignan et al., *Chest*, 2008

Pathophysiology of CMS



Study I. Population studied

- 10 CMS patients treated by placebo (PLA, 44 ± 9 yrs)
- 10 CMS patients treated by 250 mg ACZ daily (D250, 43 ± 9 yrs).
- 10 CMS patients treated by 500 mg ACZ daily (D500, 41 ± 6 yrs).
- 10 normal subjects with a hematocrit ≤ 55% (CON, 39 ± 9 yrs)

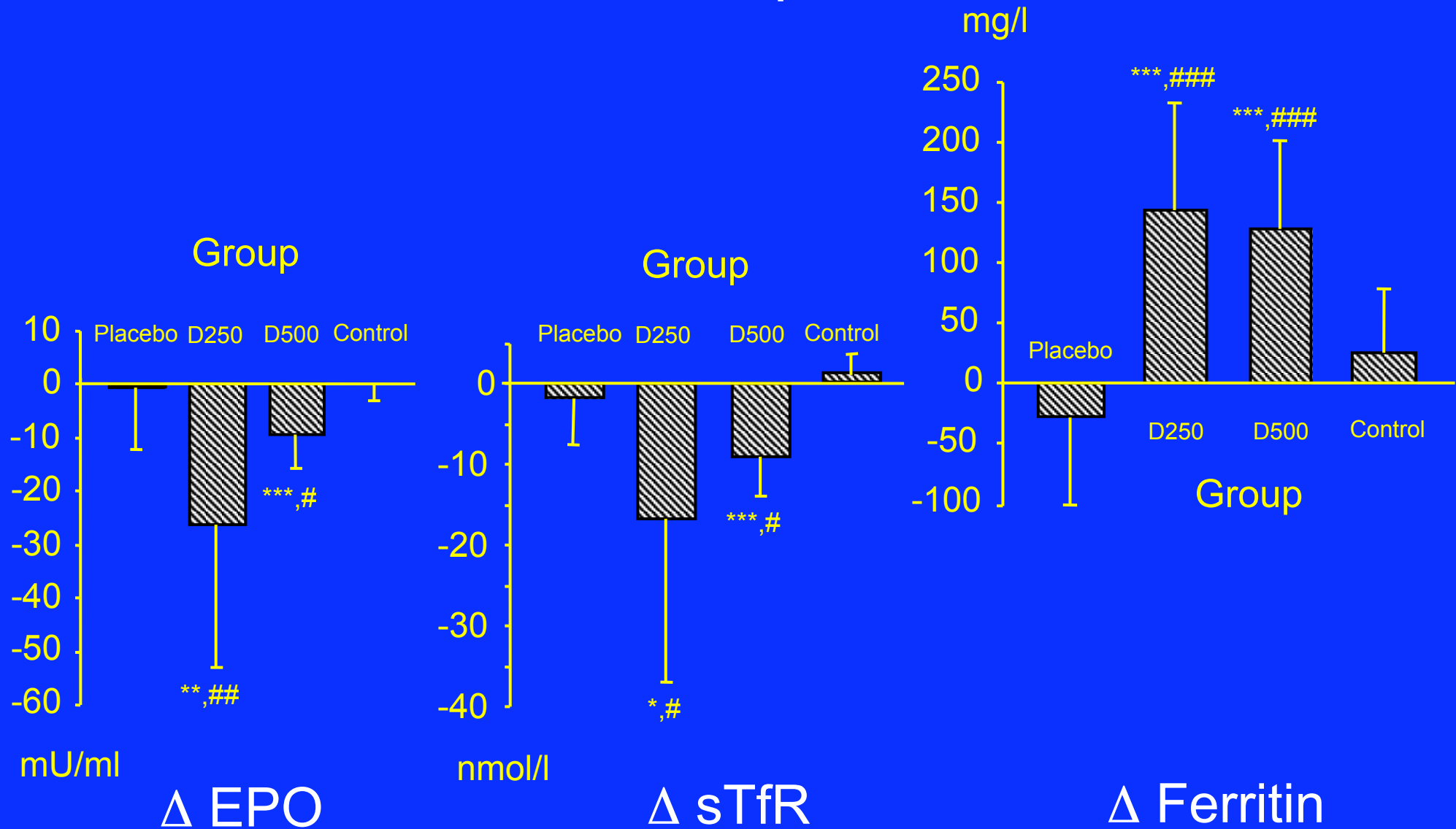
Treatment for 3 weeks

All measurements were made at the *Instituto de Investigacion de Altura* (Cerro de Pasco, 4,300 m)

Characteristics of the CMS population

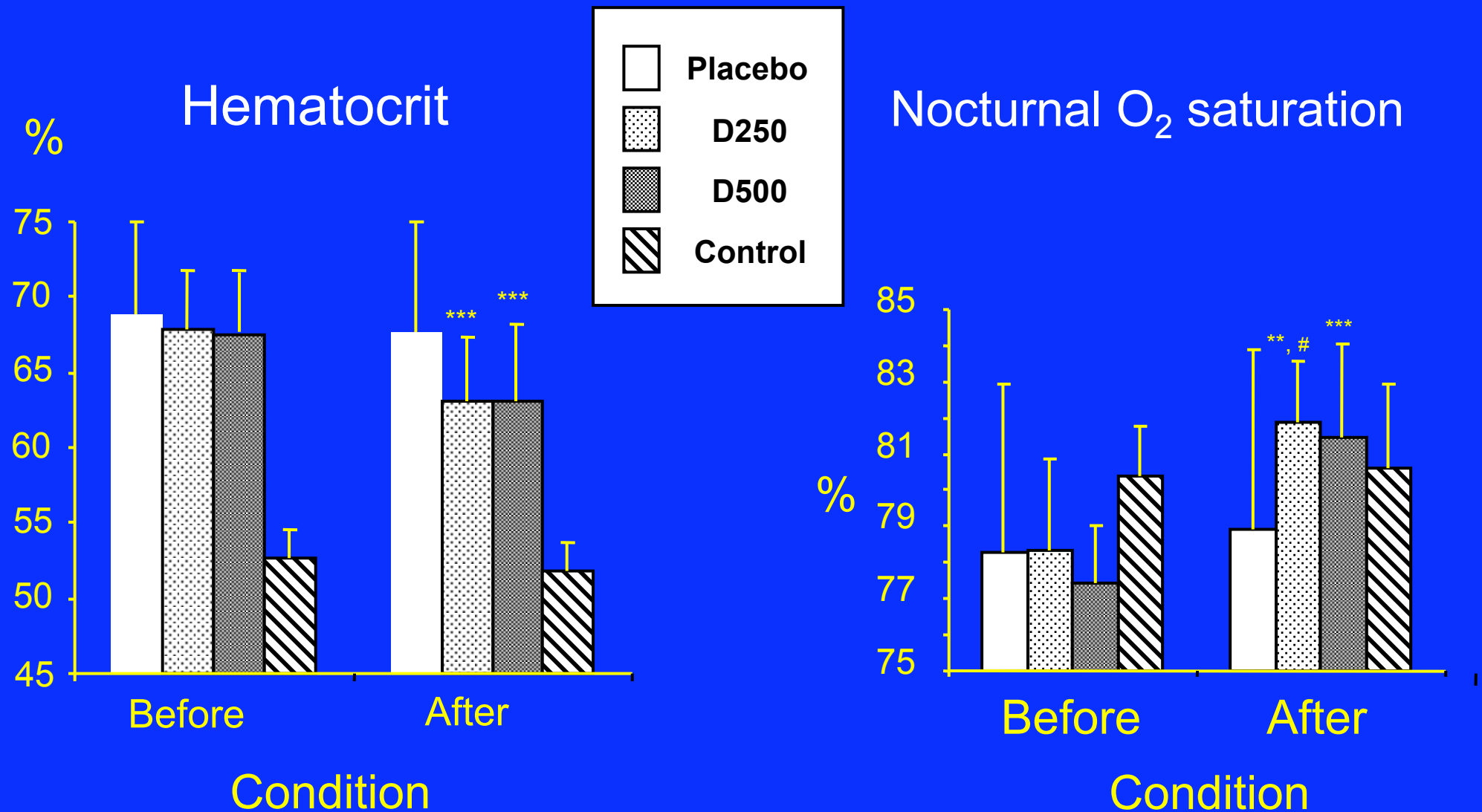
	Hematocrit (%)	Erythropoietin (mU/ml)	Ferritin (μ g/l)	Sol. transferrin receptors (nmole/l)
CMS patients (<i>n</i> =28)	68.1 \pm 4.8 (60 - 78)	26.4 \pm 21.5 (5.1 - 102.7)	120 \pm 107 (5 - 434)	38.1 \pm 17.1 (11 - 85)
Control group (<i>n</i> =10)	52.7 \pm 1.8 (49 - 55)	11.1 \pm 2.5 (7.3 - 14.7)	101 \pm 53 (18 - 168)	21.9 \pm 4.7 (15 - 28)
<i>P</i>	<0.001	<0.02	n.s.	<0.005

Effects of ACZ on hematopoiesis



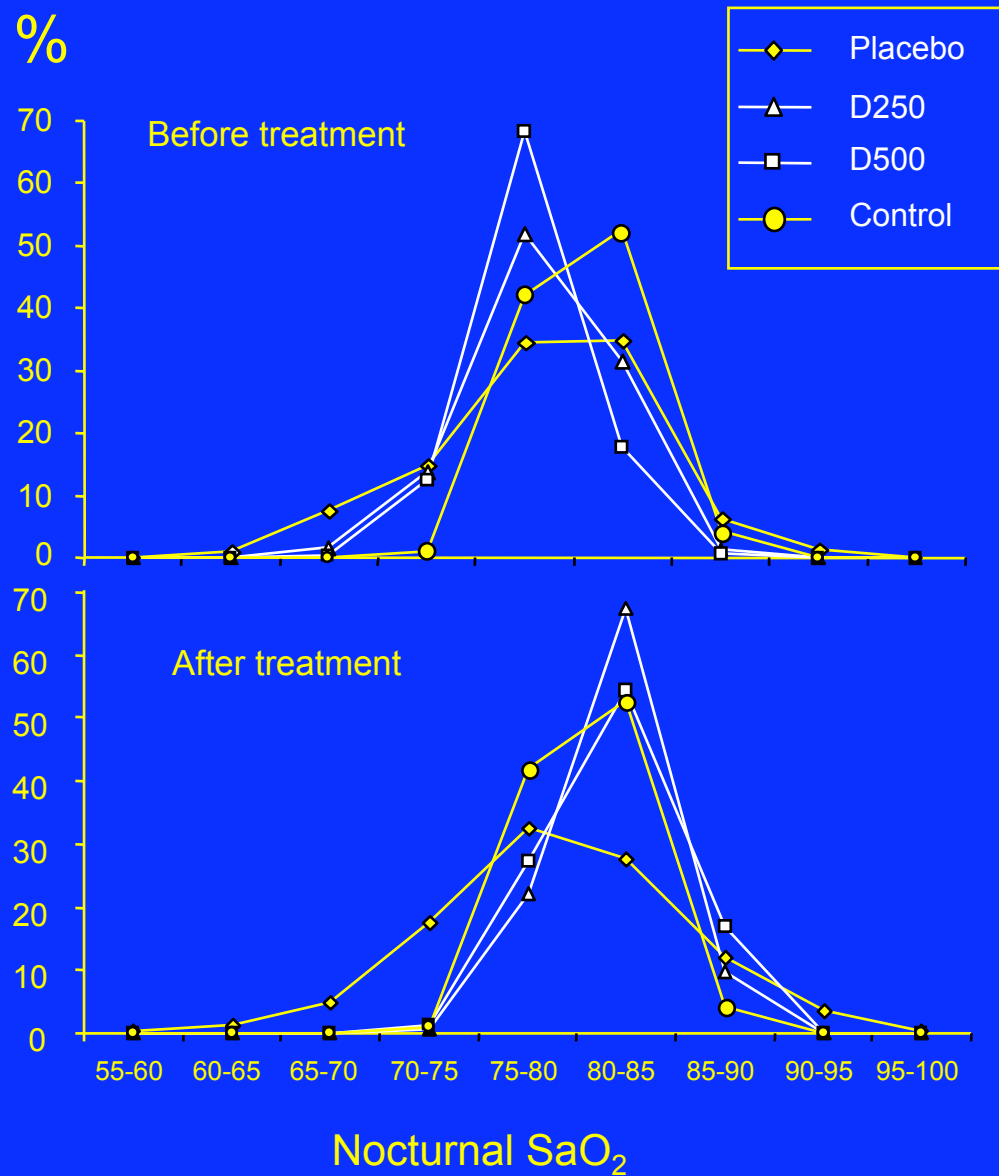
*, **, ***, $P < 0.05$, $P < 0.01$, $P < 0.001$ after vs before treatment. #, ##, ###, $P < 0.05$, $P < 0.01$, $P < 0.001$ vs Placebo

ACZ decreases hematocrit thanks to an increase in SaO₂



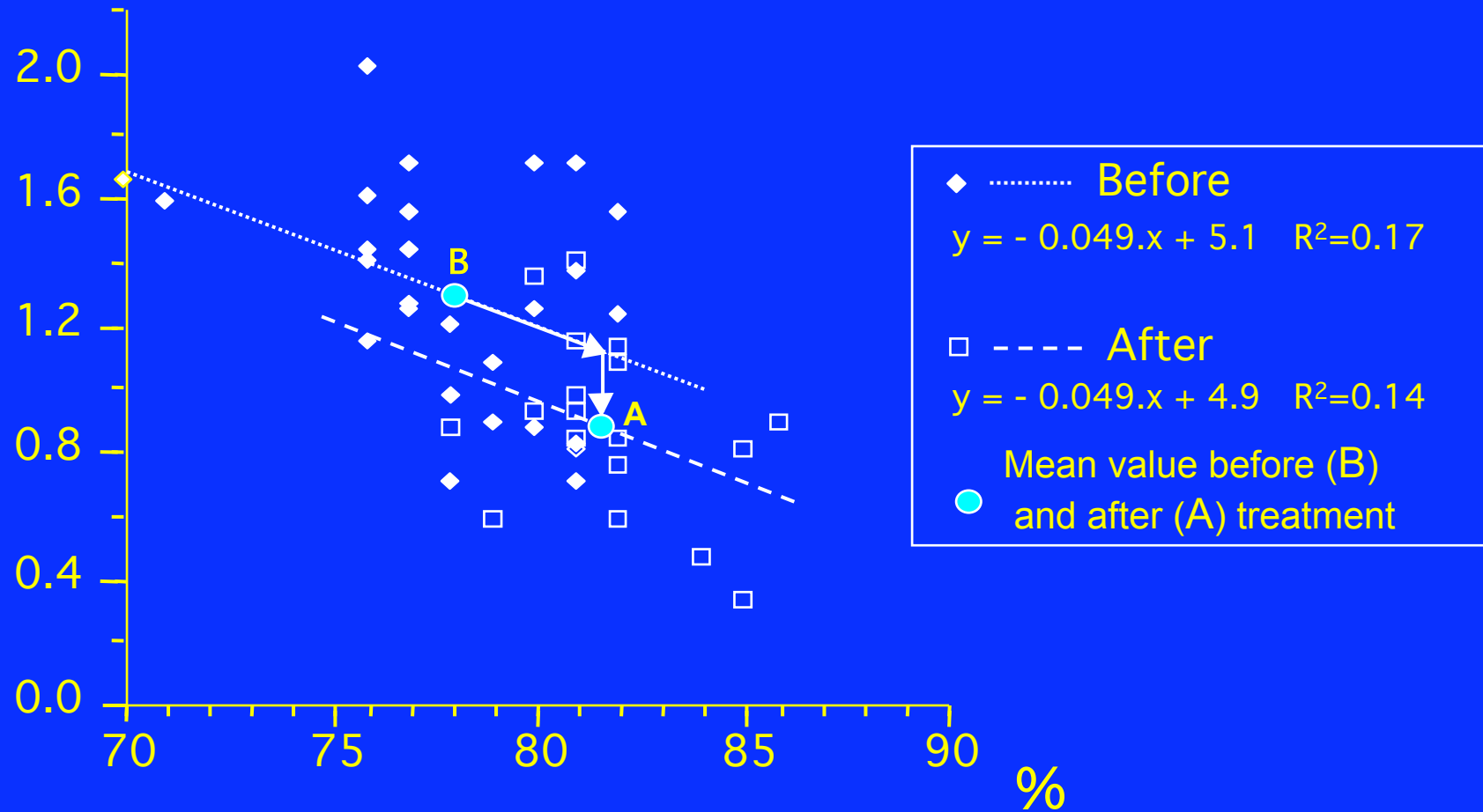
** , *** , $P < 0.01$ and $P < 0.001$ after versus before treatment

Frequency distribution of nocturnal SaO₂



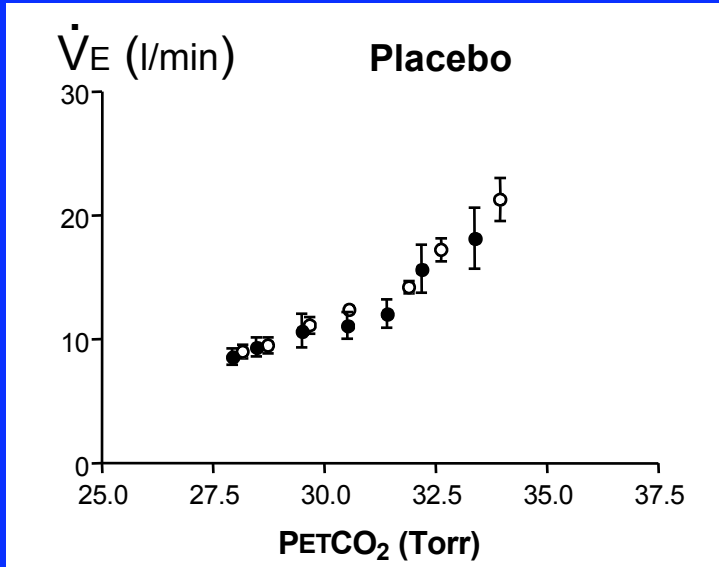
Dual effect of acetazolamide

log EPO

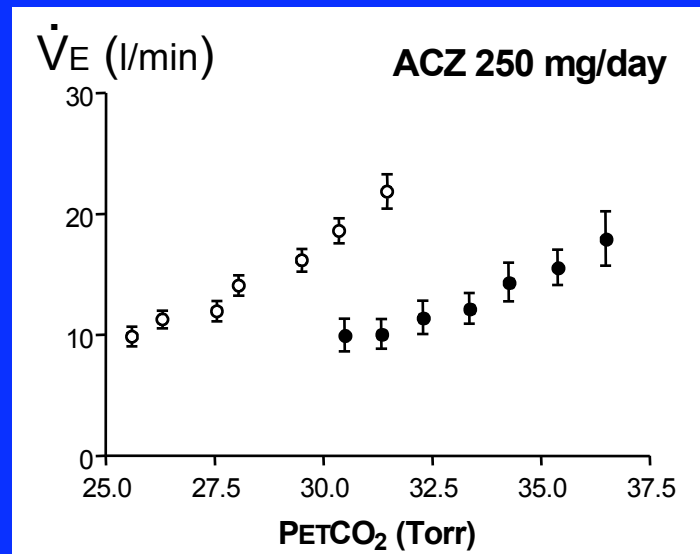
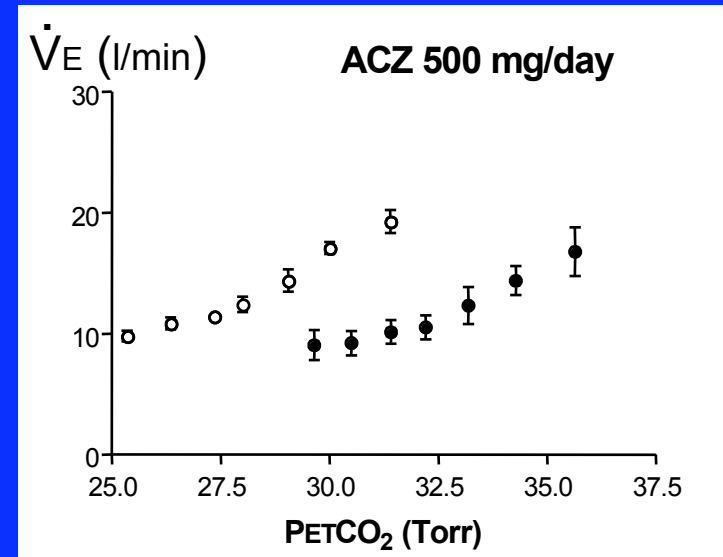


Nocturnal SaO₂

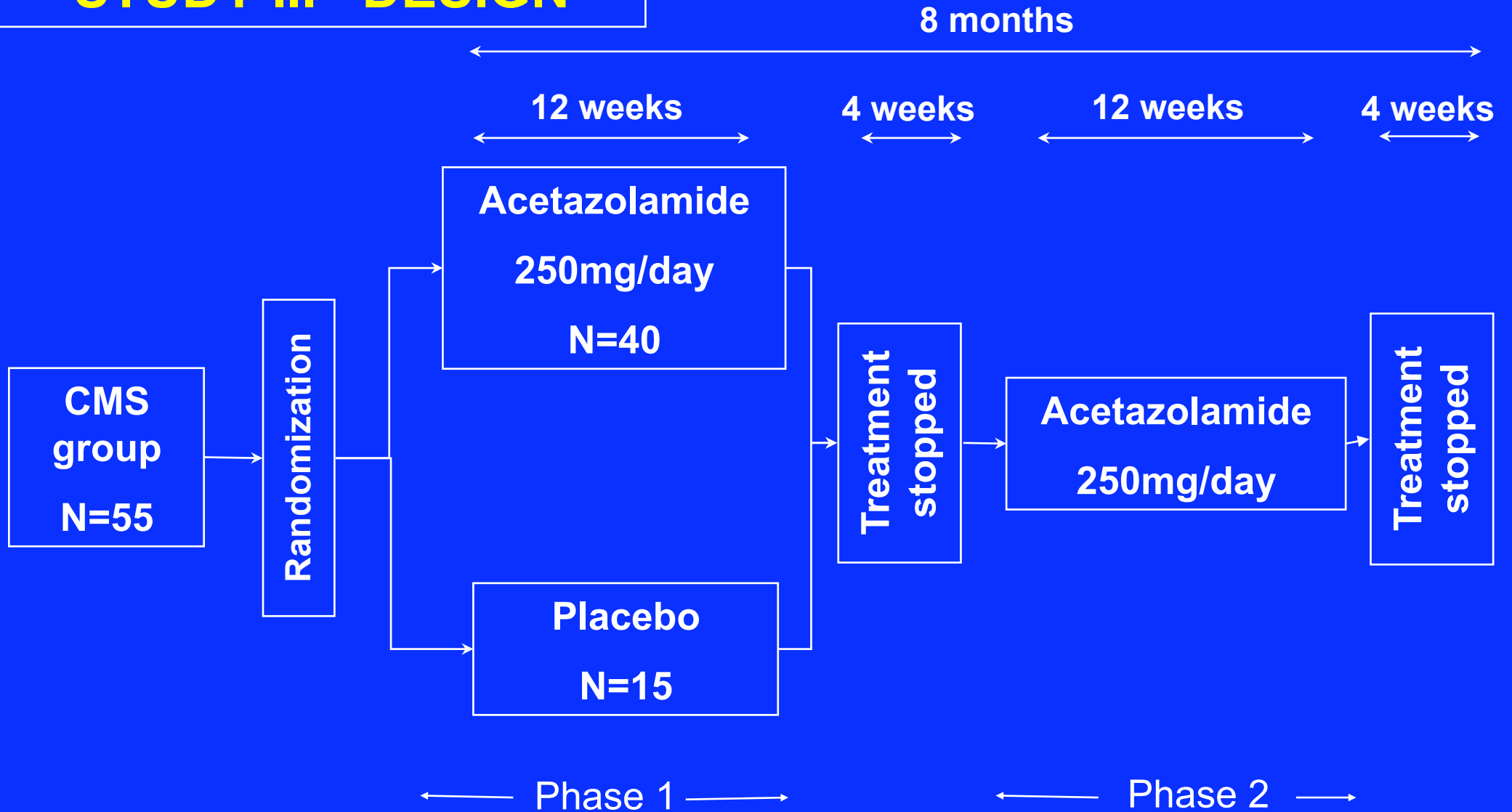
Acute ventilatory response to CO₂ in CMS



● Pre-ACZ
○ Post-ACZ

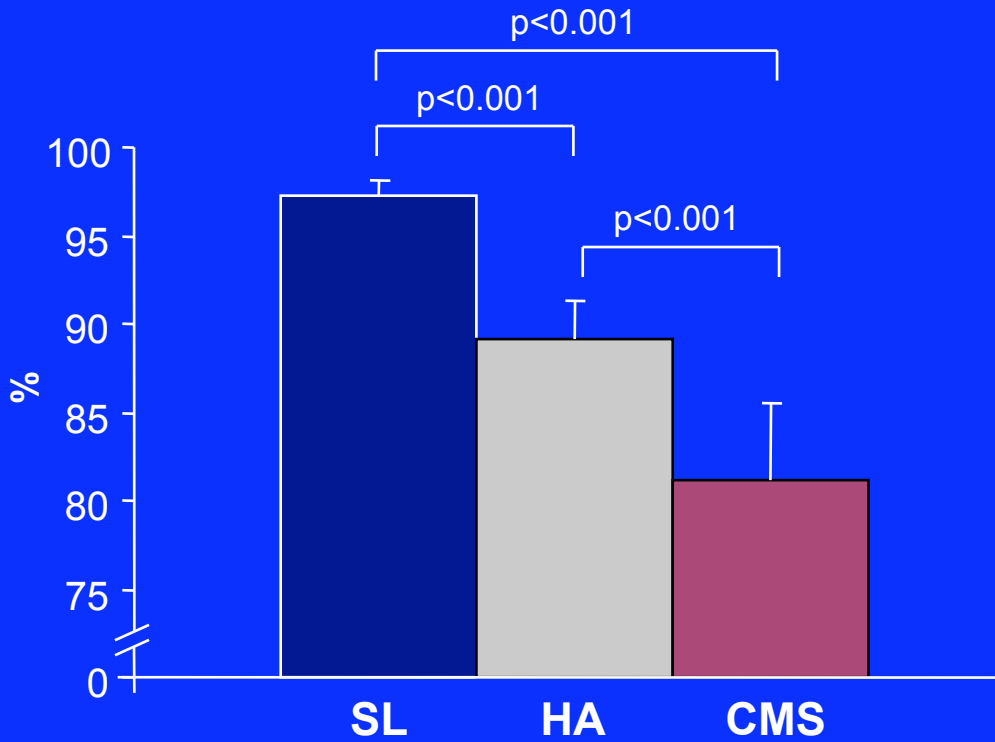


STUDY II. DESIGN

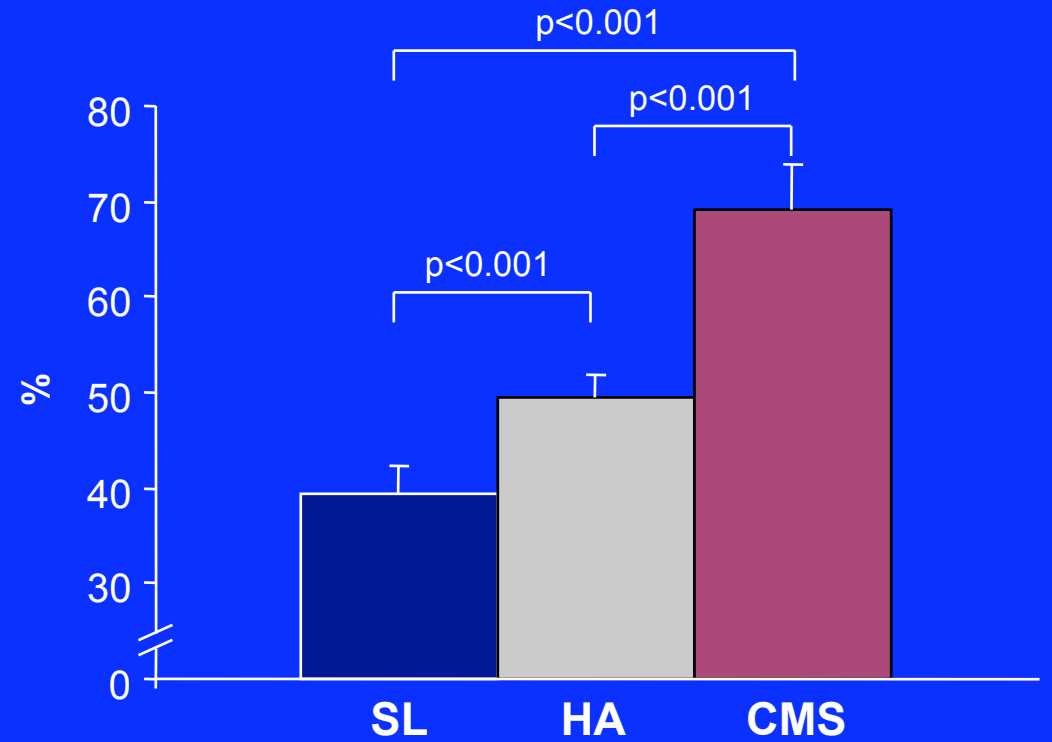


CMS: Chronic Mountain Sickness

Baseline characteristics



SaO₂



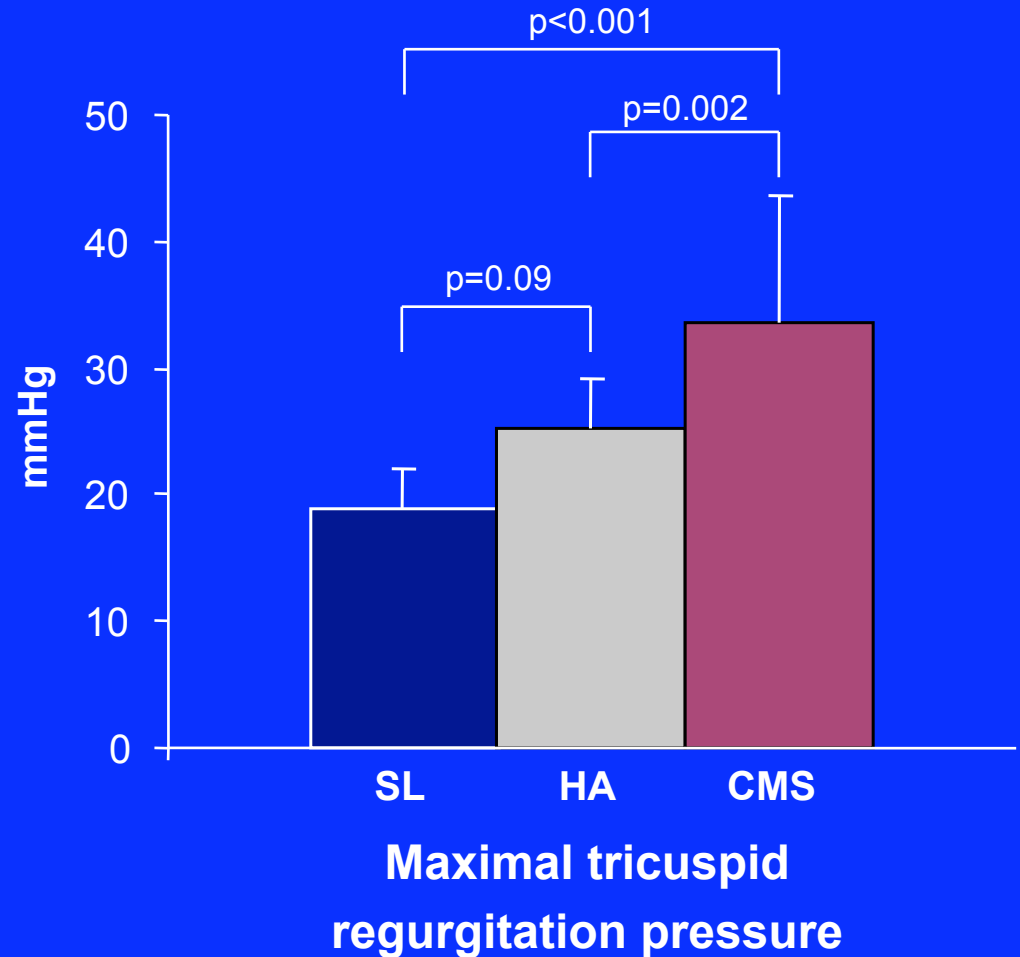
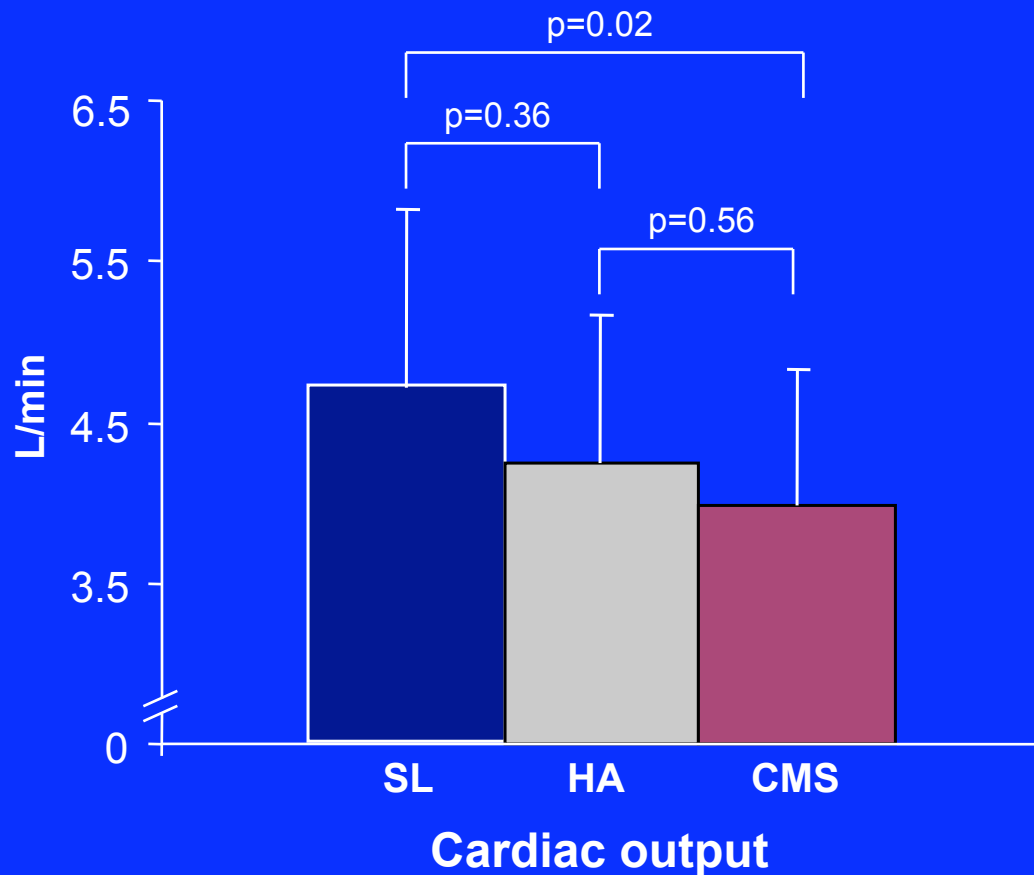
Hematocrit

SL: Sea level control group (N=15)

HA: High altitude control group (N=15)

CMS: Patient group (N=55)

Baseline echographic characteristics

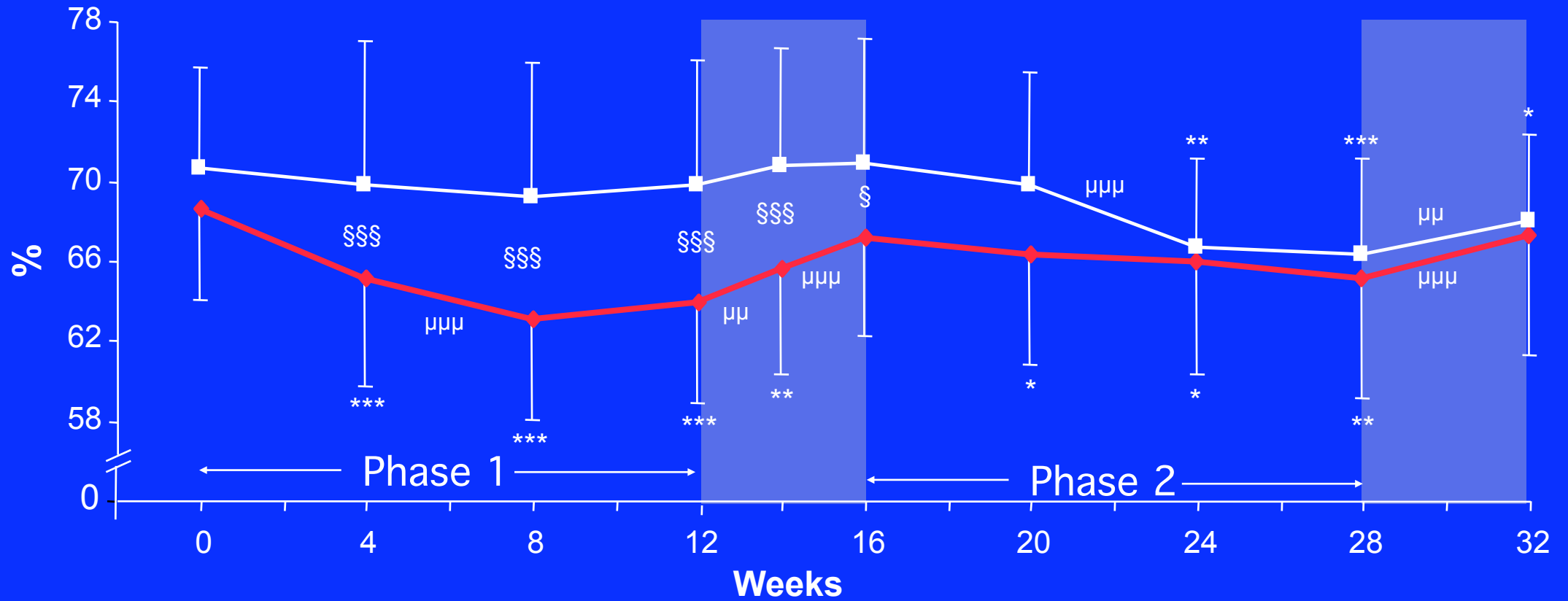


SL: Sea level control group (N=15)
HA: High altitude control group (N=15)
CMS: Patient group (N=55)

Maignan et al., Chest 2008

Hematocrit

—◆— acetazolamide / acetazolamide
 —■— placebo / acetazolamide



☐ : : phases without treatment

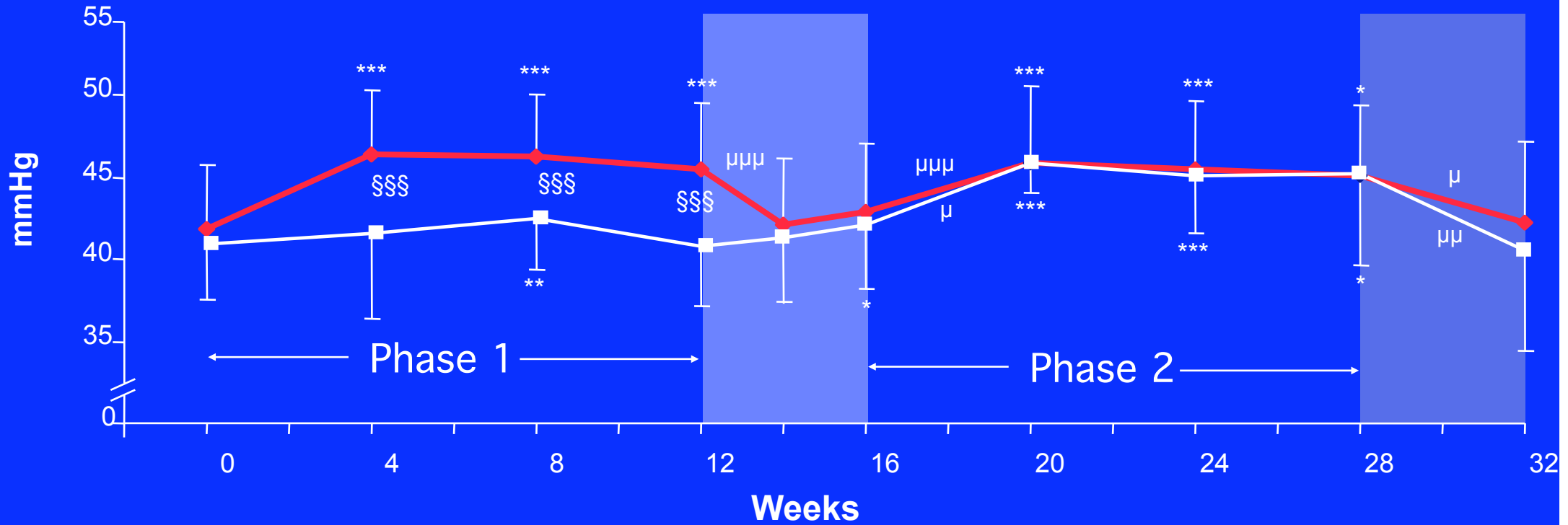
*** / ** / * : p<0.001 / p<0.01 / p<0.05 , when compared to baseline, in the same group

§§§ / § : p<0.001 / p<0.05, when compared between groups at the same time

μμμ / μμ : p<0.001 / p<0.01, when compared variation between the two proximate values, in the same group

PaO₂

—◆— acetazolamide / acetazolamide
 —■— placebo / acetazolamide



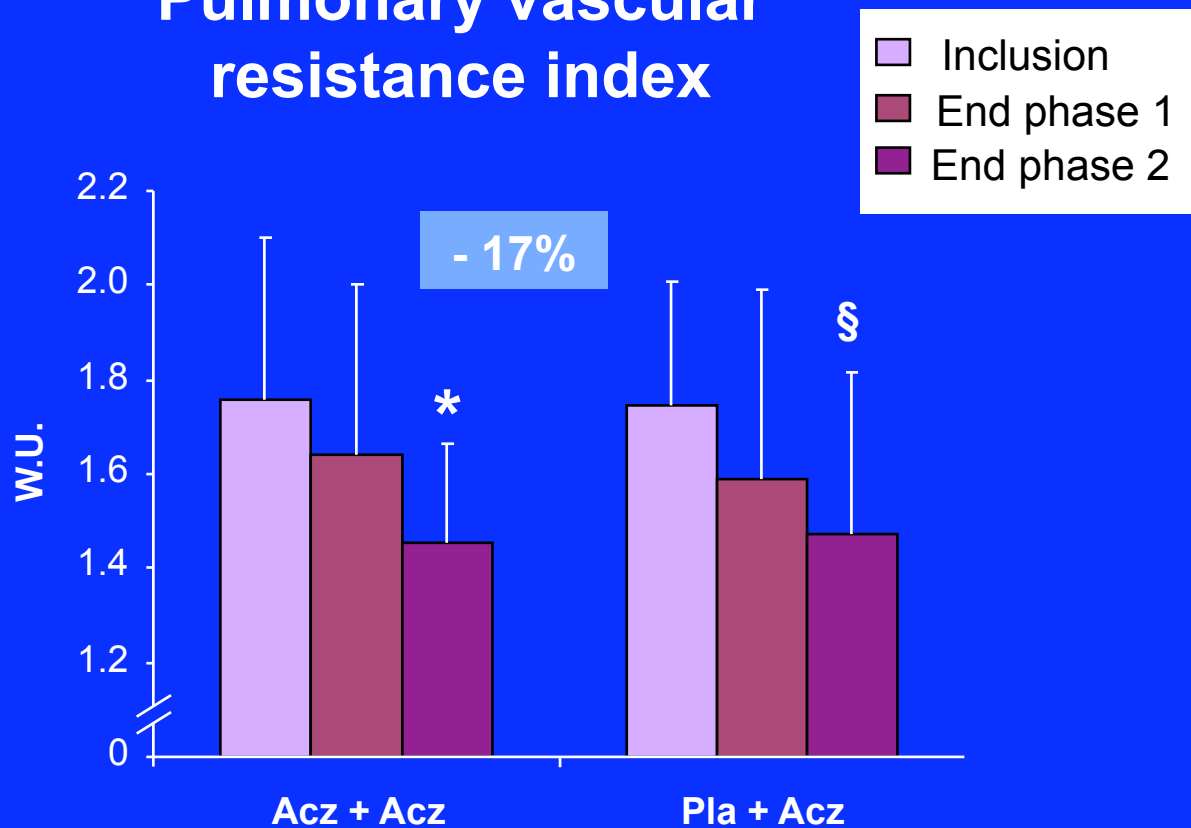
■ : : phases without treatment

*** / ** / * : p<0.001 / p<0.01 / p<0.05, when compared to baseline, in the same group

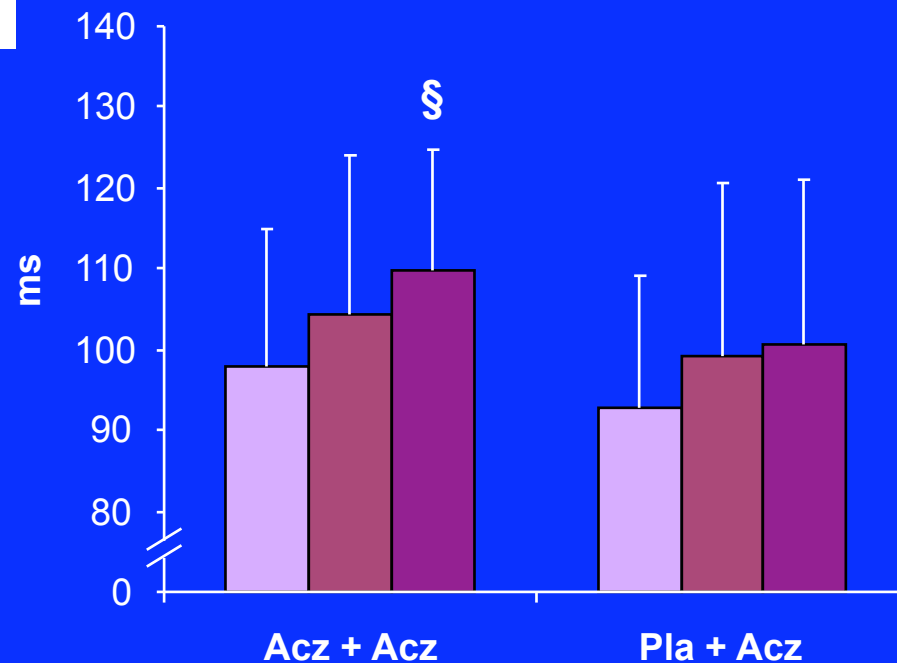
§§§ : p<0.001 when compared between groups at the same time

μμμ / μμ / μ : p<0.001 / p<0.01 / p<0.05, when compared variation between the two proximate values, in the same group

Pulmonary vascular resistance index



Pulmonary acceleration time



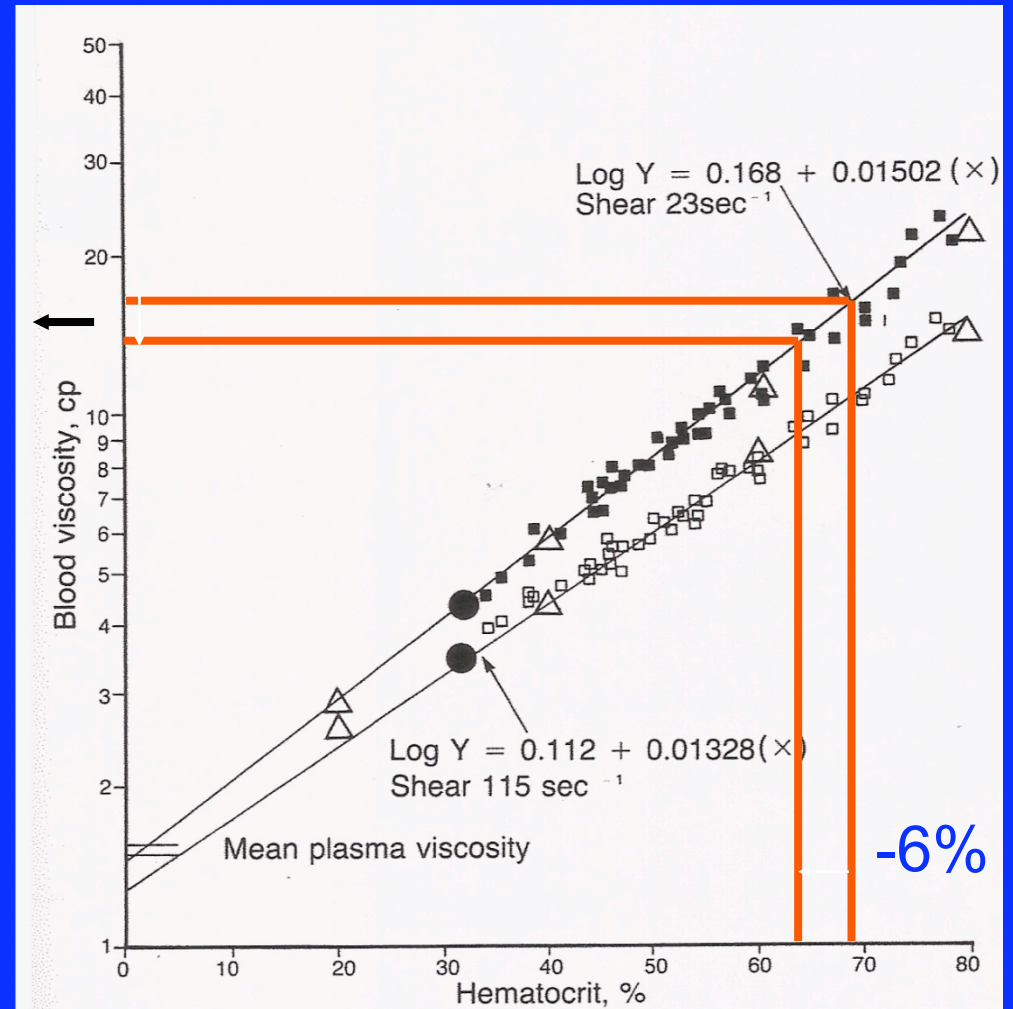
Reduction of pulmonary vascular resistance with Acz.

* $p < 0.001$ and § $p < 0.02$ vs inclusion

$$R_p = 8 \cdot \text{Viscosity} \cdot l / \pi \cdot r^4$$

Variation in viscosity: **-16%**

Variation in pulmonary vascular resistance: **-17%**



From Winslow and Monge, 1987

Variations of pulmonary vascular resistance index

Acetazolamide group	Number of patients with PVR > 2W.U.	Number of patients with PVR < 2W.U.
INCLUSION	8	19
END OF PHASE 2	0	22

p=0.005

PVR: Pulmonary vascular resistance

PVR > 2 Wood Units if the ratio of peak tricuspid regurgitant velocity to the right ventricular outflow tract time-velocity integral is superior than 0.175

Experimental studies (F. Favret et coll.)

6 groups of 12 male Wistar rats treated or not with ACZ
(40 mg/kg/jour)

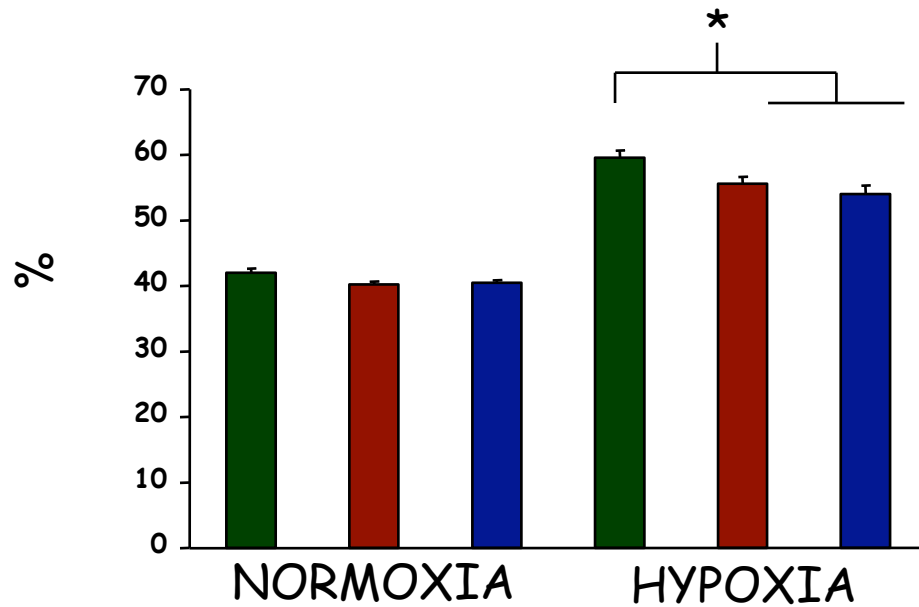
3 normoxic (NX) groups and 3 hypoxic (HX) groups

21 Days NX (760 mmHg) or HX (380 mmHg)

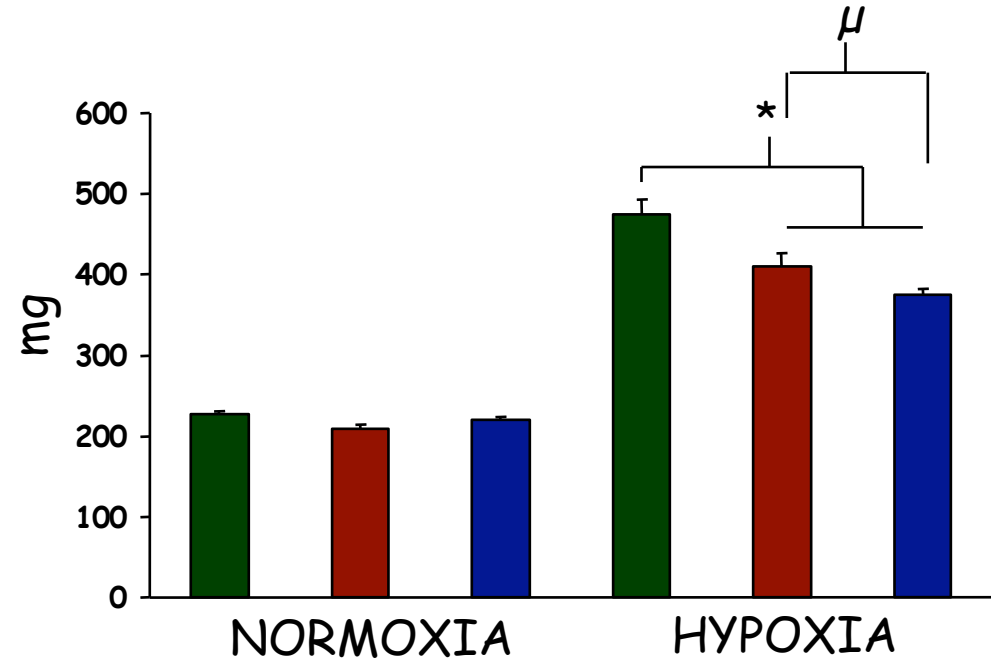


ACZ decreases Hematocrit and reduces RV hypertrophy

Hematocrit



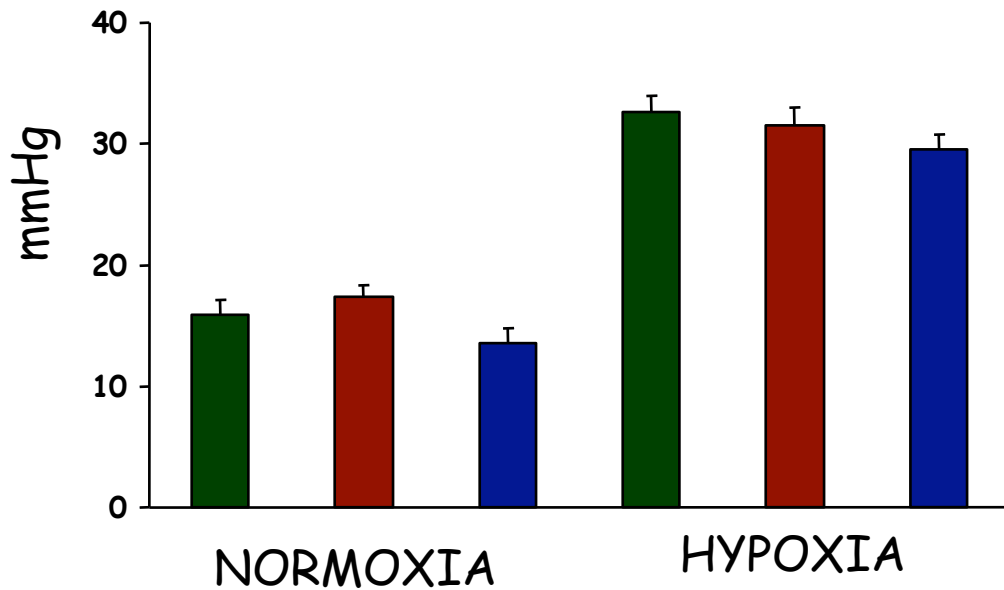
Right ventricular weight



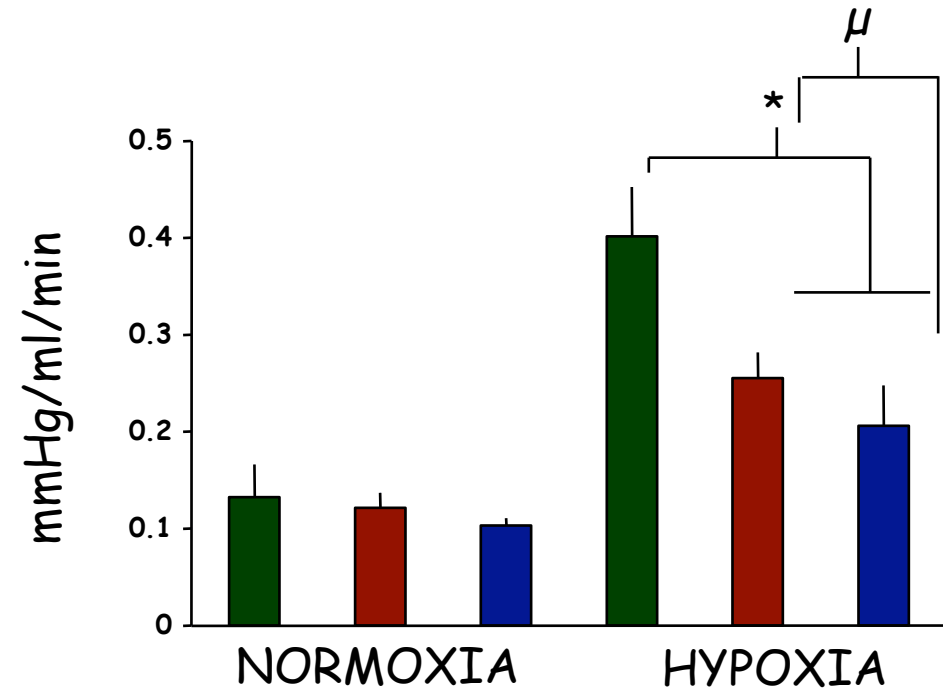
- Controls
- ACZ Curative
- ACZ Preventive

ACZ decreases pulmonary vascular resistance

Pulmonary artery pressure

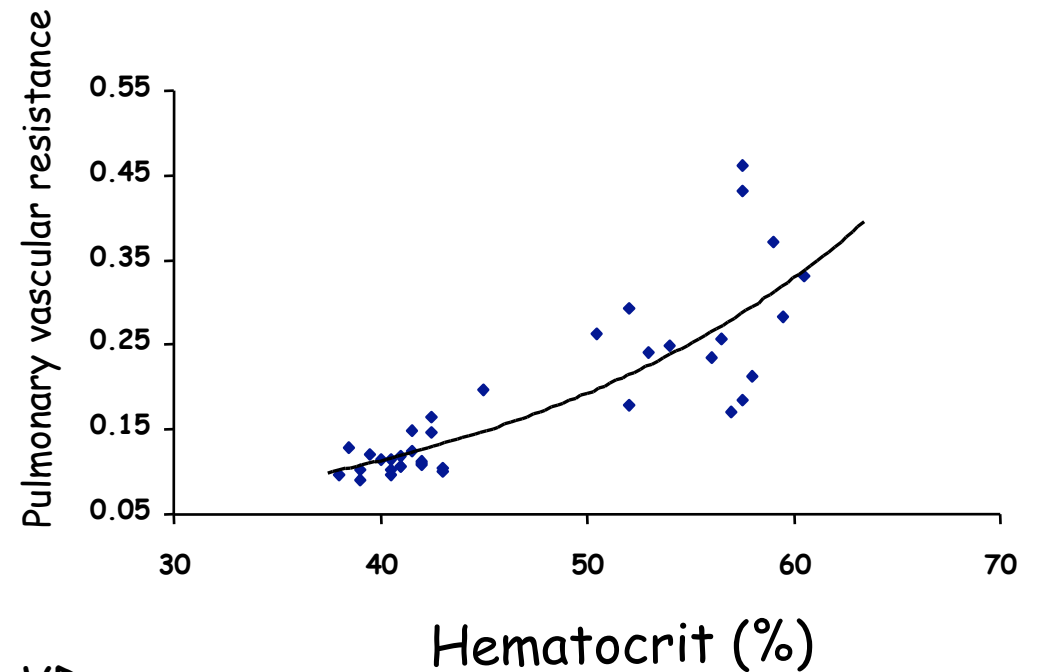
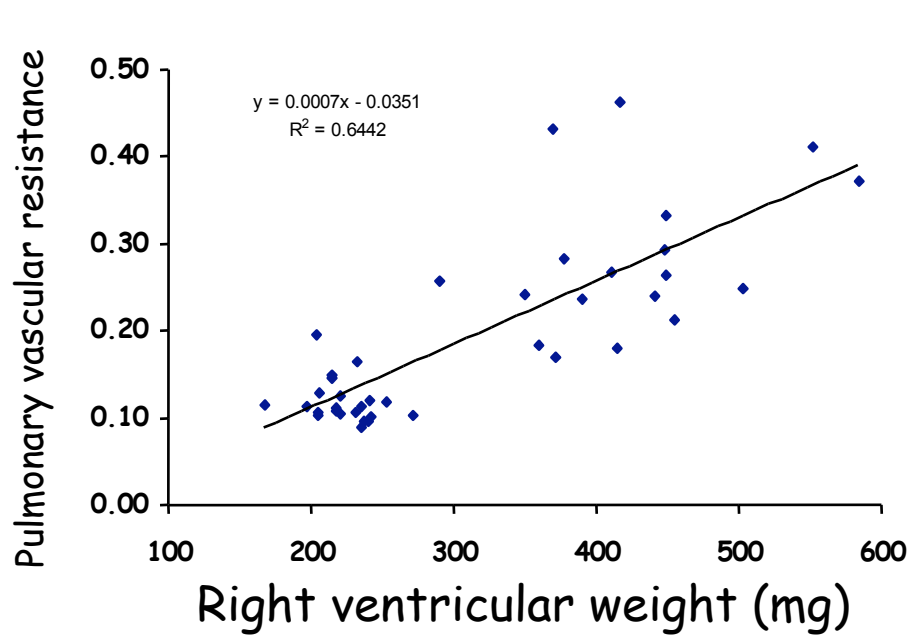


Pulmonary vascular resistance



- Control
- ACZ Curative
- ACZ Preventive

ACZ-induced reduction in RV hypertrophy is parallel to a decreased expression of PKC ϵ



PKC ϵ VD



NX



HX

C ACZ-P ACZ-C

Conclusion

Acetazolamide (ACZ) is the first efficient pharmacological treatment of chronic mountain sickness without adverse effects, probably by reducing nocturnal hypoventilation.

ACZ reduces pulmonary vascular resistance and RV hypertrophy (rats).

Its **low cost** may allow a wide development with a considerable positive impact on **public health** in high altitude regions.

Other drugs such as **ACE inhibitors** should be considered.