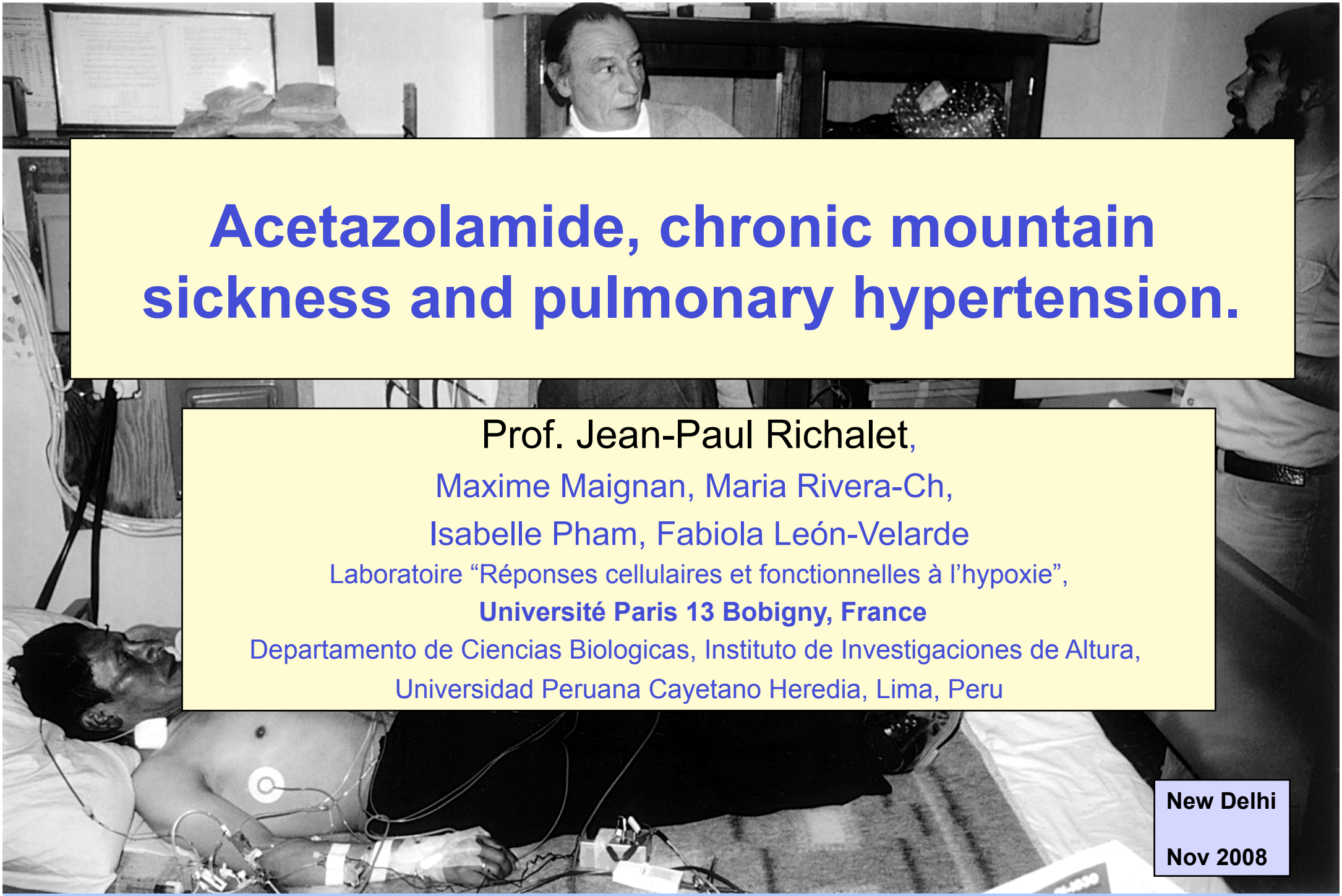

Acetazolamide, chronic mountain sickness and pulmonary hypertension.

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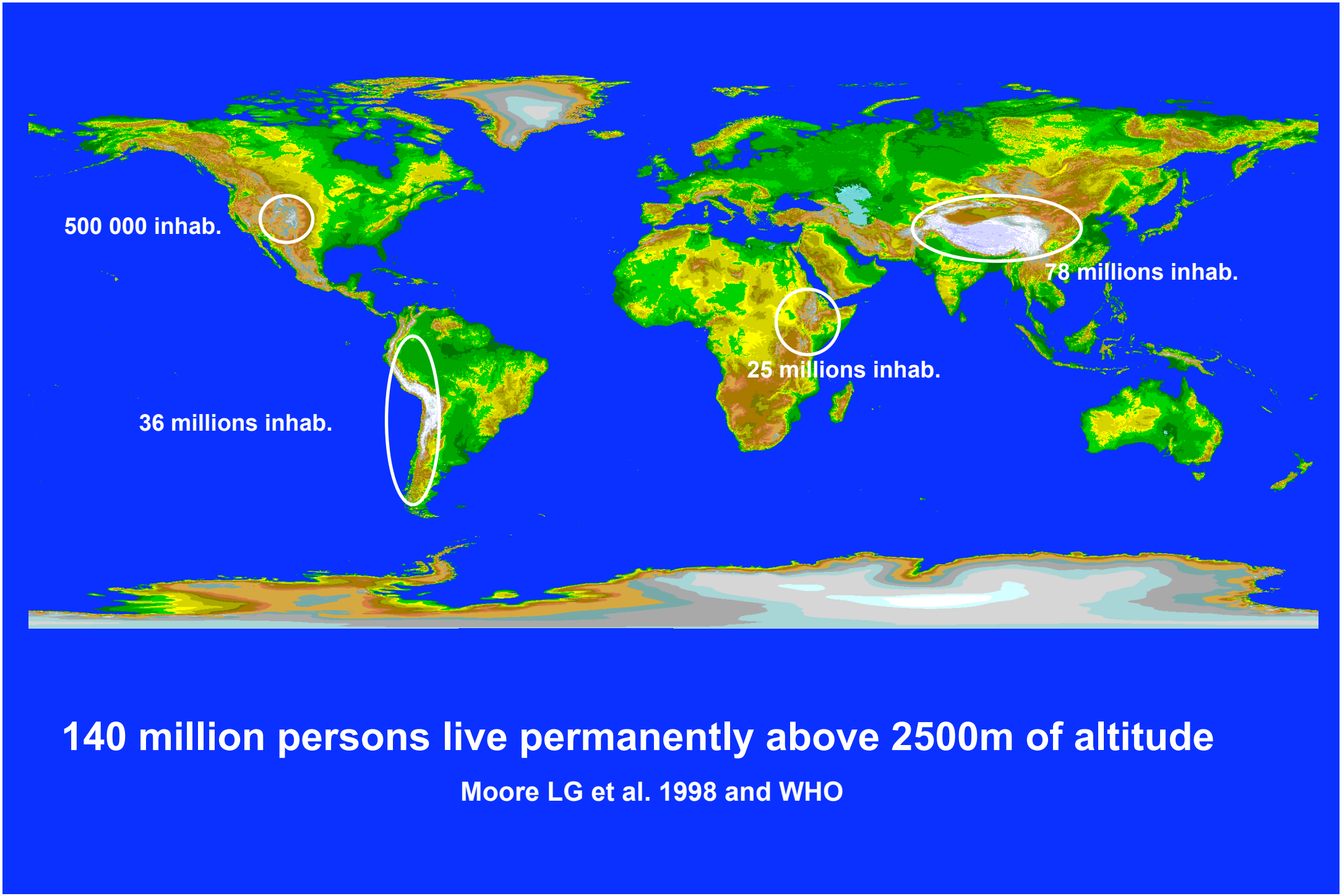
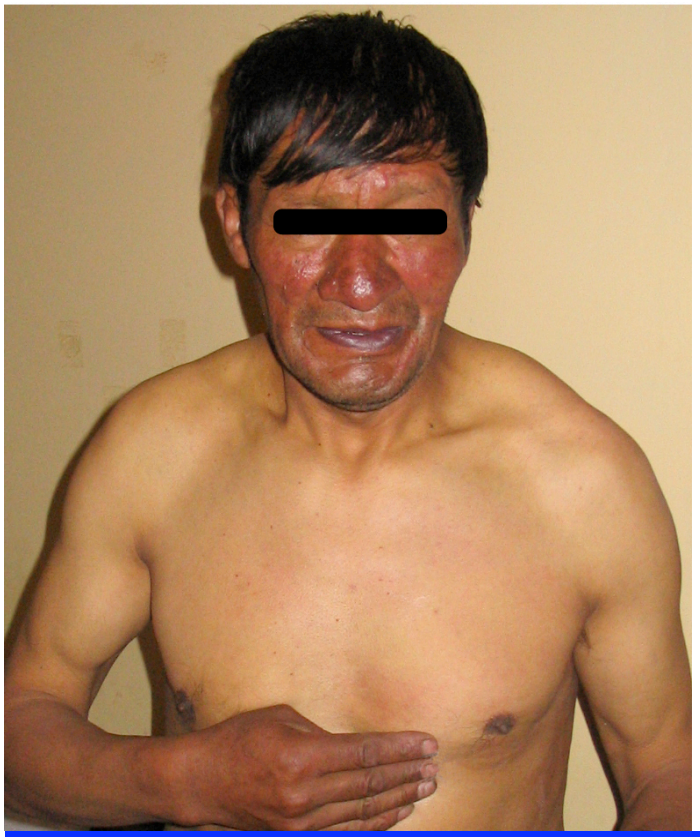
Nov 2008



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.

- In Bolivia, 3 million persons live between 3,000 and 5,500 m.

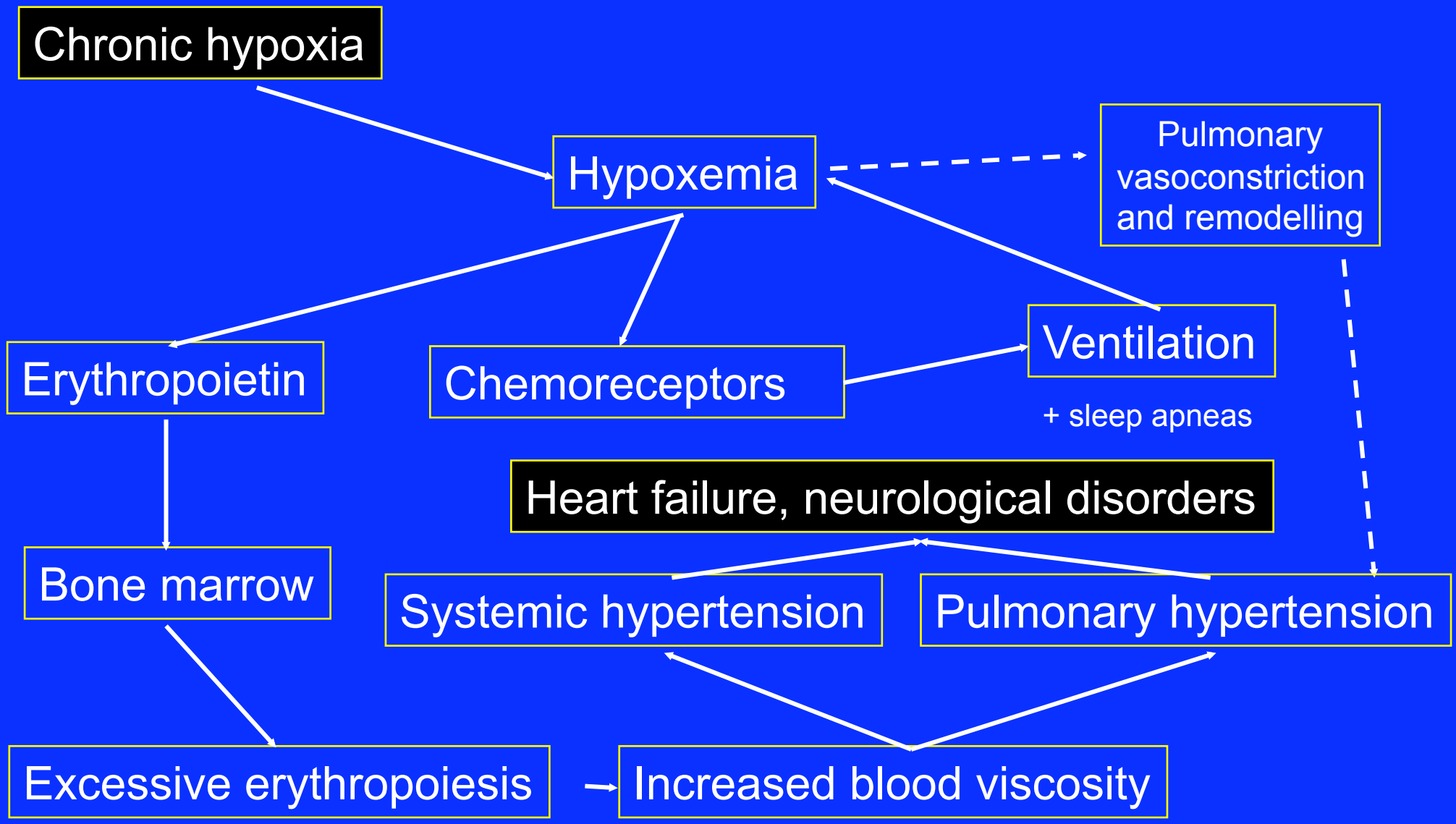
In La Paz, (3,200 to 4,050 m, 1 million inhab.), the prevalence of CMS of 5.2% : 50,000 persons (Spielvogel et al., 1981).

- In Cerro de Pasco, Peru (4,300 m, 80,000 inhab.), the prevalence of CMS is 14.8% to 18.2% : 12,000 to 15,000 persons (Monge et al., 1989; Leon Velarde, 1993).

CMS in PERU


Peru
ECUADOR
COLOMBIA
BRAZIL
BOLIVIA
PACIFIC
Equator 0°
5° S
10° S
15° S
70° W
65° W
0 150 Miles
0 150 Kilometers
Golfo de Guayaquil
Tumbes
Talara
Piura
Punta Negra
Chiclayo
Cajamarca
Trujillo
Chimbote
Nev. Huascarán 22,205 ft. (6,768 m)
Huaraz
Andoas
Iquitos
Nauta
Putumayo
Amazon
Yavarí
Caballococha
Chulucanas
Huancabamba
Moyobamba
Tarapoto
Yurimaguas
Ucayali
Marañón
Huallaga
La Montaña
Pucallpa
Juruá
Purus
Esperanza
Huánuco
Atalaya
Cerro de Pasco
Huacho
Callao
Lima
Huancayo
Huancavelica
Ayacucho
Pisco
Abancay
Cuzco
Manu National Park
Machu Picchu
Puerto Maldonado
Abuná
Juliaca
Puno
Lago Titicaca
Arequipa
Moquegua
Tacna
Grande
Huaraz (3200m)
120.000 inhab
6.000 CMS (5%)
Cerro de Pasco (4300m)
72.000 inhab,
10.800 CMS (15%)
Cuzco (3400m)
270.000 inhab
17.550 CMS (5.5%)
Puno (3800m)
201.000 inhab
15.575 CMS (7.5%)
© MAPQUEST.COM

Pathophysiology of CMS



Treatments of CMS

- Displacement to lower altitudes
  - Negative socio-economical consequences
- Blood letting
  - Transient effects
- ACE inhibitors (enalapril), by increasing renal blood flow and reducing renal O_2 consumption
- Medroxyprogesterone, almitrine or domperidone, by increasing ventilation

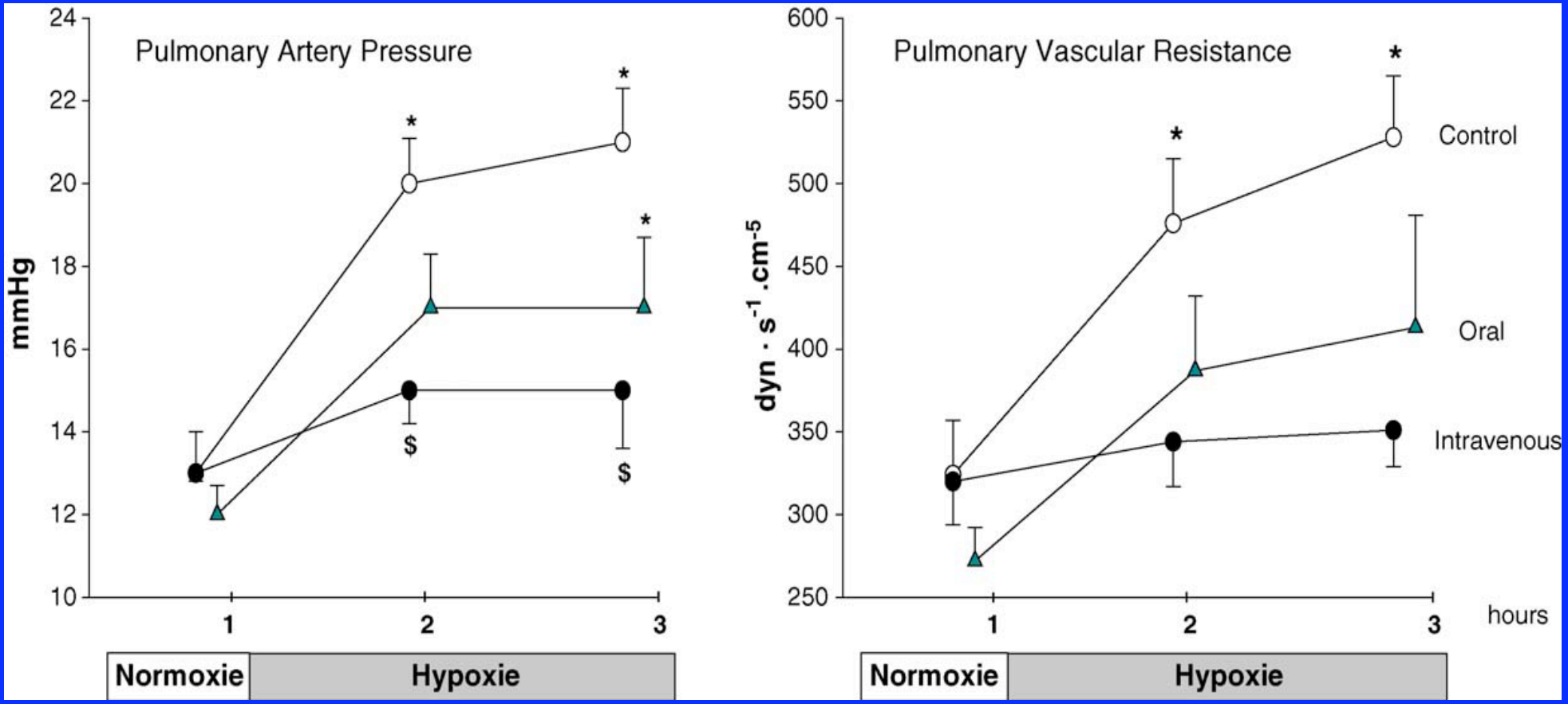
Treatments of CMS

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 and 2008)

Acetazolamide and acute hypoxia-induced pulmonary hypertension



In dogs, ACZ 5mg/kg. ***From Swenson et al. 2006***

Study I. ACZ treatment for 3 weeks and CMS at 4,300m

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)

Richalet et al., AJRCCM, 172:1427-33, 2005

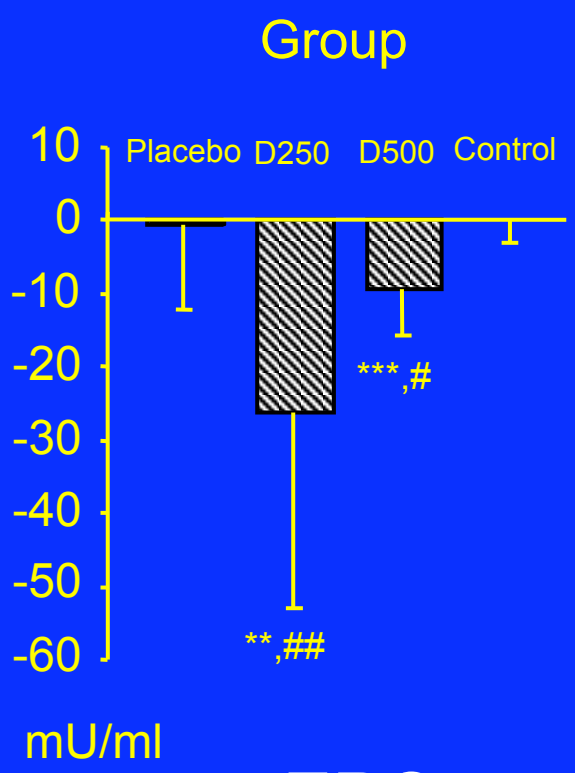
Characteristics of the CMS population (1)

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

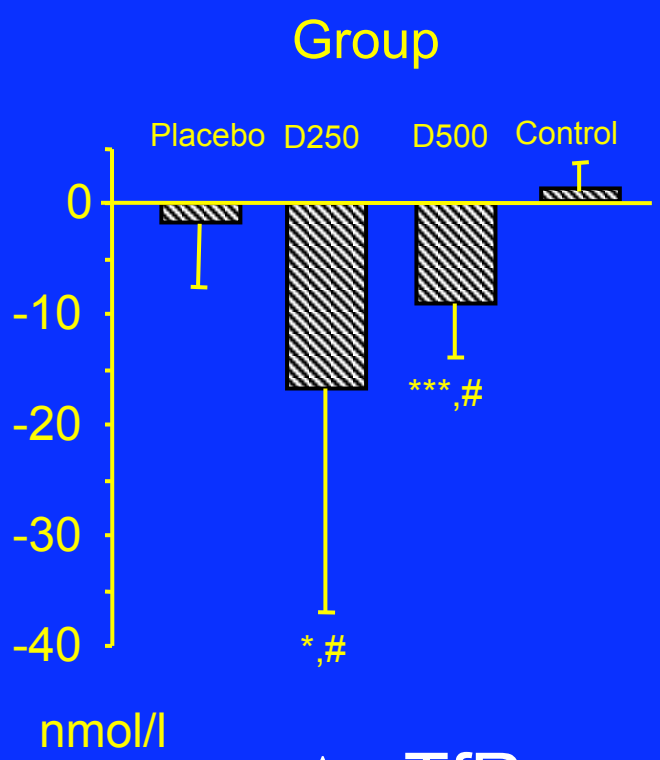
Characteristics of the CMS population (2)

	SaO_2 (%)	Apnea - hypopnea index (nb/h)	Systolic AP (mmHg)	Diastolic AP (mmHg)	CMS score (a.u.)
CMS patients (*n*=28)	78.0 ± 3.2 (70 - 84)	2.9 ± 4.2 (0 - 16.2)	121 ± 12 (100 - 150)	73 ± 11 (60 - 100)	17.7 ± 9.2 (0 - 32)
Control group (*n*=10)	80.4 ± 1.3 (79 - 83)	3.8 ± 3.2 (0.4 - 10.3)	104 ± 8 (90 - 120)	62± 8 (50 - 80)	5.8 ± 7.2 (0 - 21)
P	<0.02	n.s.	<0.001	<0.01	<0.001

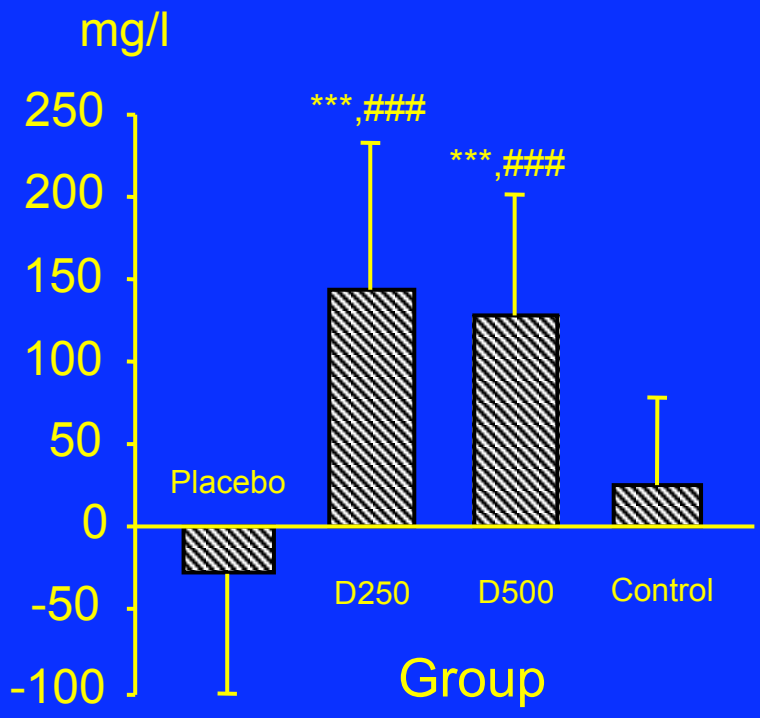
Hematopoiesis



Δ EPO

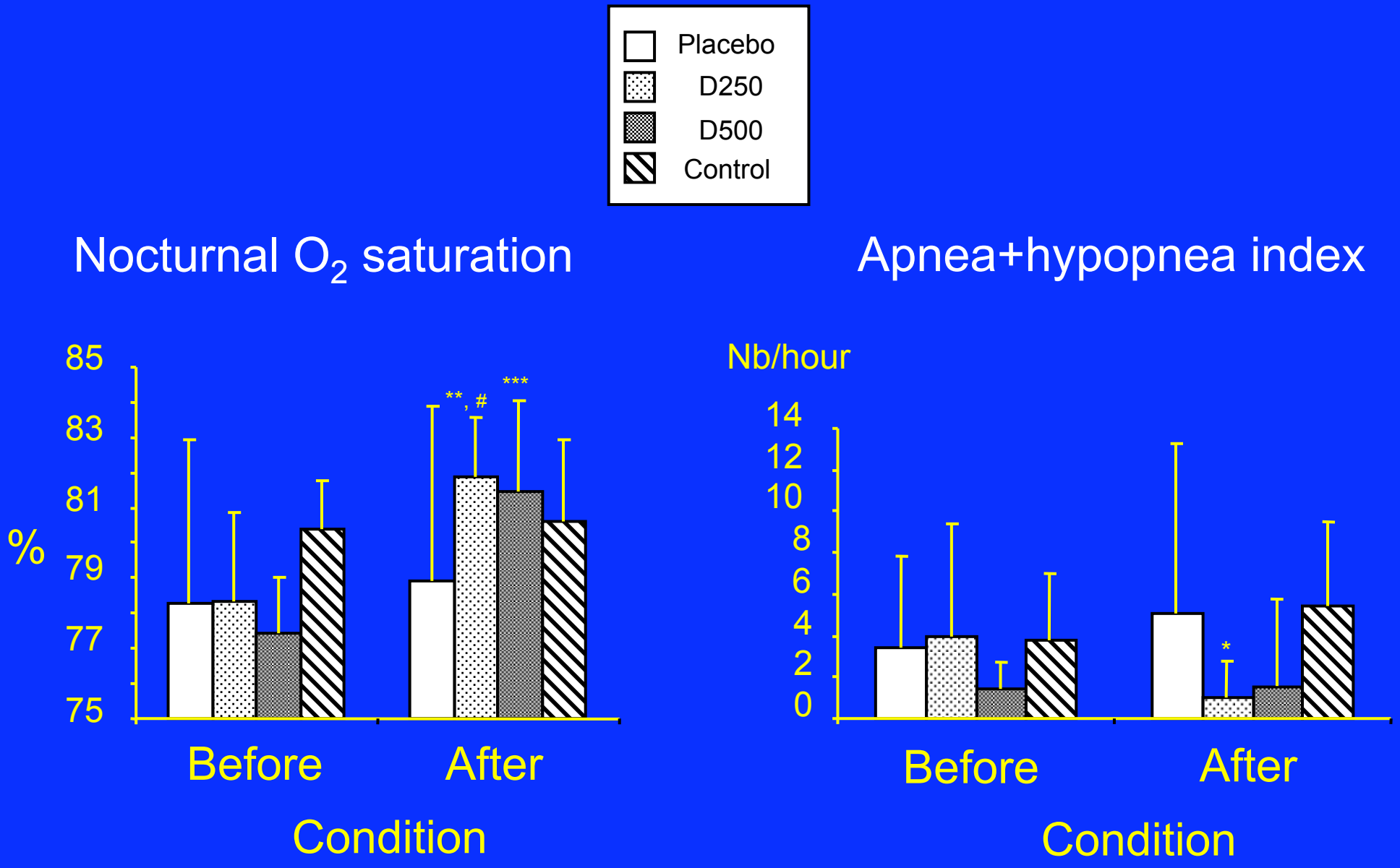


Δ sTfR



Δ Ferritin

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



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

Study I. ACZ treatment for 3 weeks and CMS at 4,300m

Conclusion

Erythropoiesis is blunted by ACZ (250 mg):

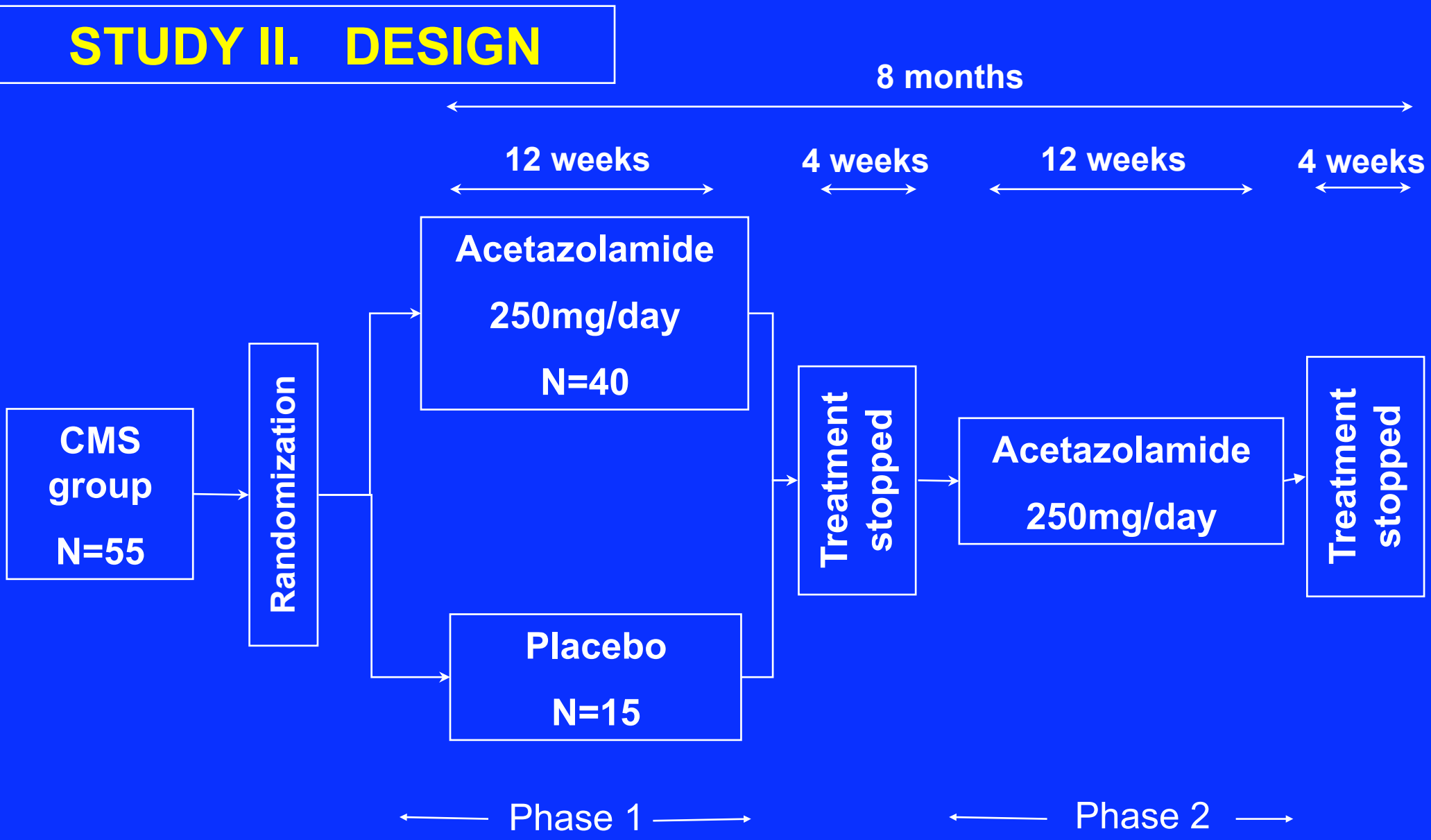
- Hematocrit decreased by 7.1 %
- Serum EPO decreased by 67%
- Soluble transferrin receptors decreased by 11.1%

Through an effect on ventilation and hypoxemia

- Arterial O_2 saturation increased by 4.3 %

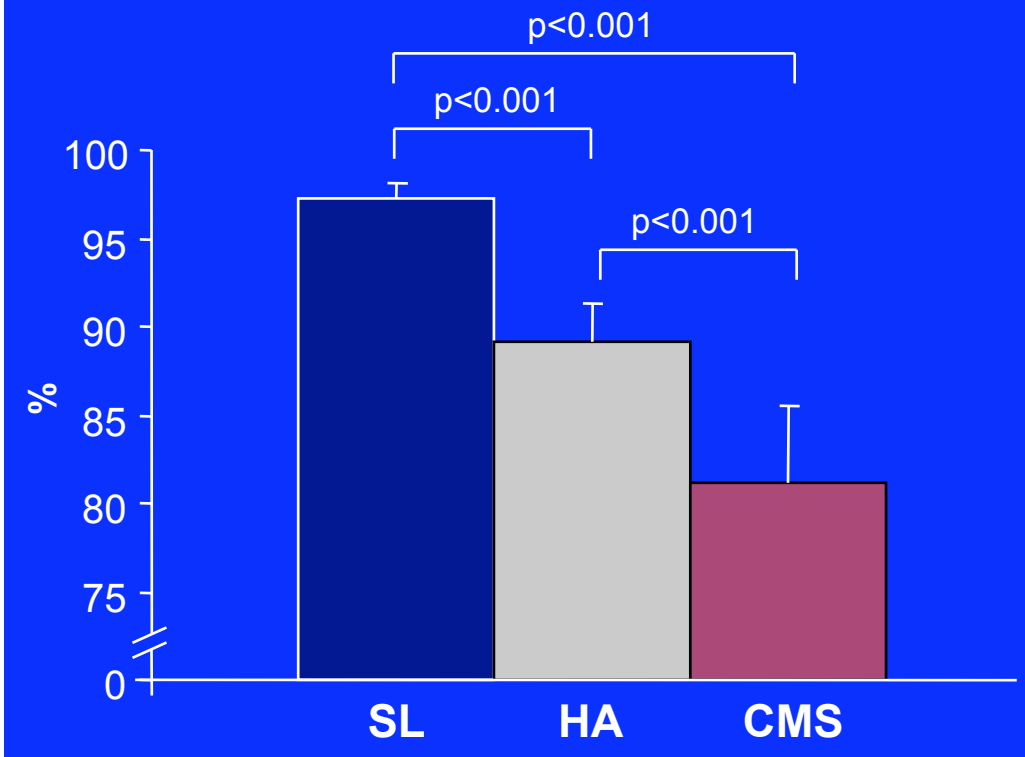
Richalet et al., AJRCCM, 172:1427-33, 2005

STUDY II. DESIGN

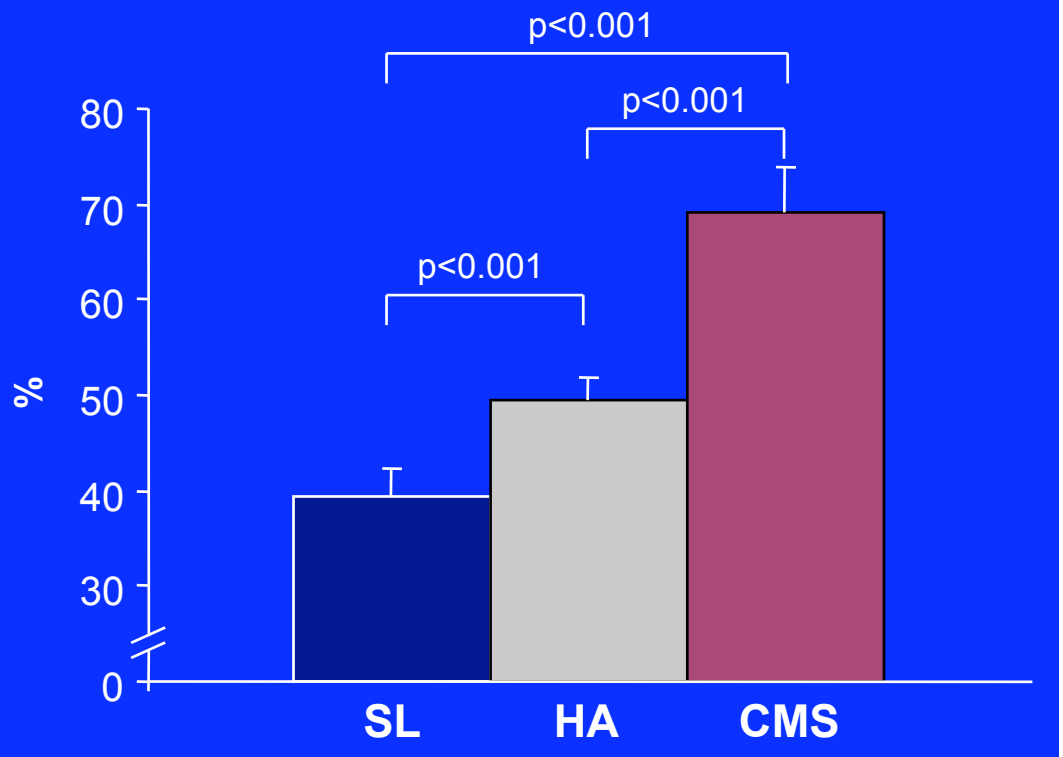


CMS: Chronic Mountain Sickness

Baseline characteristics



SaO_2



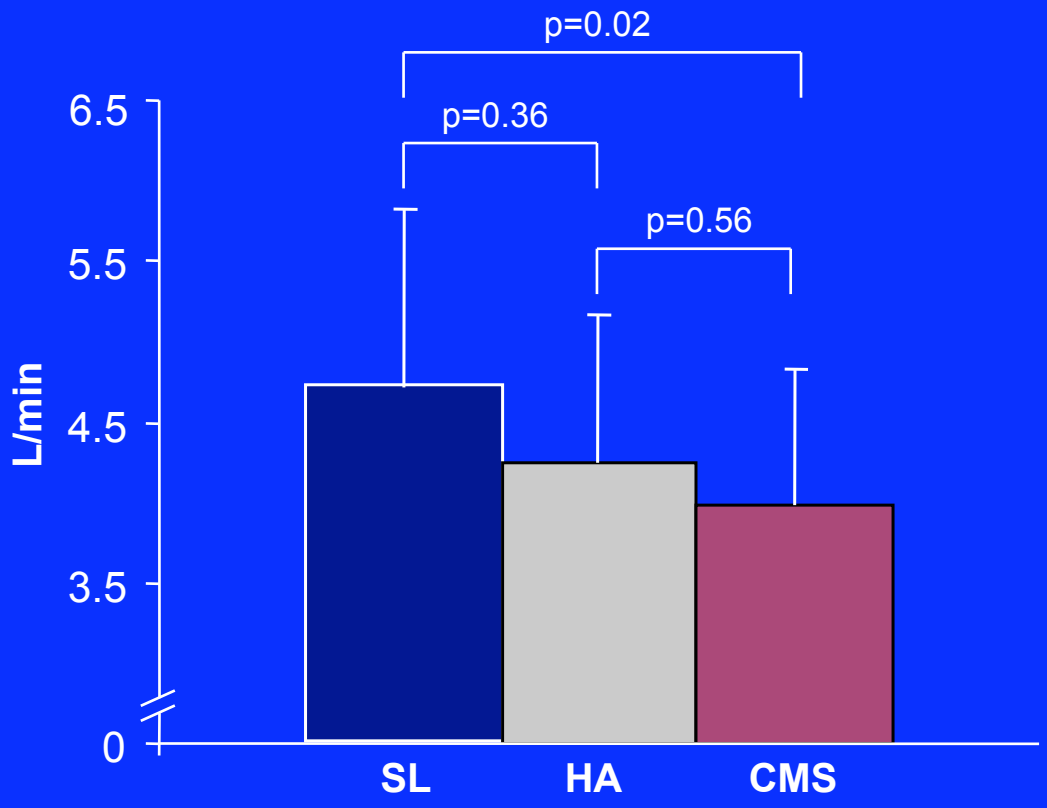
Hematocrit

SL: Sea level control group (N=15)

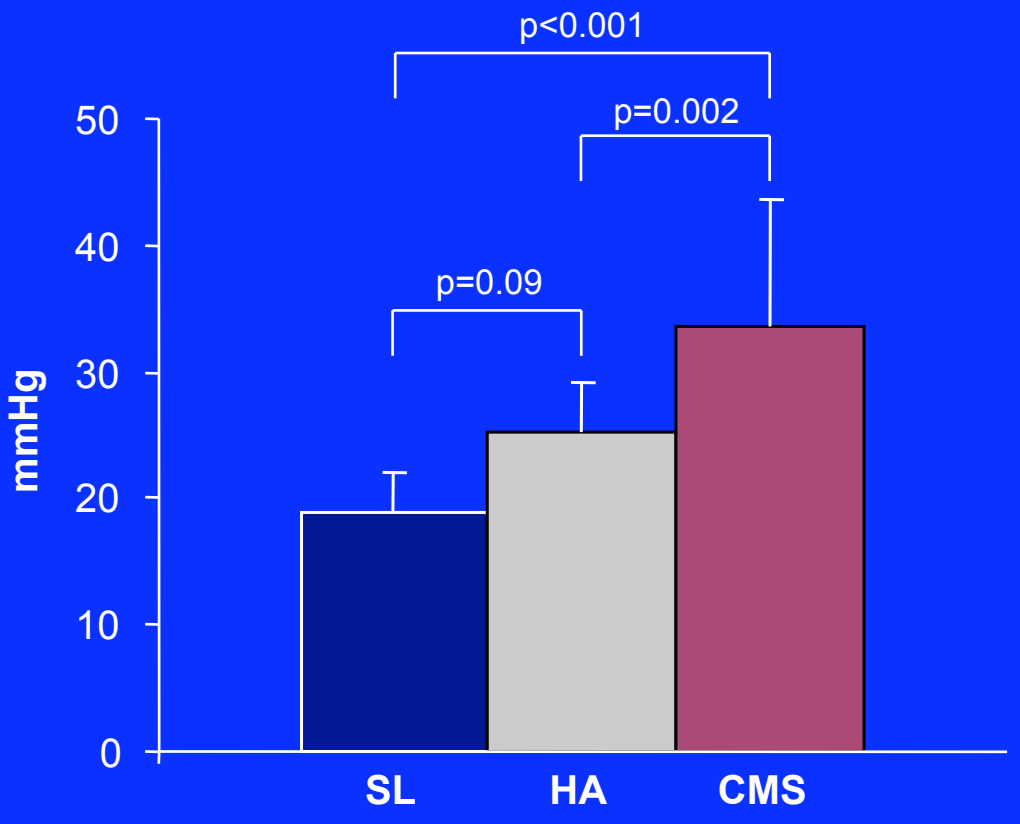
HA: High altitude control group (N=15)

CMS: Patient group (N=55)

Baseline echographic characteristics



Cardiac output



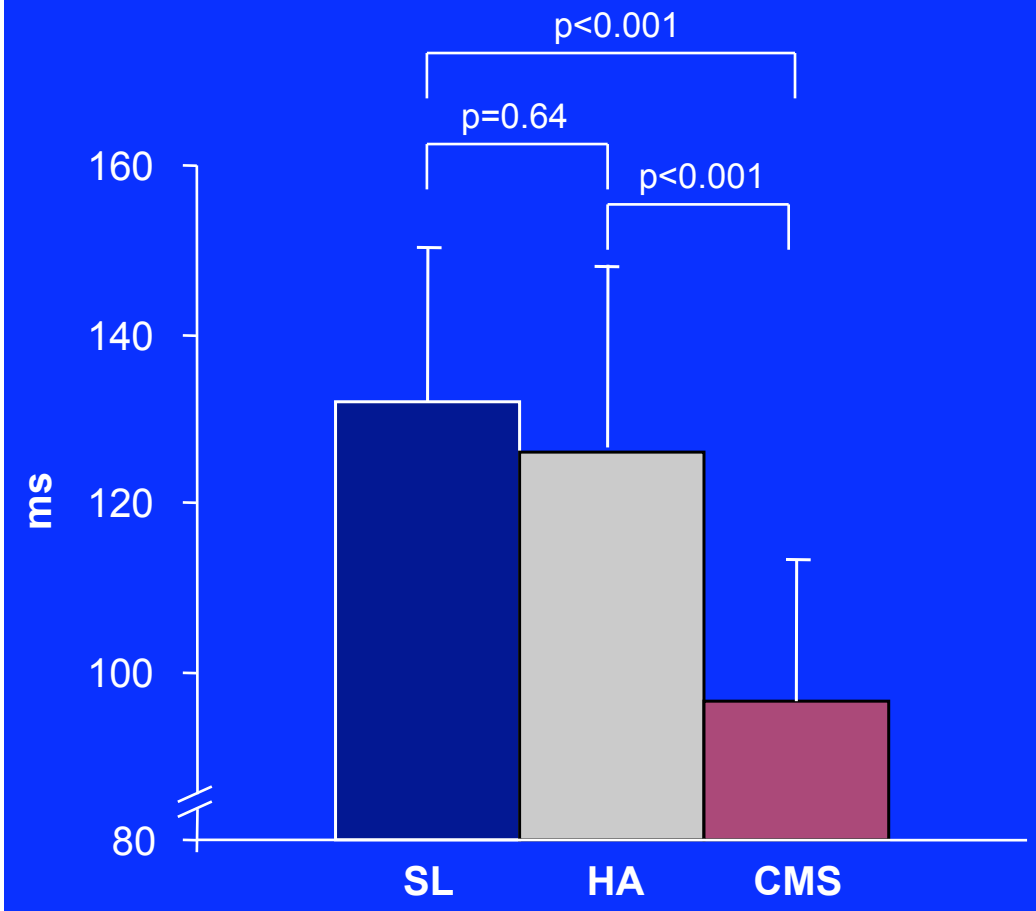
Maximal tricuspid regurgitation pressure

SL: Sea level control group (N=15)

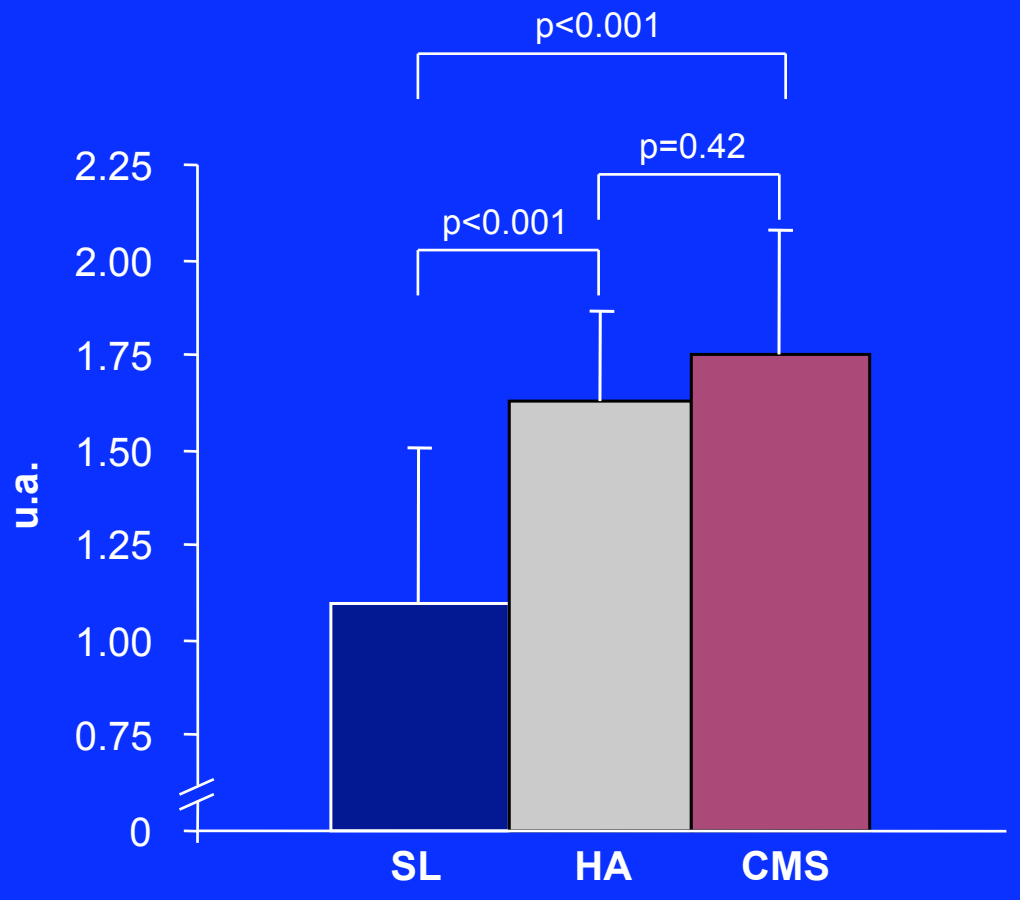
HA: High altitude control group (N=15)

CMS: Patient group (N=55)

Baseline echographic characteristics



Pulmonary acceleration time



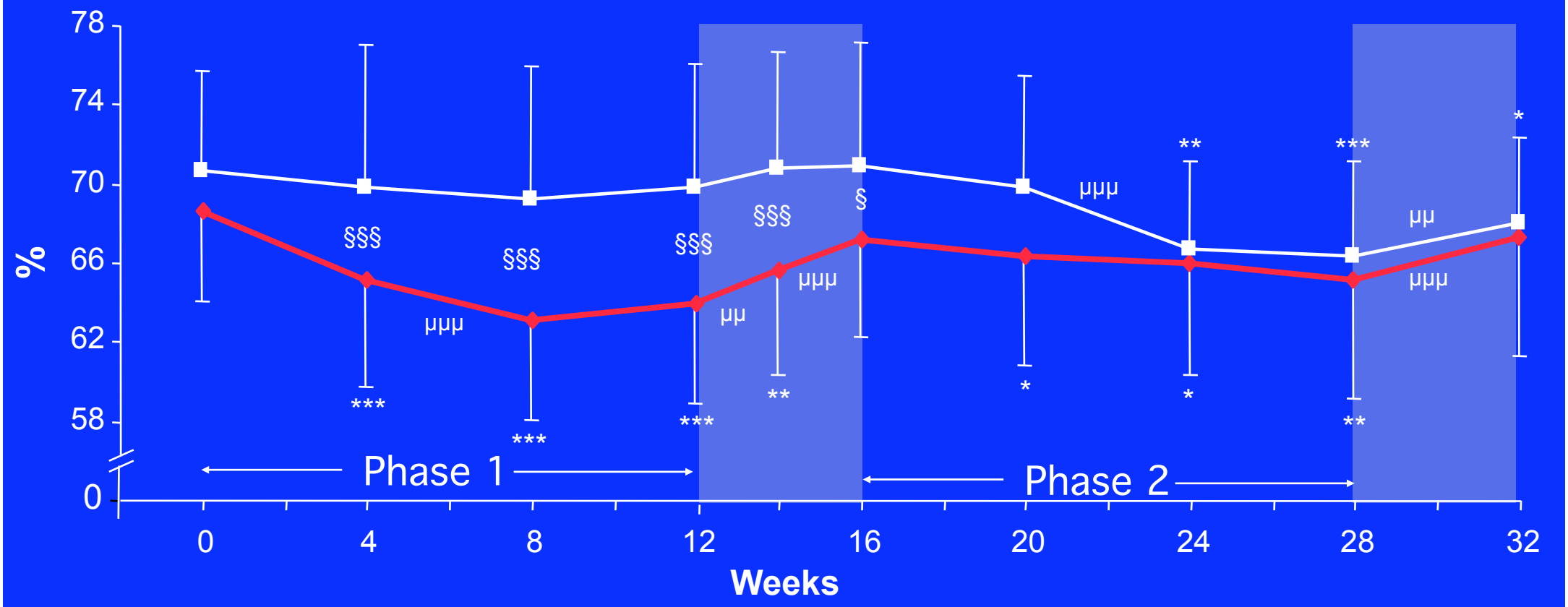
Pulmonary vascular resistance index[1]

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

[1]: Calculated as ((peak tricuspid regurgitant velocity / right ventricular outflow tract time-velocity integral) x 10) + 0.16.

Abbas et al. JACC, 2003

Hematocrit

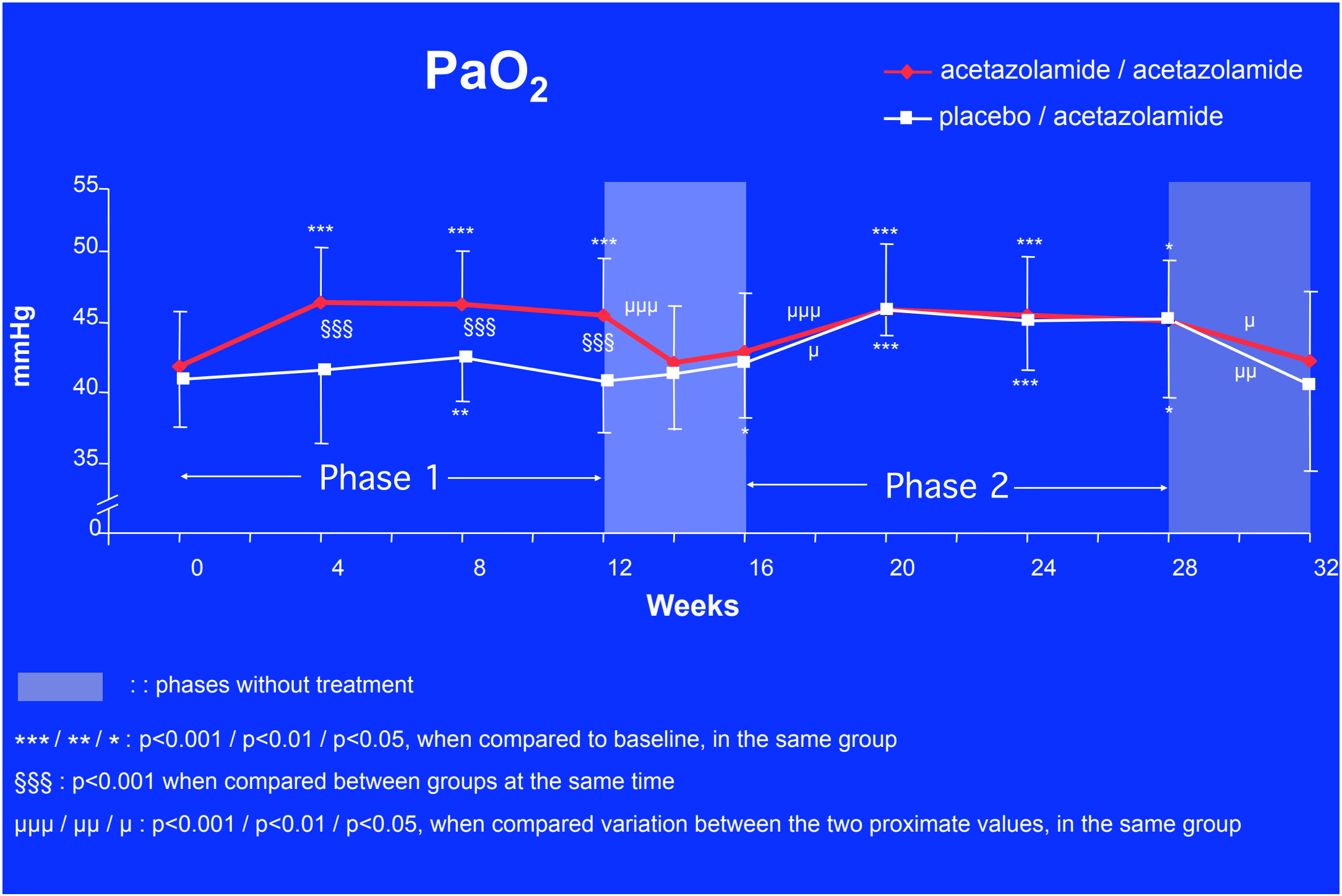


: : phases without treatment

*** / ** / * : 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



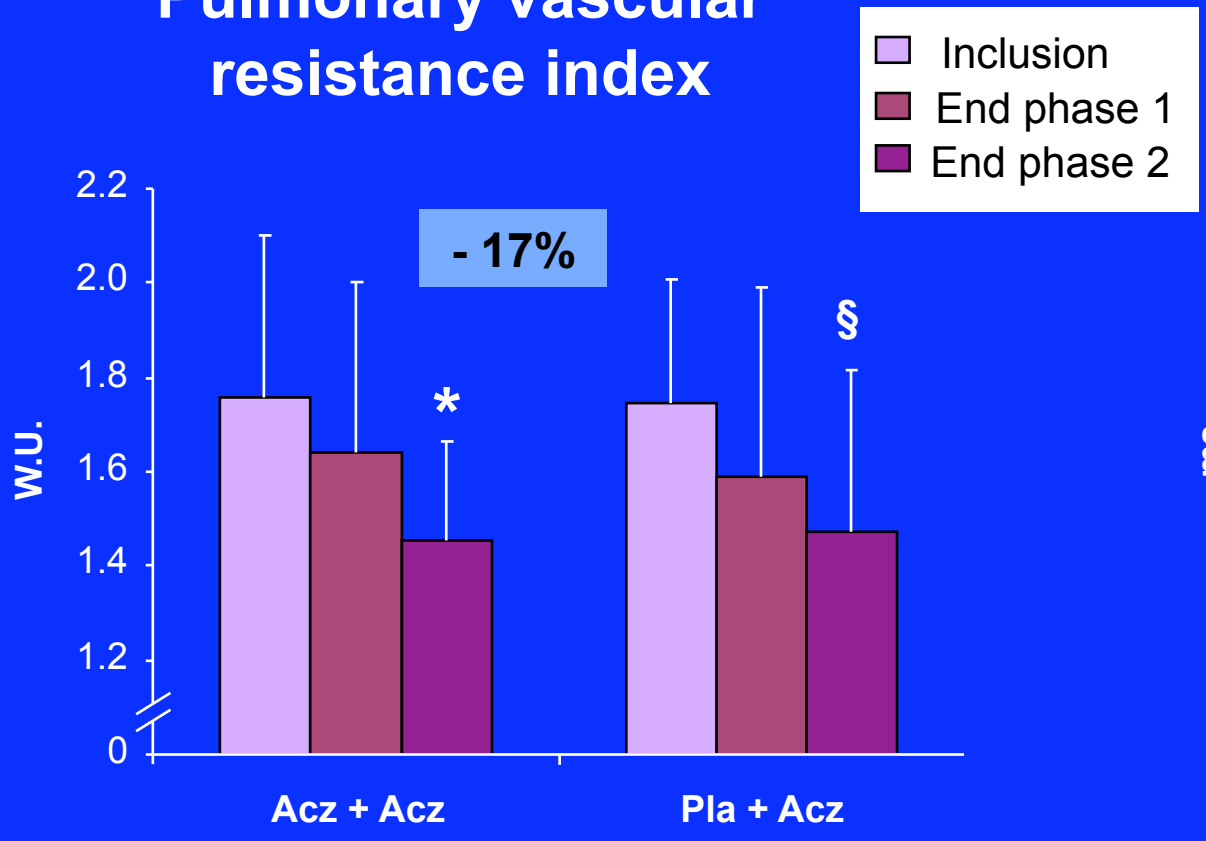
: : phases without treatment

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

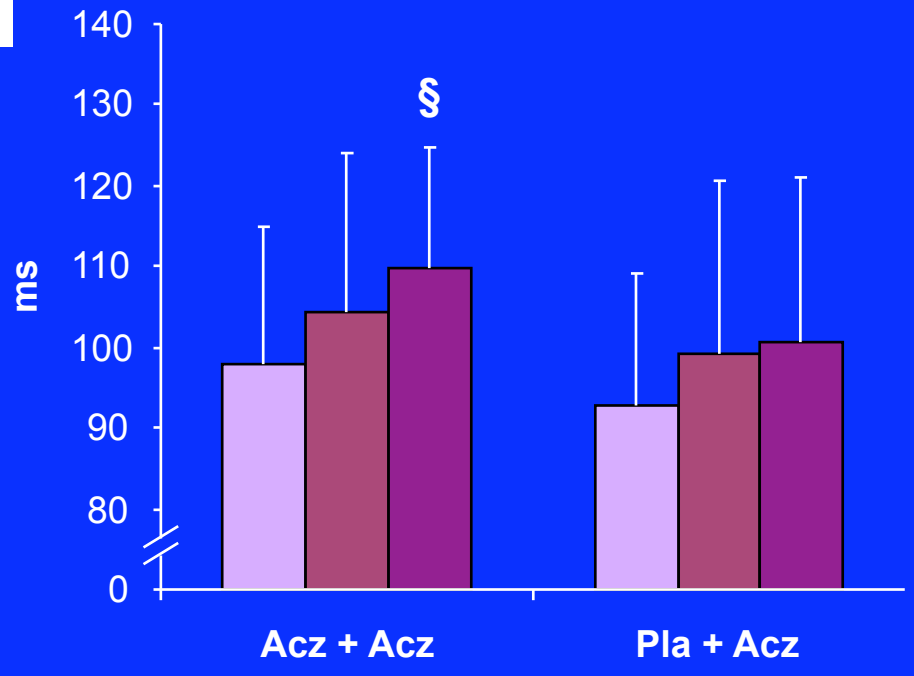
§§§ : p<0.001 when compared between groups at the same time

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



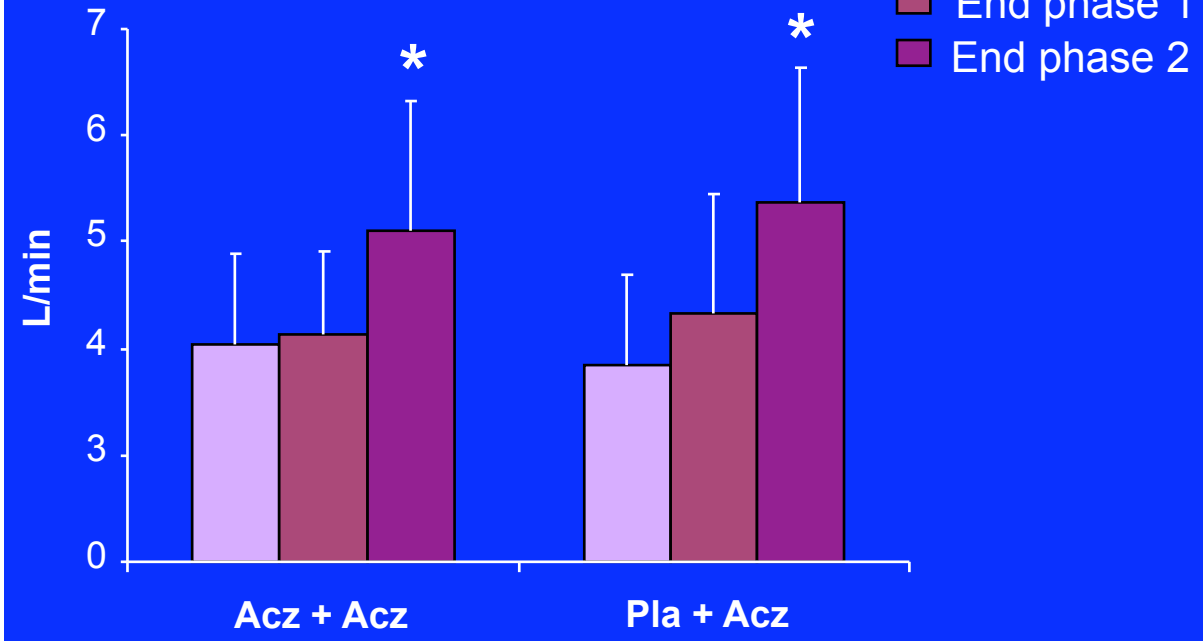
Pulmonary acceleration time



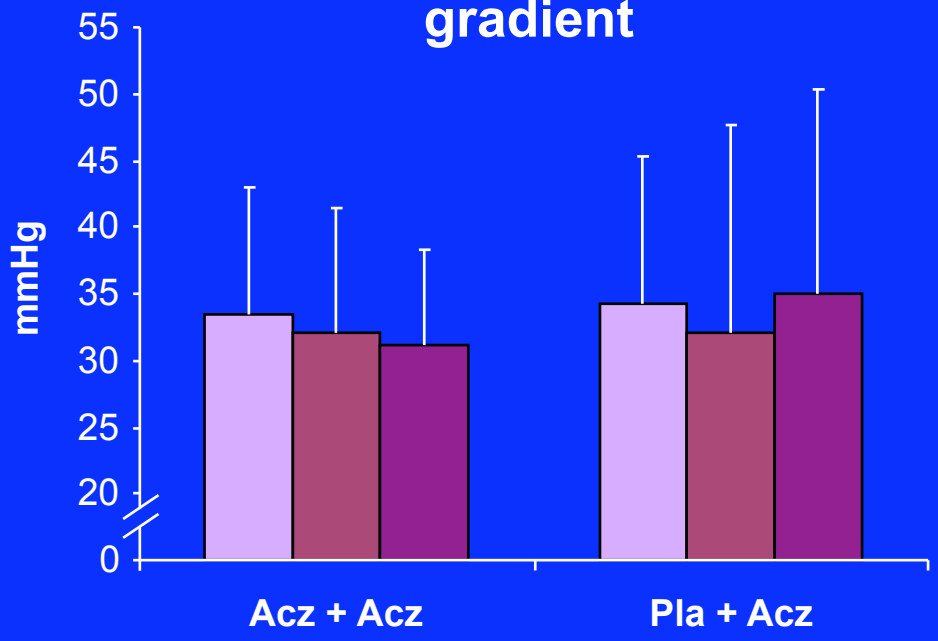
Reduction of pulmonary vascular resistance with Acz.

* p<0.001 and § p<0.02 vs inclusion

Cardiac output



Maximal tricuspid regurgitation pressure gradient



Increase in cardiac output,

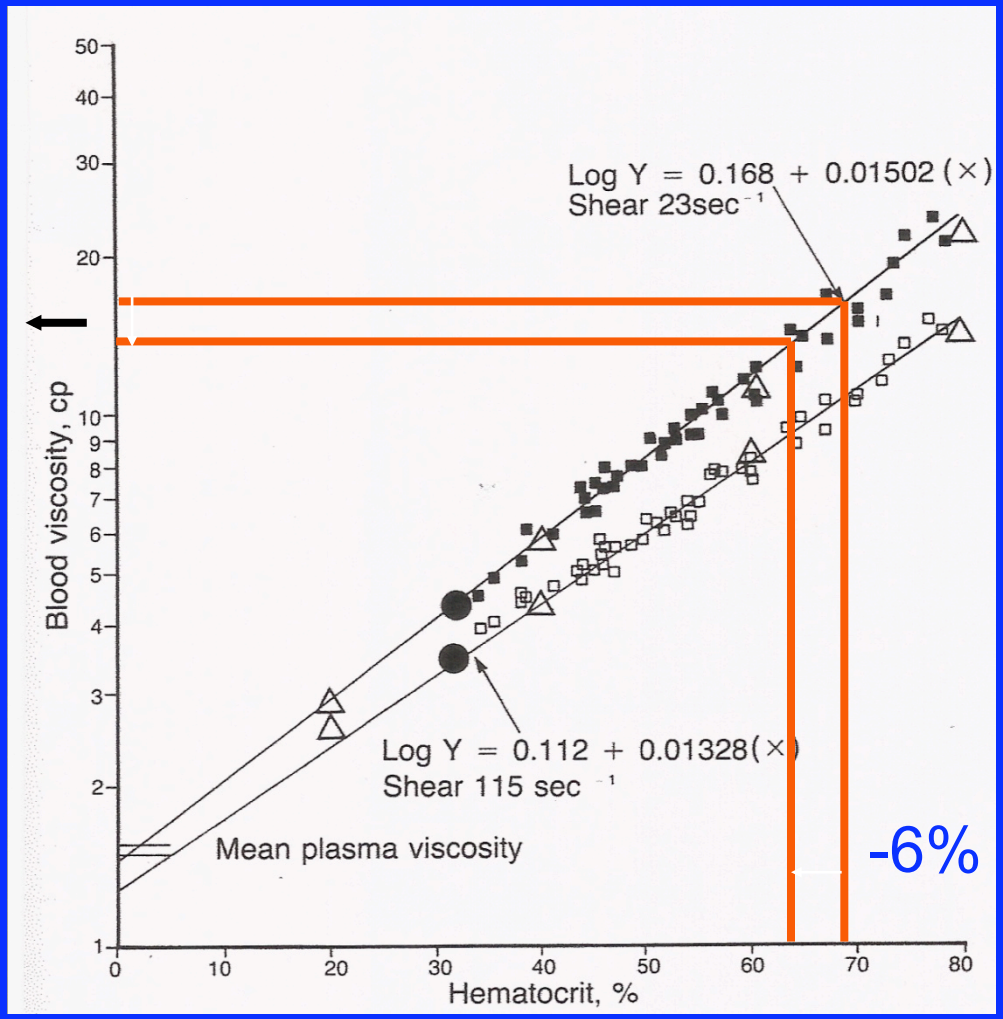
no change in pulmonary pressure with Acz

* p<0.001 vs inclusion

$Rp = 8.Viscosity.l/\pi.r^4$

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

Conclusion

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

Its effects on pulmonary vascular resistance need further investigation.

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