Risiko Höhenkrankheit
Prophylaxe und Therapie

Marco Maggiorini

Medical Intensive Care Unit

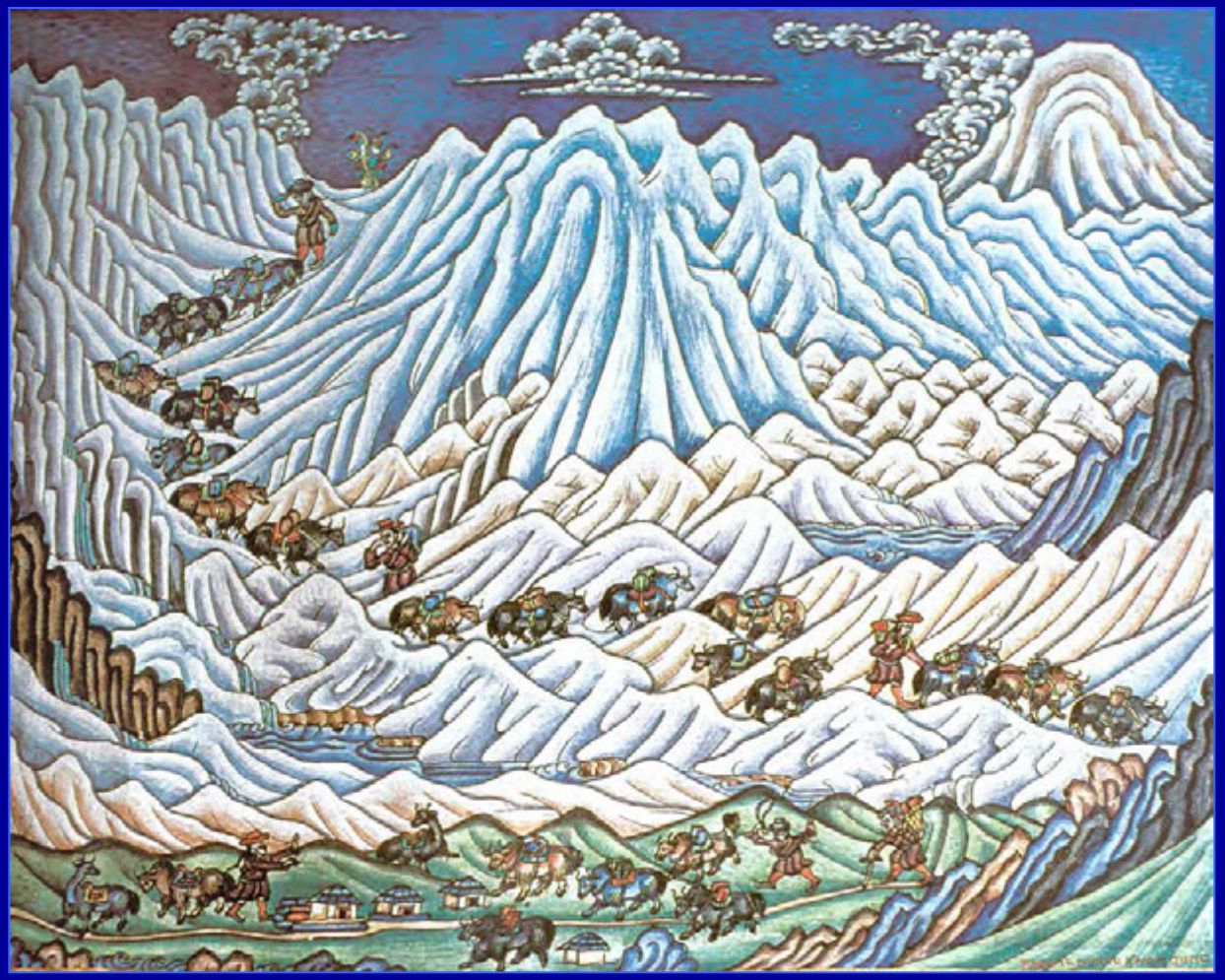
University Hospital Zurich

Risk High Altitude Illness: Prophylaxis and Treatment

- Agenda
  - High altitude illness definition (summary)
    - AMS & HAPE
  - AMS prevention and treatment
    - Risk assessment
    - Non-medical preventive options
    - Medical preventive and treatment options
  - HAPE prevention and treatment
    - Risk assessment
    - Non-medical preventive options
    - Medical preventive and treatment options

High Altitude Illness Phenotype

High Altitude illness First Report



Chinese Headache Mountain c. 30 BC

(Tseen Han Shoo Book 96)

"...Again passing the Great Headache Mountains, the Little Headache mountain, the Red Lands and the Fever Slope, men's bodies became feverish, they lose color and are attacked with headache and vomiting".

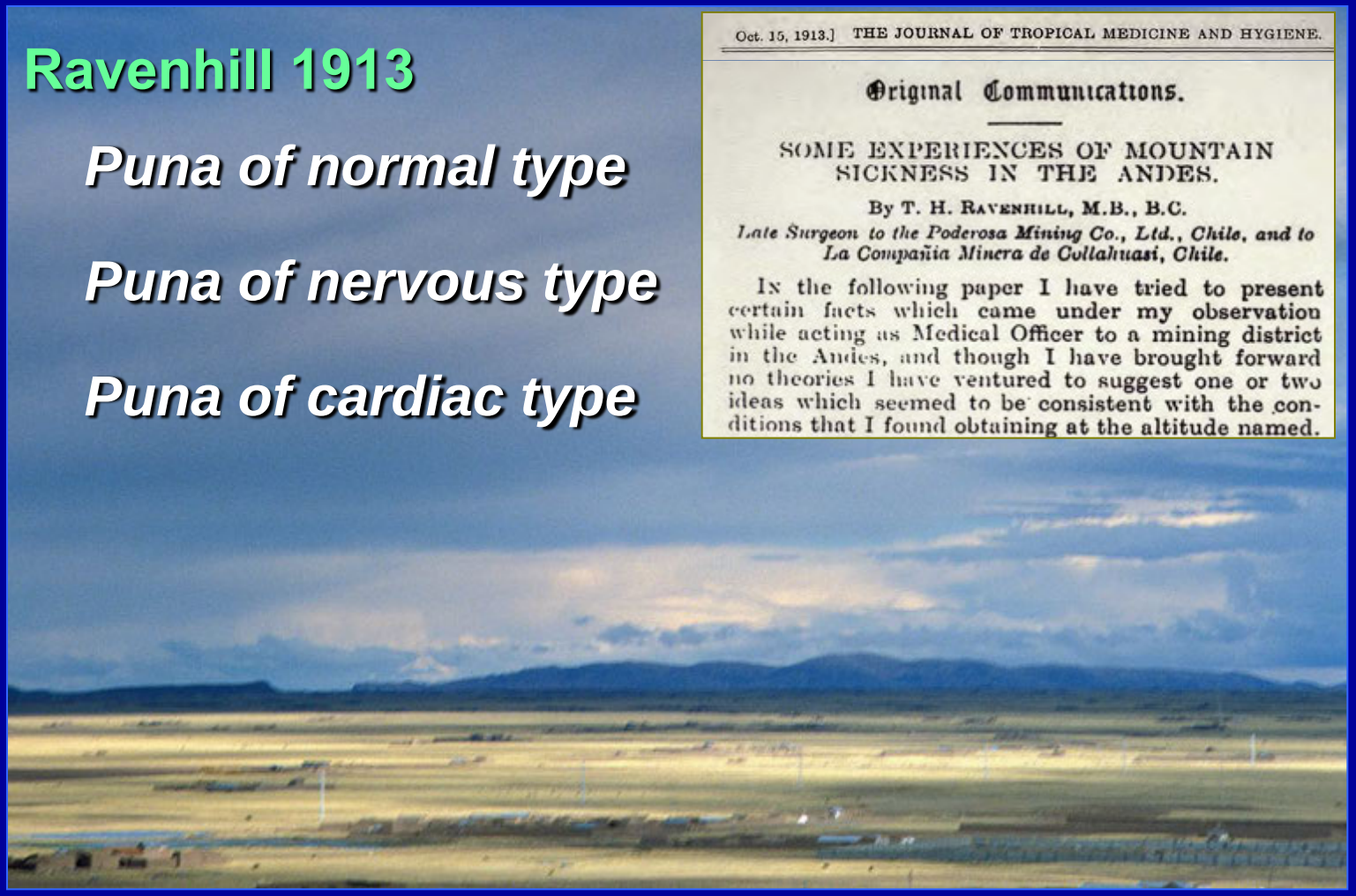
High altitude illness: First Classification

Ravenhill 1913

Puna of normal type

Puna of nervous type

Puna of cardiac type



Oct. 15, 1913.] THE JOURNAL OF TROPICAL MEDICINE AND HYGIENE.

Original Communications.

SOME EXPERIENCES OF MOUNTAIN SICKNESS IN THE ANDES.

By T. H. Ravenhill, M.B., B.C.

Late Surgeon to the Poderosa Mining Co., Ltd., Chile, and to La Compañia Minera de Collahuasi, Chile.

In the following paper I have tried to present certain facts which came under my observation while acting as Medical Officer to a mining district in the Andes, and though I have brought forward no theories I have ventured to suggest one or two ideas which seemed to be consistent with the conditions that I found obtaining at the altitude named.

High altitude illnesses: Contemporary Classification

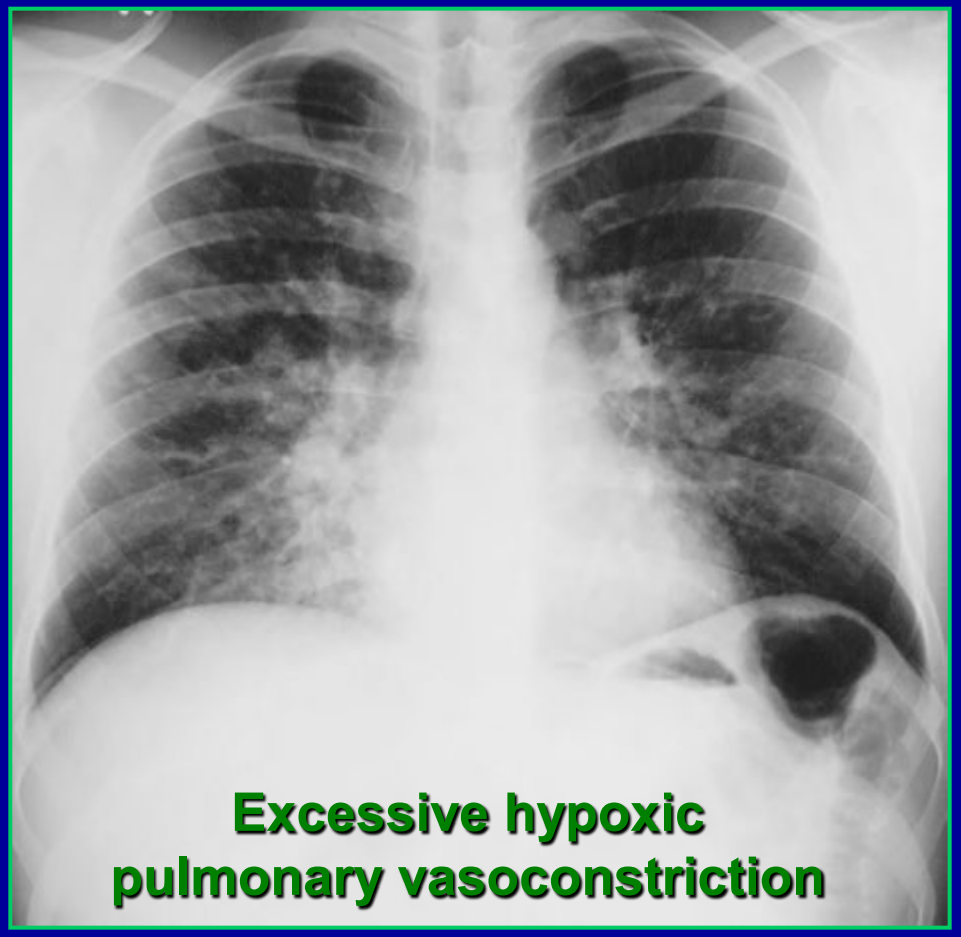
Acute mountain sickness/HACE

Axiatl T_2-weighted MRI in HACE

Edema of the splenium

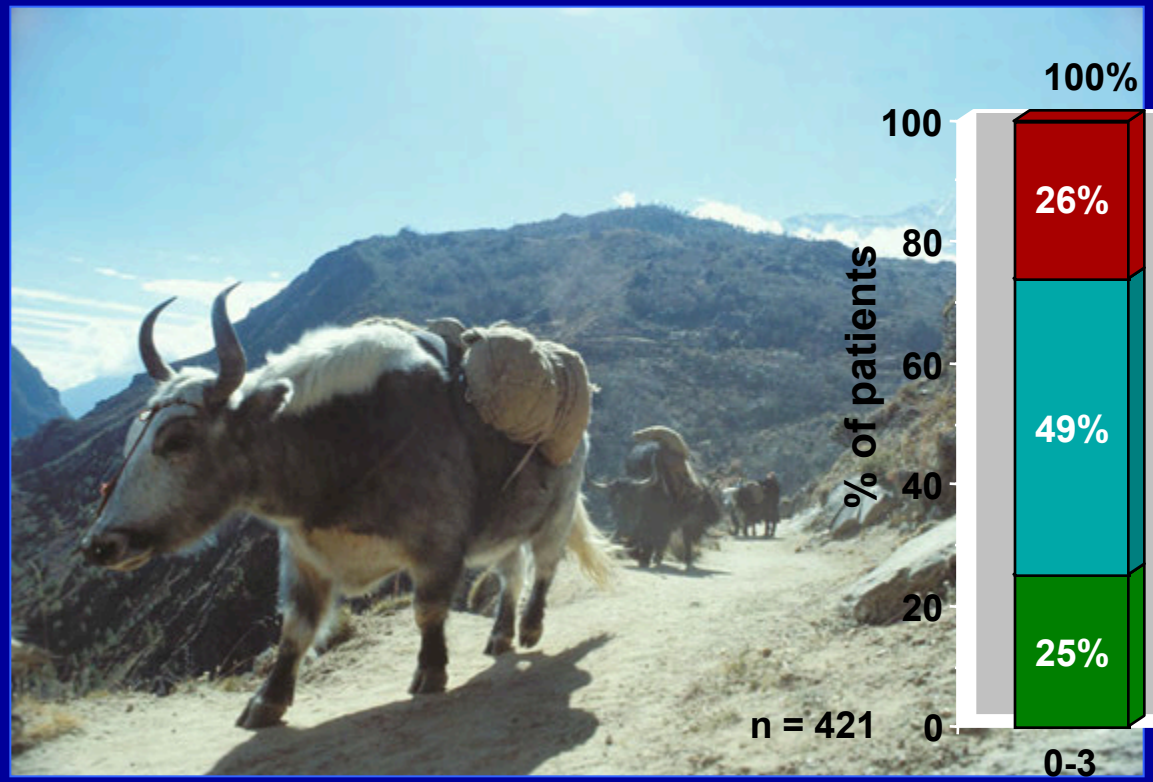
Hackett et al JAMA 1998; 280: 1920-25

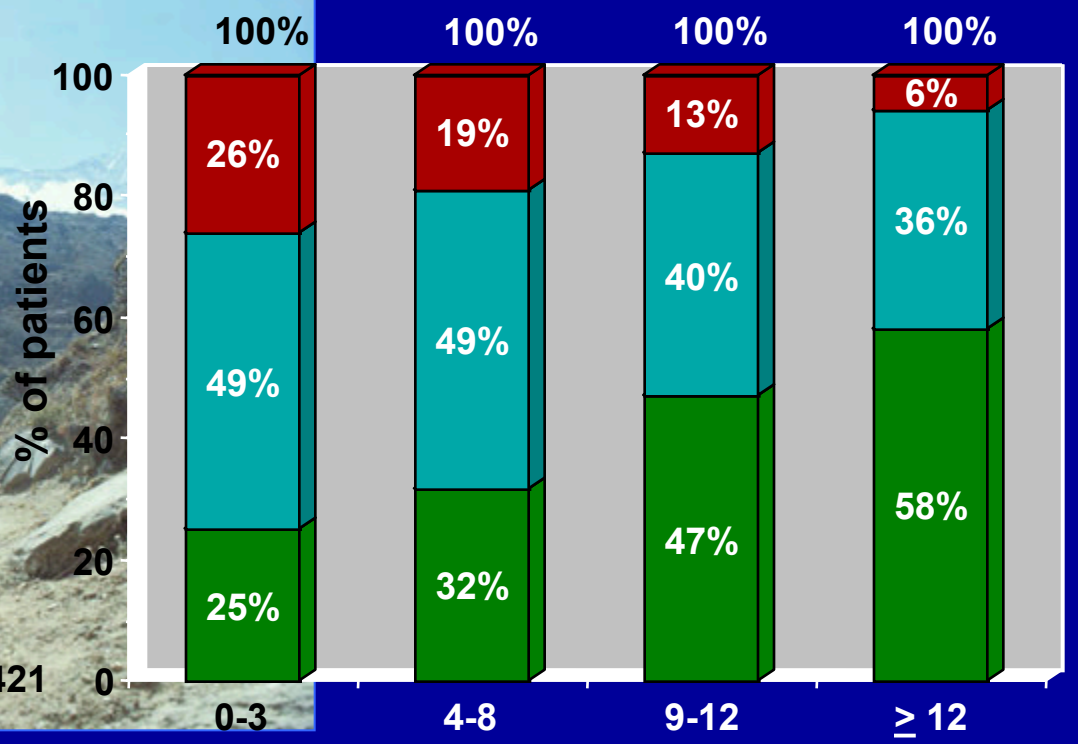
High altitude pulmonary edema



Excessive hypoxic pulmonary vasoconstriction

Prevention of high altitude illness

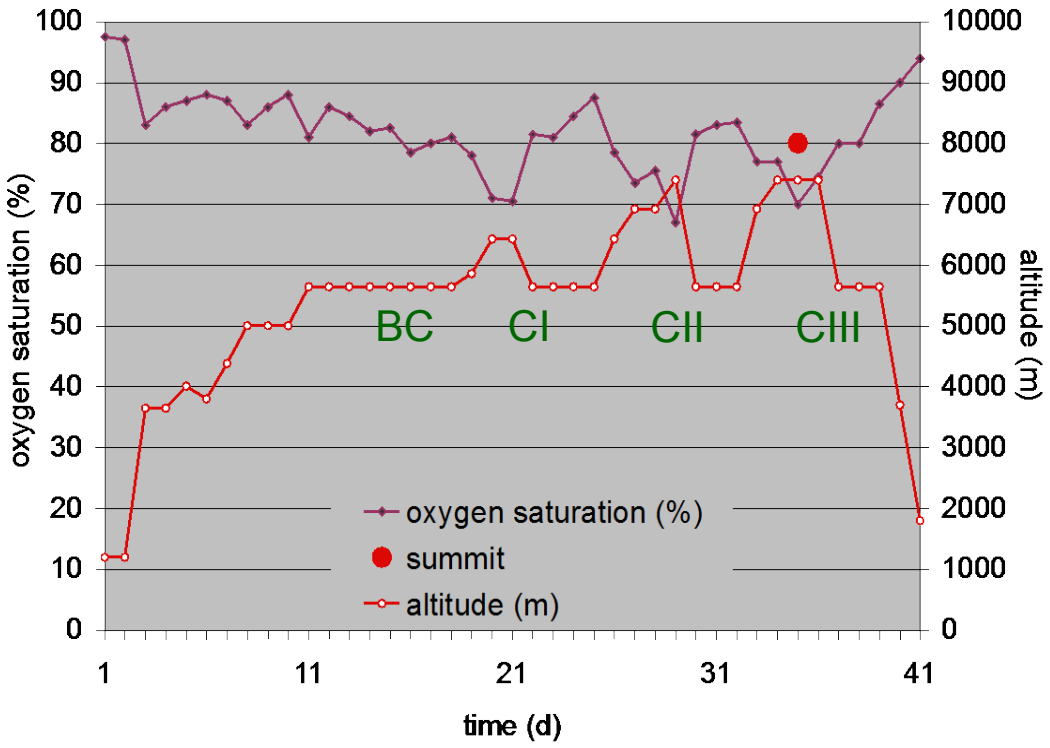




Rate of ascent < 600 m / day

Elite Mountaineers Expedition to Shisha Pagma 8005 m

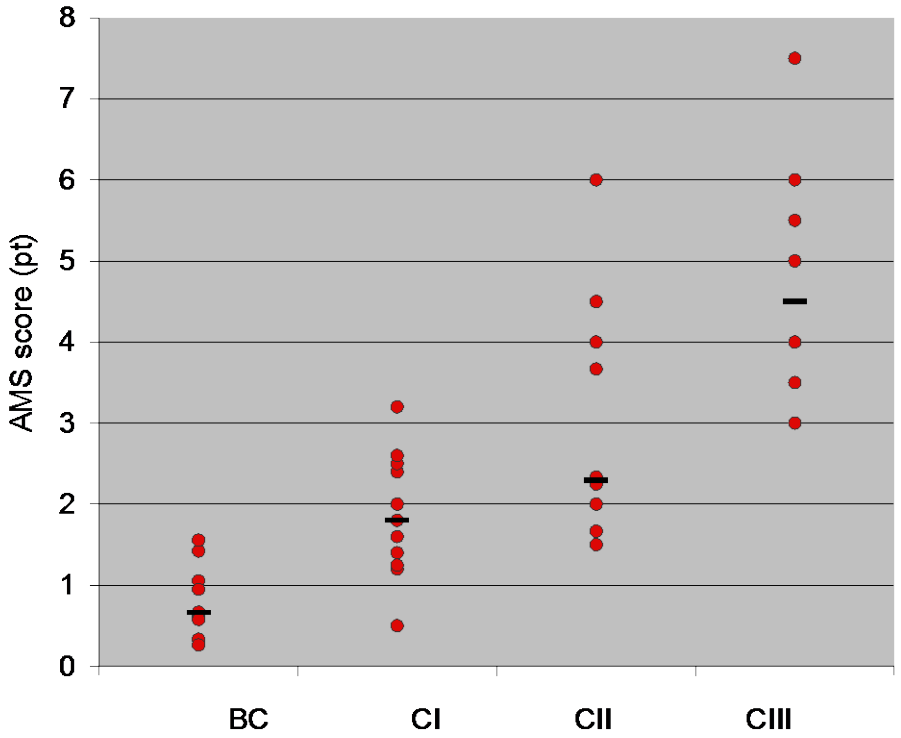
Ascent profile and SpO_2 12 elite mountaineers



Merz et al High Alt Med & Biol 2006

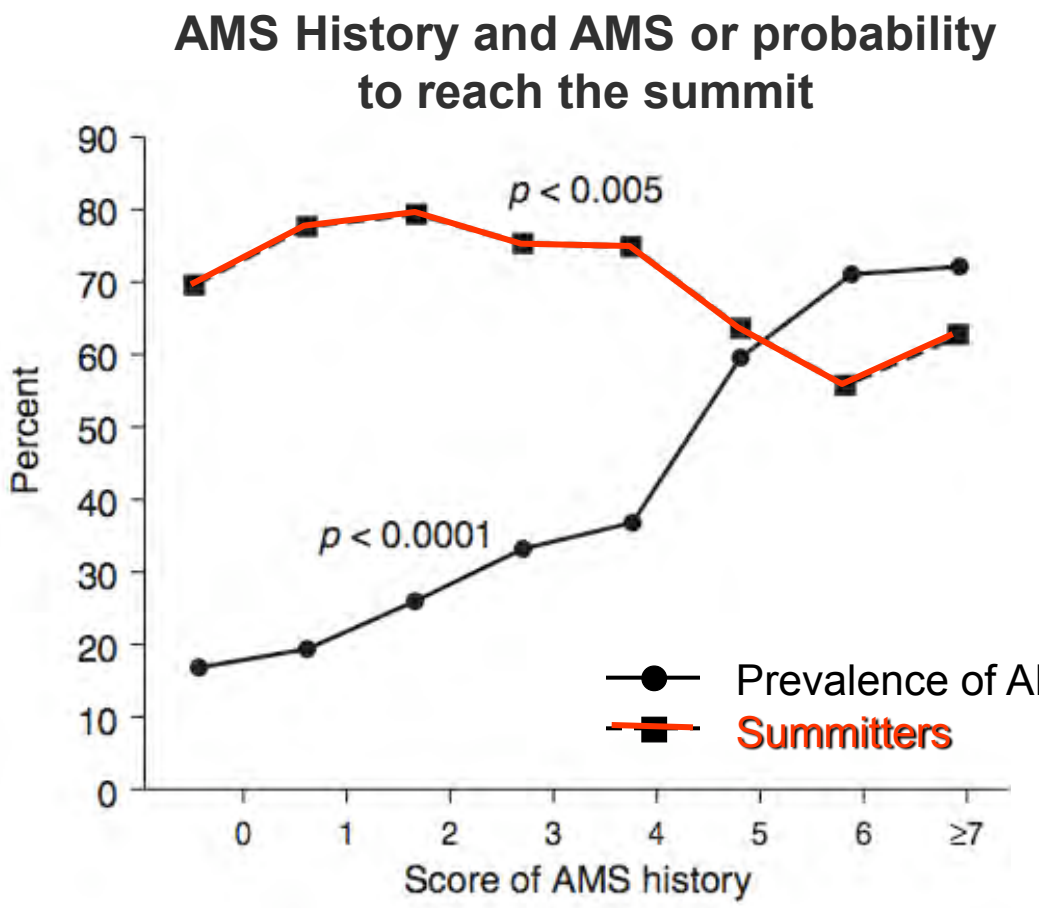
AMS: Individual Susceptibility

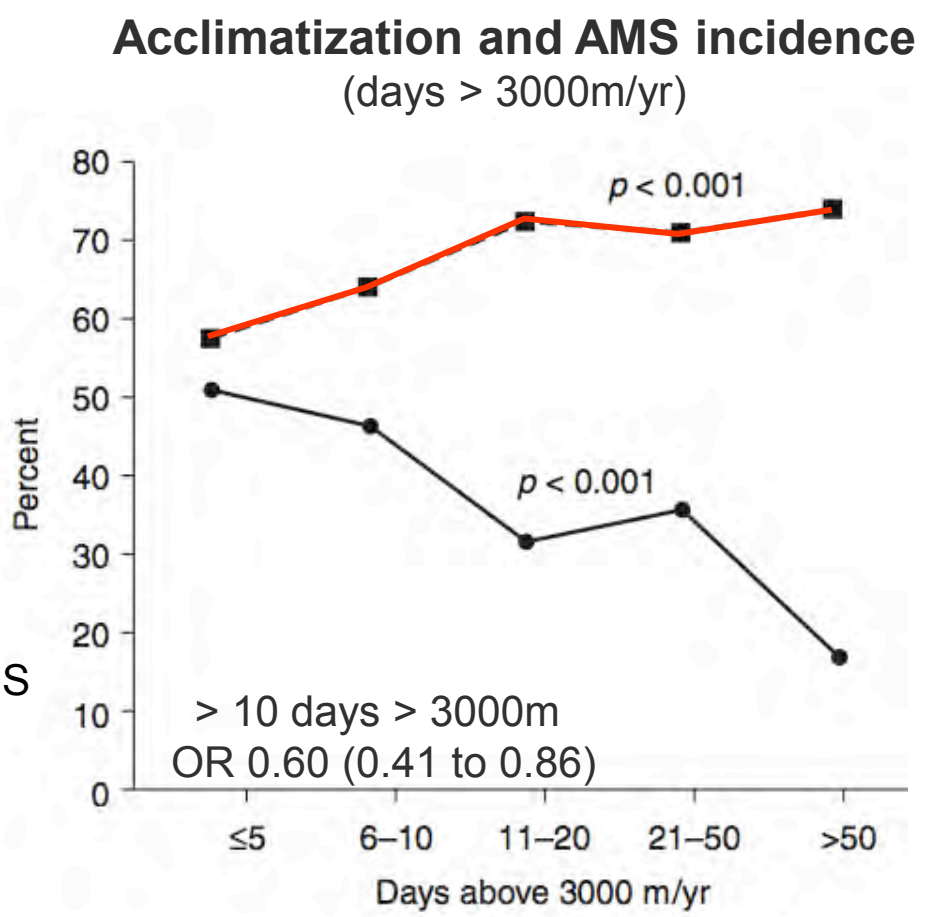
AMS-score during the expedition to Chichapagma 8005m of 12 elite mountaineers: High individual variability of AMS incidence



Merz et al High Alt Med & Biol 2006

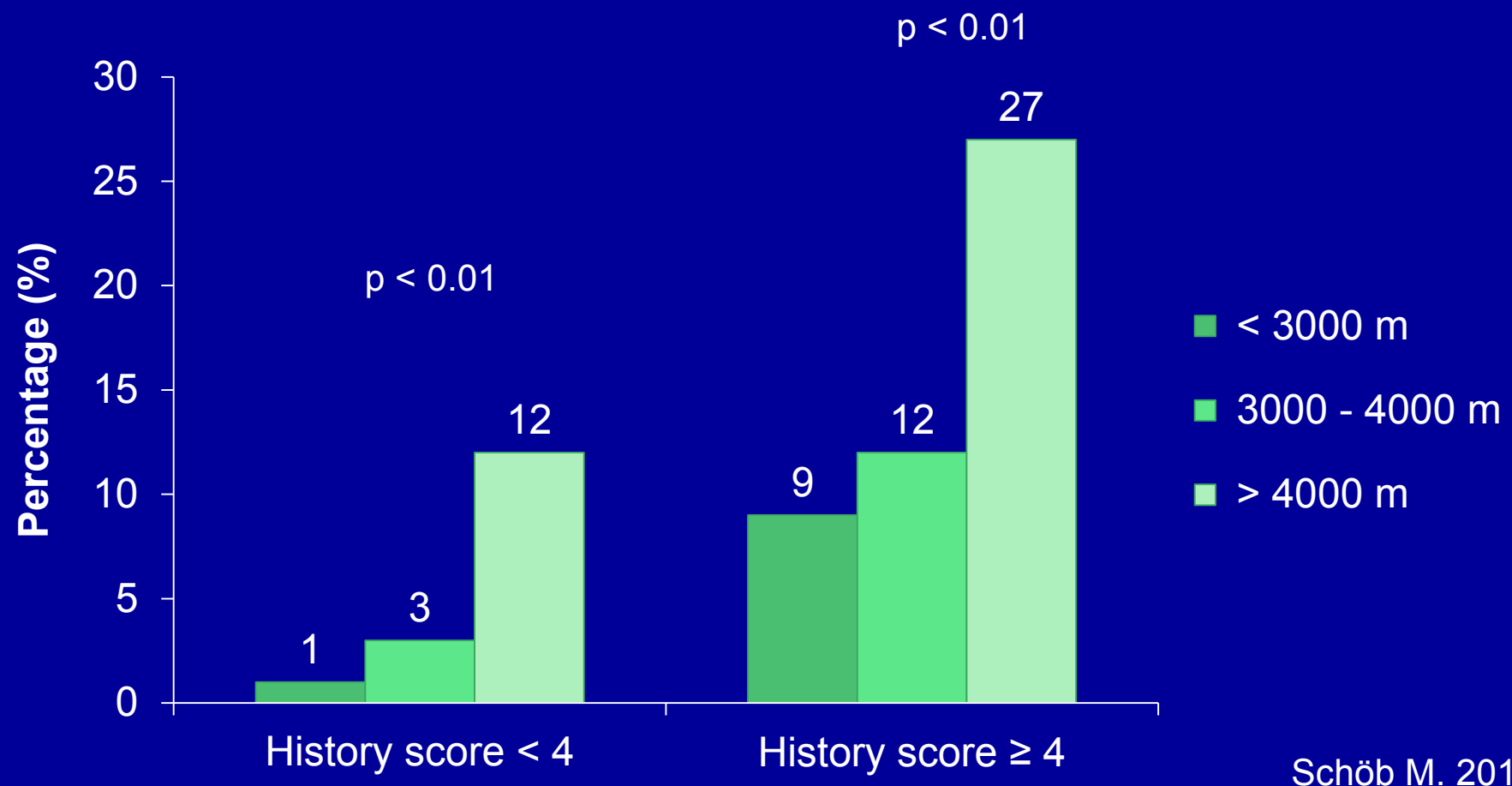
Individual AMS susceptibility and succeeding at the Mont Aconcagua (6962m)





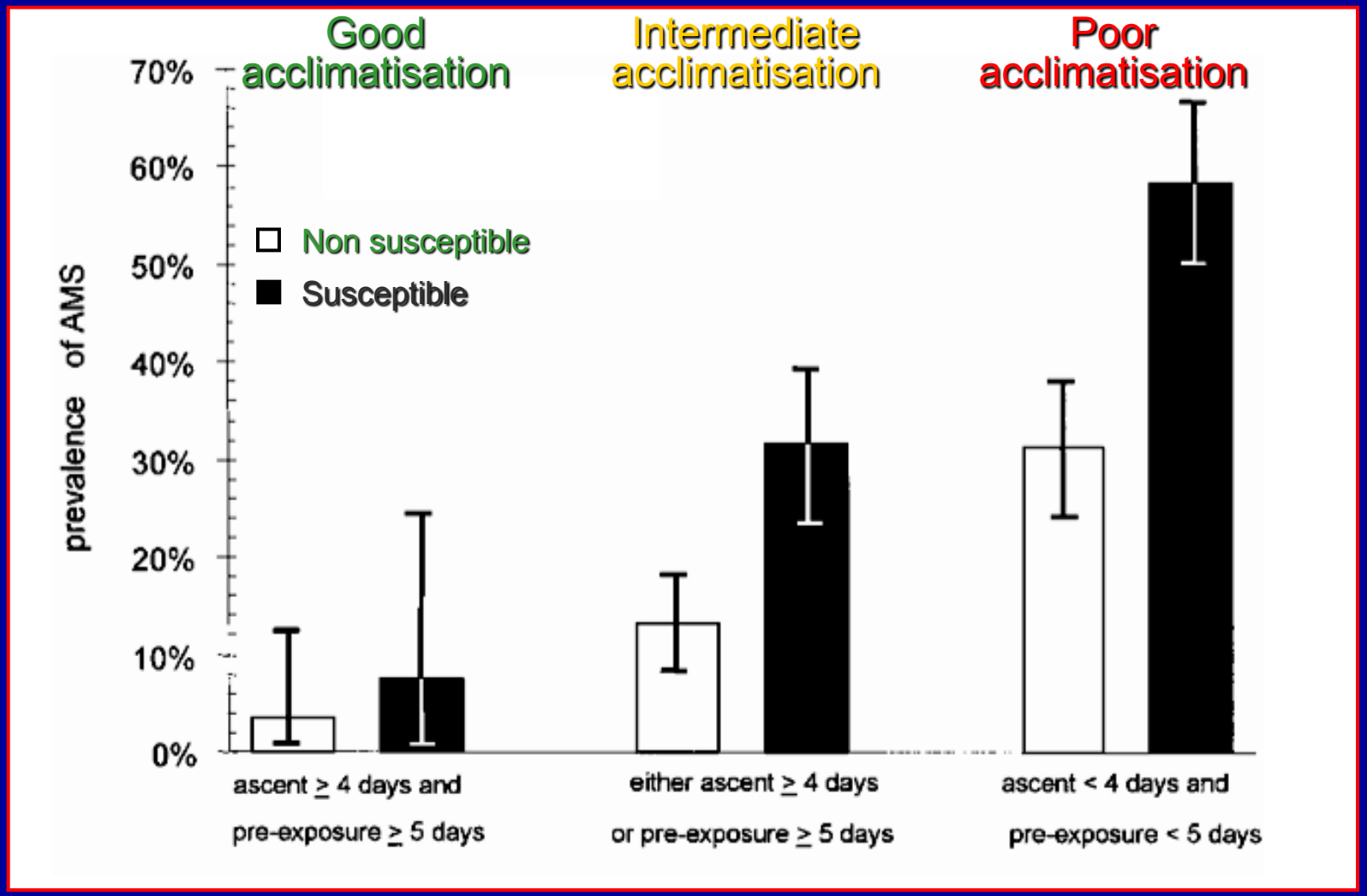
Pesce et al High Alt Med & Biol 2005, 6:258

Prevalence of AMS (Lake Louise Score > 4) depending on history score in 555 mountaineers



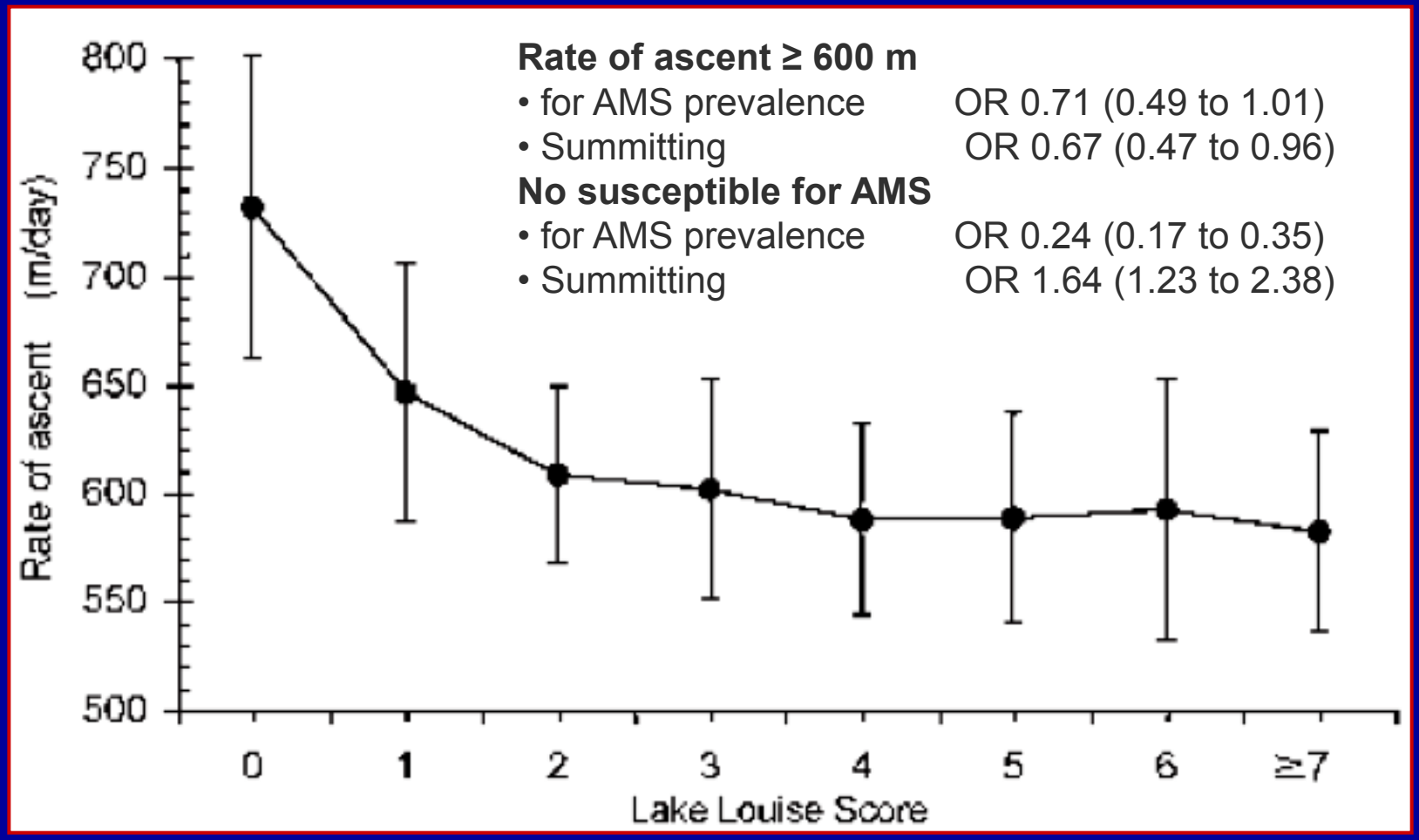
Schöb M. 2013

Individual susceptibility is the major risk factor for AMS at 4559m



Schneider et al Med Sci Sports Exerc 2002;; 34:1886

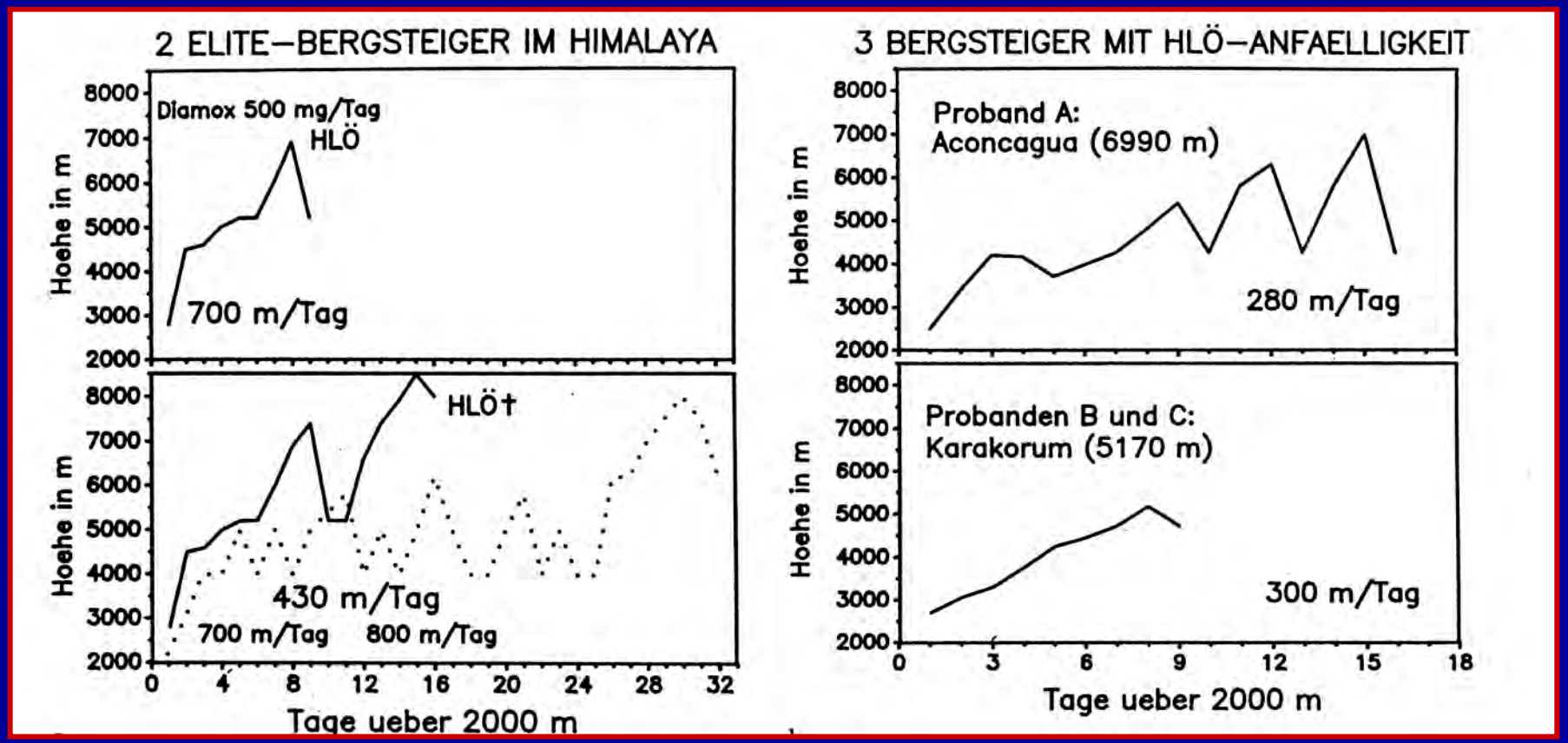
Not being susceptible individuals climb faster at the Mount Aconcagua (6962m)



Pesce et al High Alt Med & Biol 2005, 6:258

Anecdotal experiences

Question: Does an average ascent rate of < 300m/day protect from AMS, HAPE and/or HAPE?



Risk Assessment for high altitude illness

Risk	Planned Ascent and Clinical History
Low	• Slow ascent (≤500 m/day above 2500 m); • No history of AMS, HACE, or HAPE with previous exposure to similar altitude; • Persons who are partially acclimatized (exposure to high altitudes of <3000 m in preceding weeks) planning a rapid ascent (>500 m/day below 4000 m)
Moderate	• Unknown history of AMS, HACE, or HAPE and fast ascent (>500 m/day above 3000 m), i.e air craft, car, train • History of AMS, HACE, or HAPE with previous exposure to high altitude that is similar to the planned ascent planning a slow ascent (≤500 m/day between 2500 and 4000 m) or who are partially acclimatized (exposure to high altitudes of >3000 m in preceding weeks)
High	• Unknown history of AMS, HACE, or HAPE, very rapid ascent (considerably >500 m/day), and high final altitude (>4000 m); • History of AMS, HACE, or HAPE with previous exposure to high altitude that is similar to the planned ascent without partial acclimatization

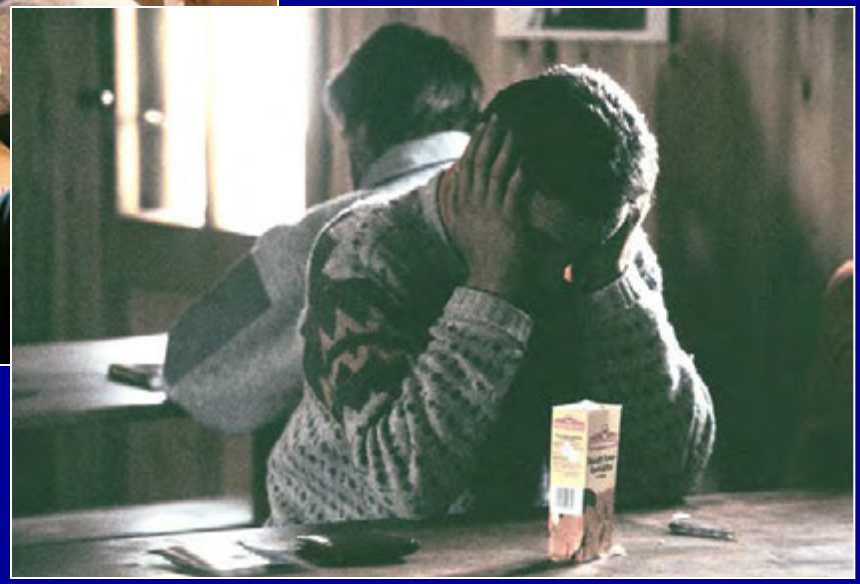
Symptoms of acute mountain sickness

Excessive fatigue

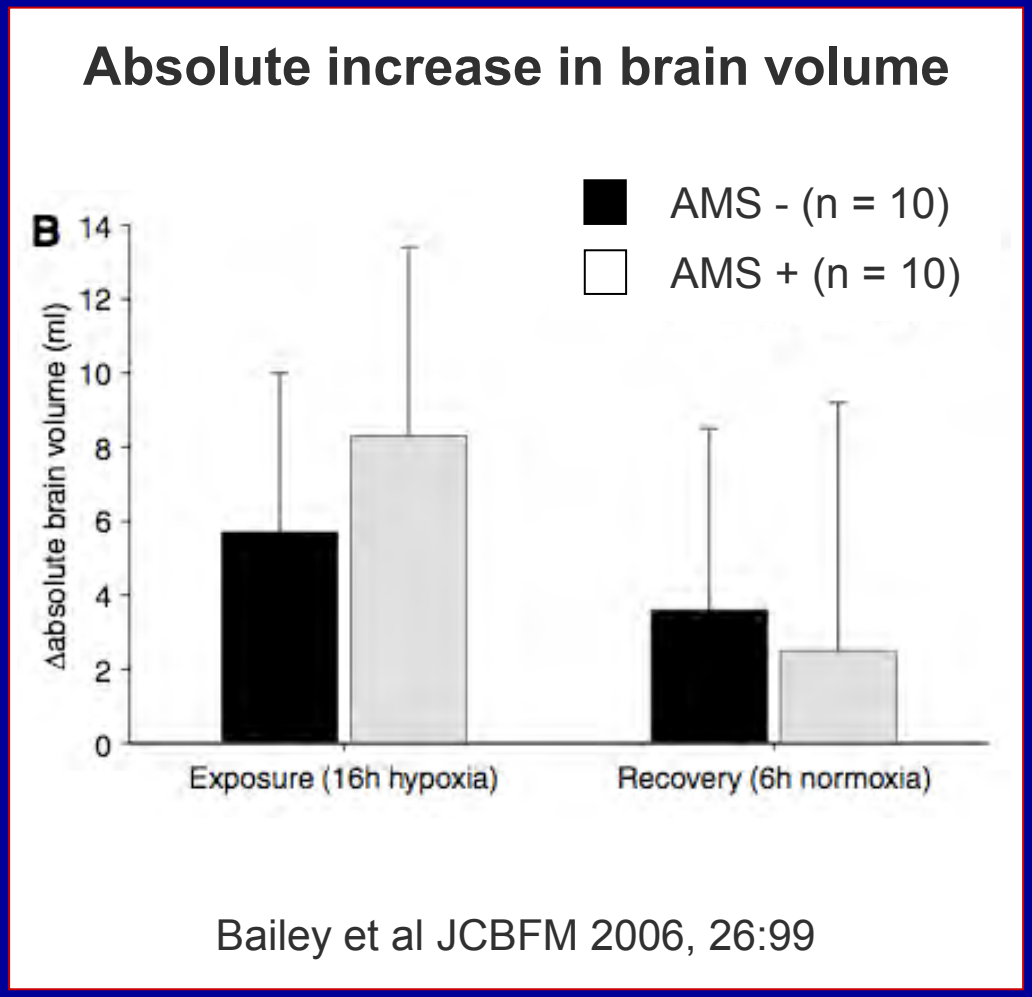
Lassitude

Nausea, Vomiting

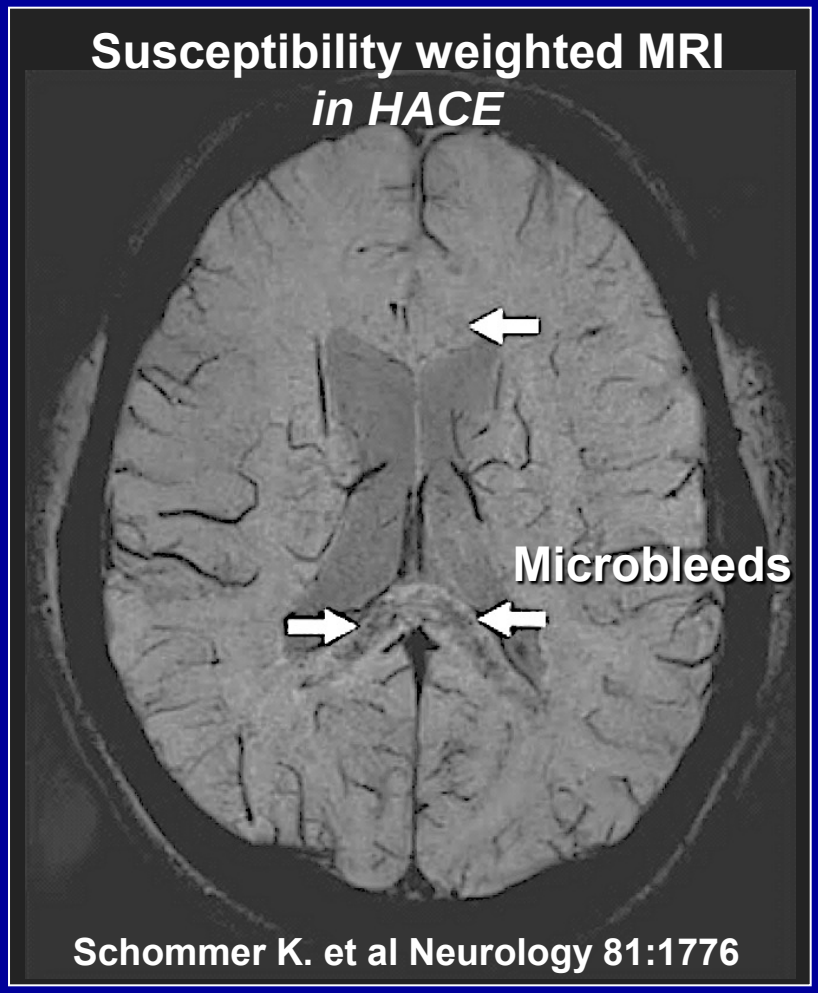
Headache



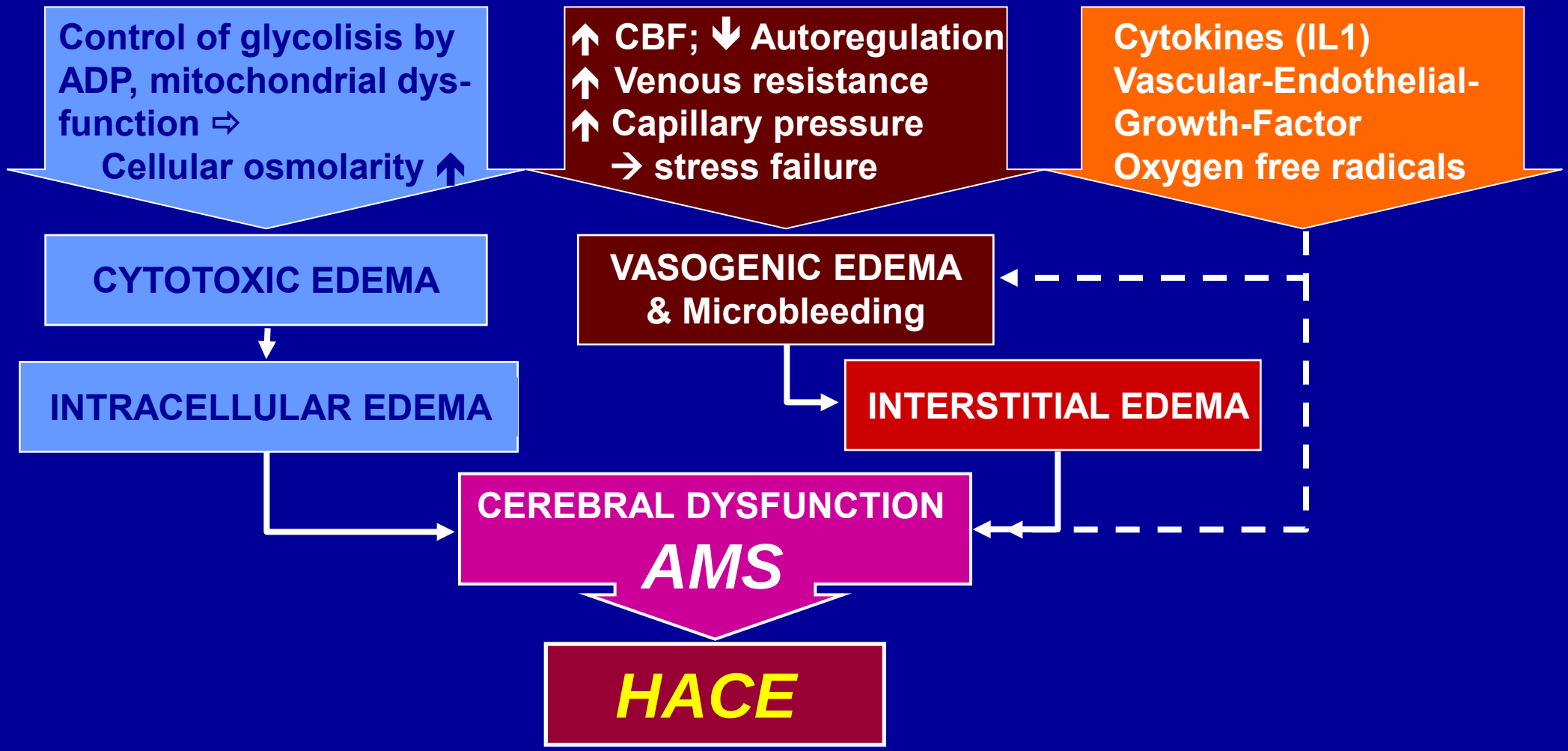
Pathophysiology of AMS: Brain swelling (edema) and microbleeds



Bailey et al JCBFM 2006, 26:99



Pathophysiology of acute mountain sickness

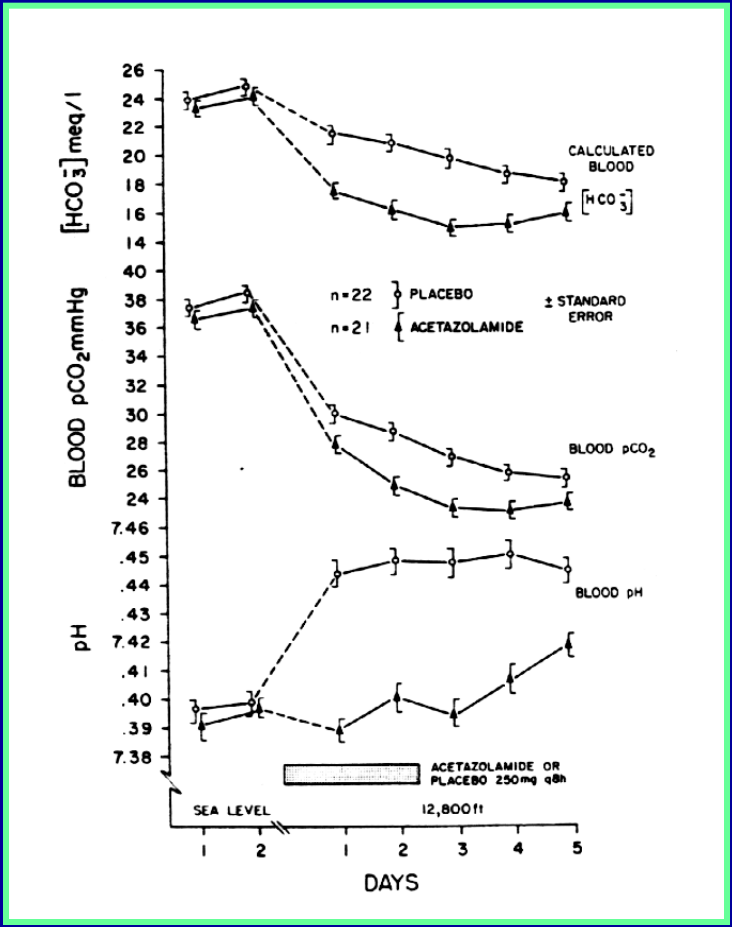


Drugs for prevention and treatment of acute mountain sickness (AMS)

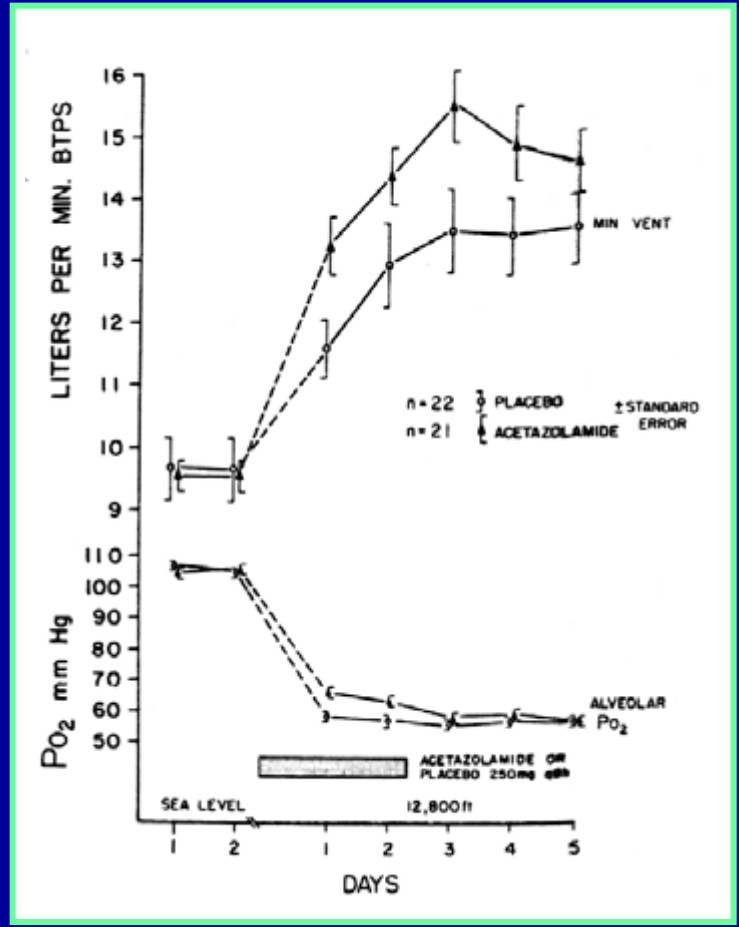
- **Symptomatic treatment**
  - ✓ Paracetamol, Aspirin, Ibuprofen
  - ✓ Protone pump inhibitors
  - ✓ Metoclopramid, Loperamid
- **Prevention of acute mountain sicknss**
  - ✓ Acetazolamide
- **Treatment of acute mountain sickness**
  - ✓ Acetazolamide (milde AMS)
  - ✓ Dexamethasone (moderate to severe AMS)

Mechanism of acetazolamide

Metabolic acidosis

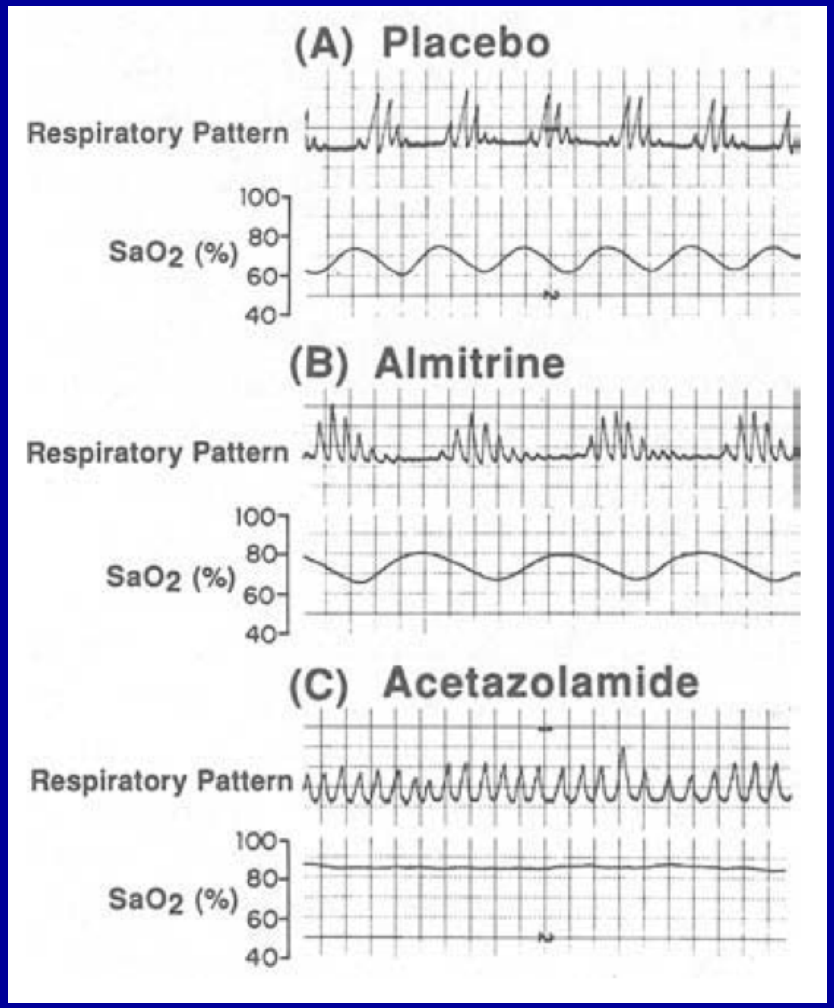


Ventilation & PaO_2



Forwand et al. N Engl J Med 1968; 279: 839-45

Acetazolamide and altitude associeted periodic breathing

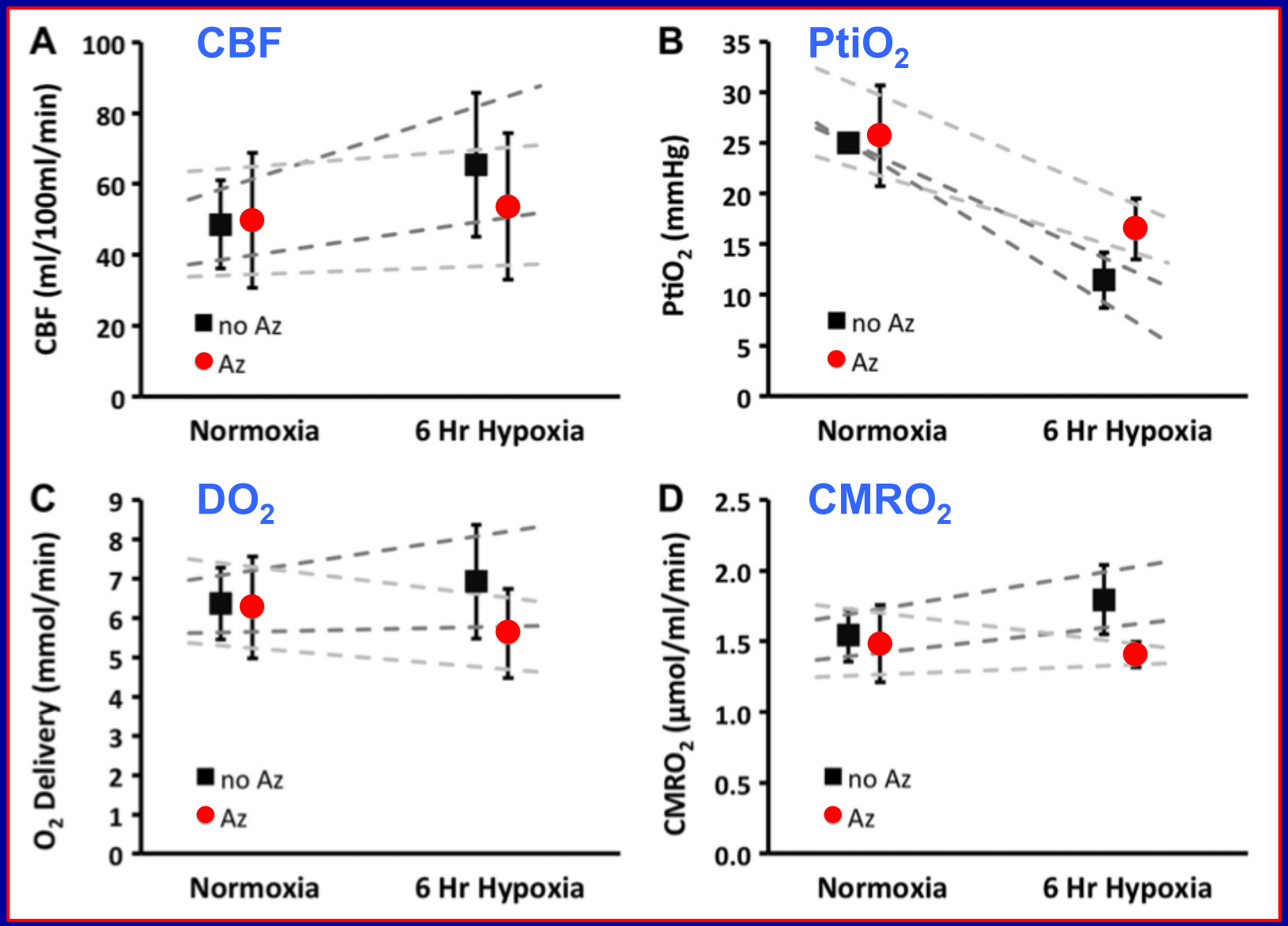


		AC	AL	PL	p value
AMS-R	*before*	0.8±0.1	1.1±0.2	0.8±0.1	ns
	after	0.6±0.1*	0.9±0.1	0.8±0.1	<0.05
PaO2	*before*	35±1	35±1	36±1	ns
	after	41±1**	39±1**	38±2	ns
(A-a)PO_2	*before*	14±1	12±1	11±1	ns
	after	10±1 **	13±1	11±2	<0.05

Pallavicini E. 1994

Hackett P. ARRD 1987

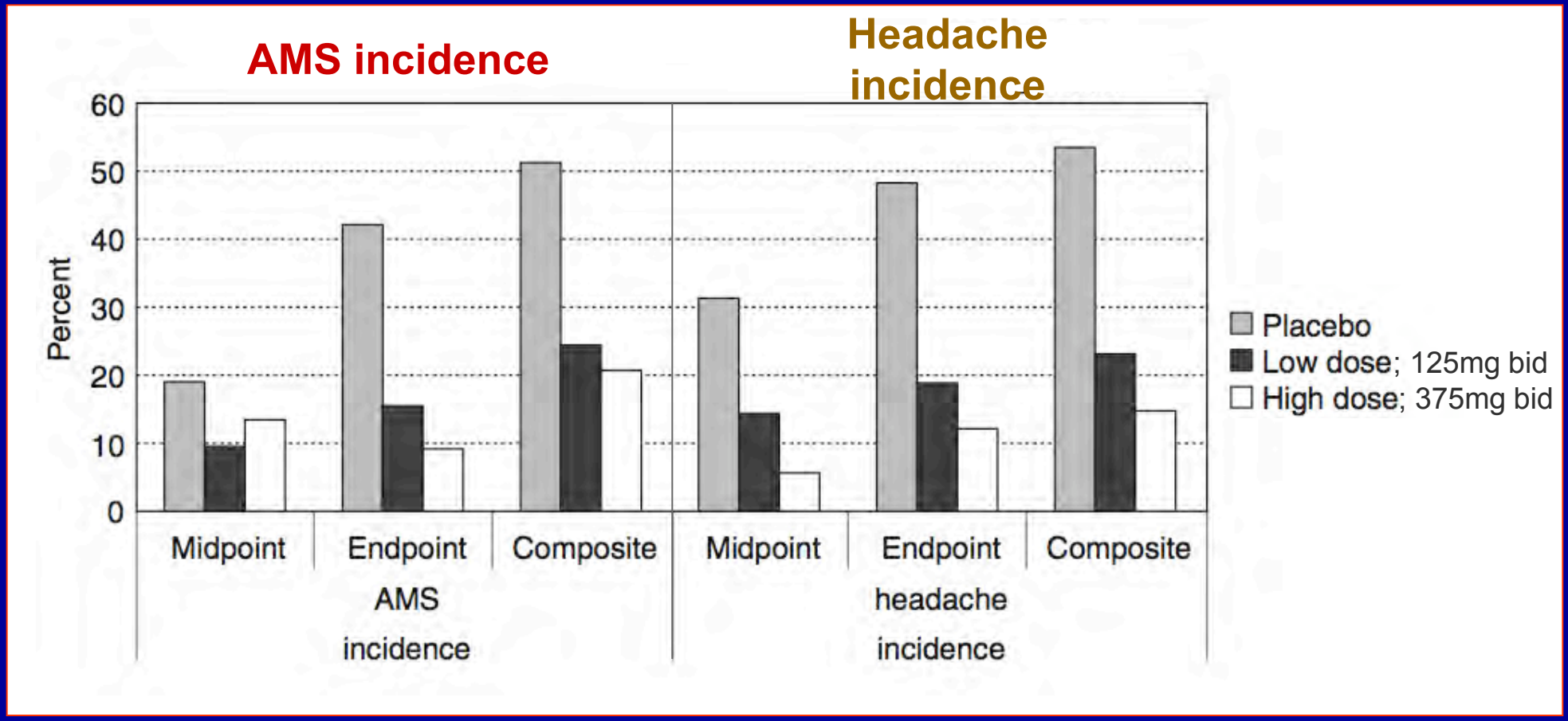
Acetazolamide prophylaxis attenuates increase in cerebal metabolic rate and tissue hypoxia



Wang K. et al. *J Appl Physiol* 2015 119: 1494

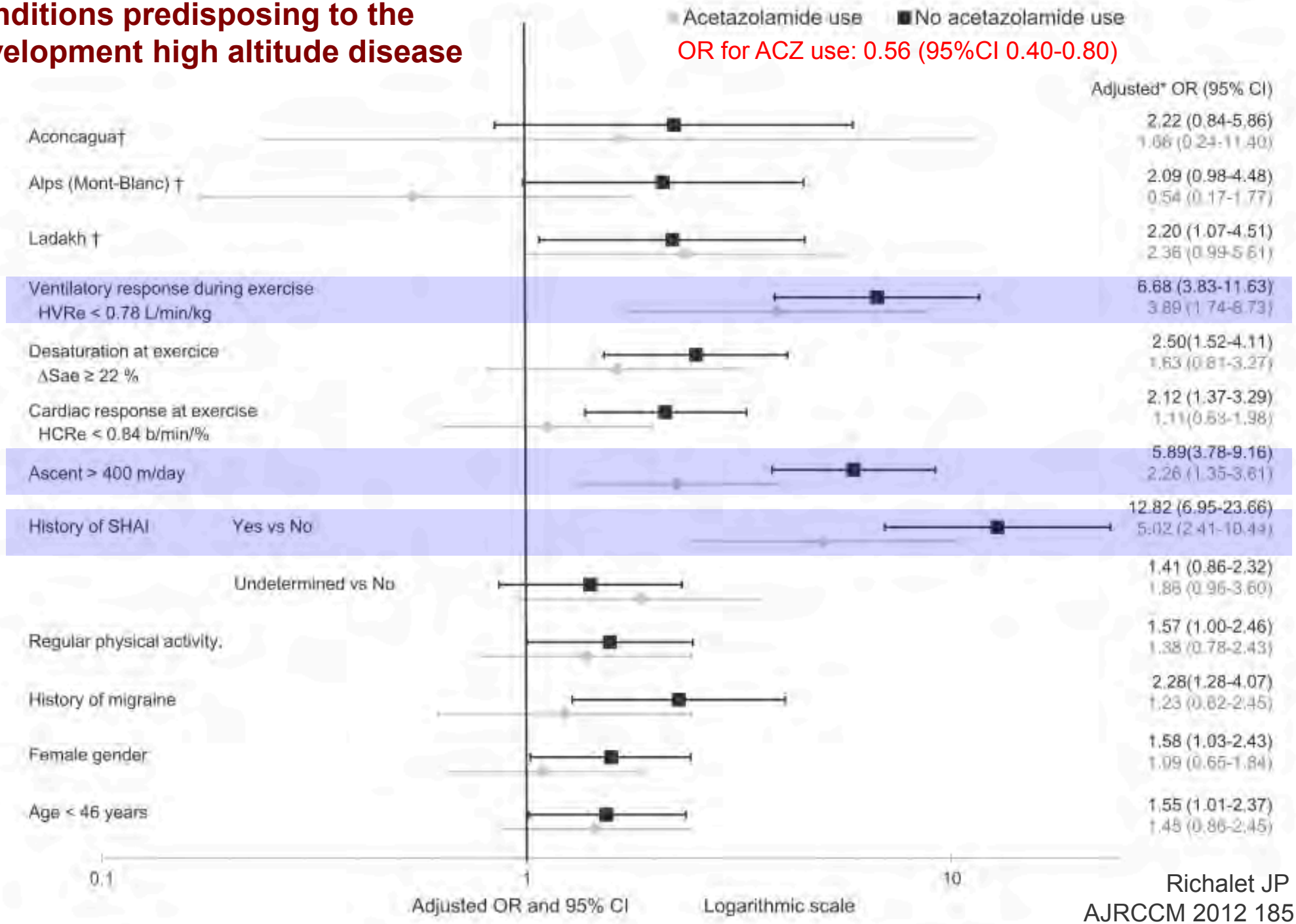
Low dose Acetazolamide (2 x125mg) for prophylaxis of AMS

Placebo controlled study in Trekkers ascending to Mt Everest base camp (5350m)



Basynat et al HAMB 2006; 7:17

Conditions predisposing to the development high altitude disease



Richalet JP et al
AJRCCM 2012 185:192

PRP Pharmacology Research & Perspectives
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ORIGINAL ARTICLE

Pharma Res Per, 4(3), 2016, e00203,

Benzolamide improves oxygenation and reduces acute mountain sickness during a high-altitude trek and has fewer side effects than acetazolamide at sea level

David J. Collier[1], Chris B. Wolff[1], Anne-Marie Hedges[1], John Nathan[2], Rod J. Flower[1], James S. Milledge[3] & Erik R. Swenson[4]

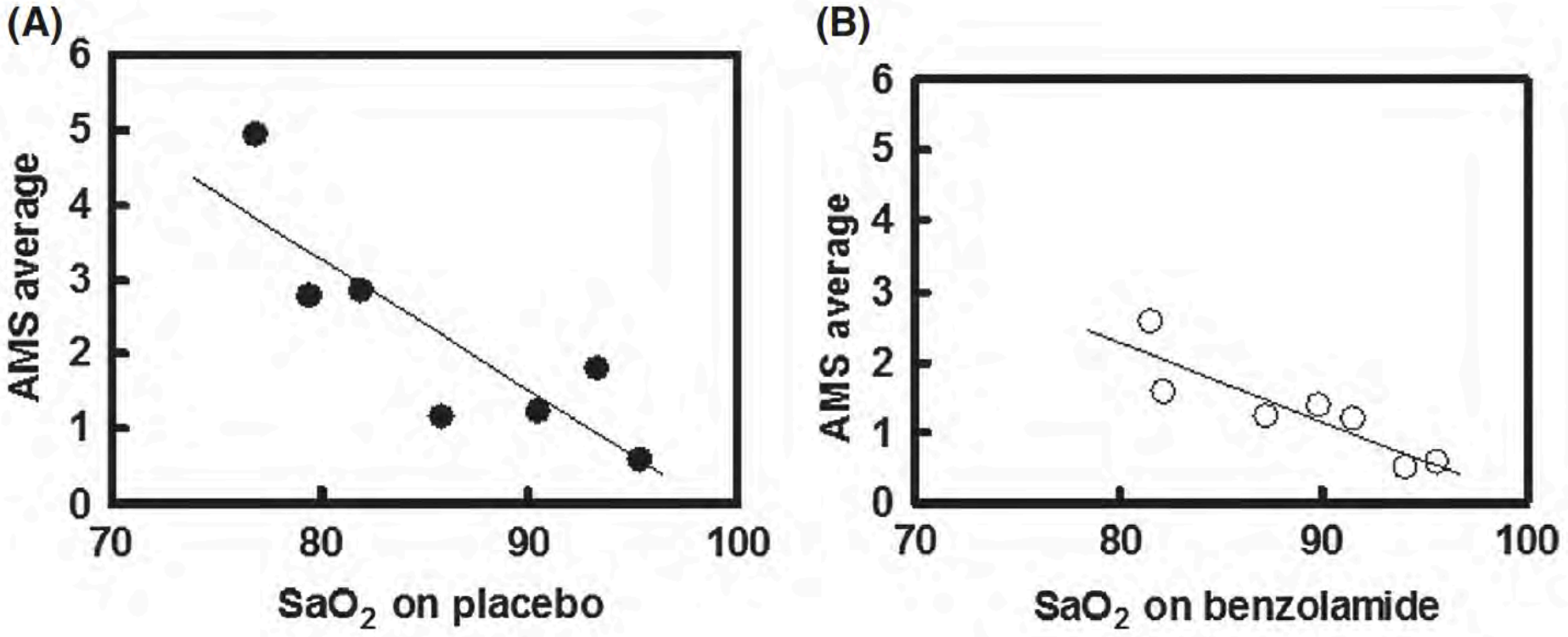

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Table 3. Change in VAS[1] score from placebo at 6.5 h after drug ingestion.

	ACTZ 250	ACTZ 500	ACTZ 1000	BENZ 200	LOR 2
Dizziness	15	18	38	−5	18
Decline in concentration	21	19	42	2	9
Sleepiness	15	22	28	0	15

[1]Visual analog score of symptom severity: range 0–100.

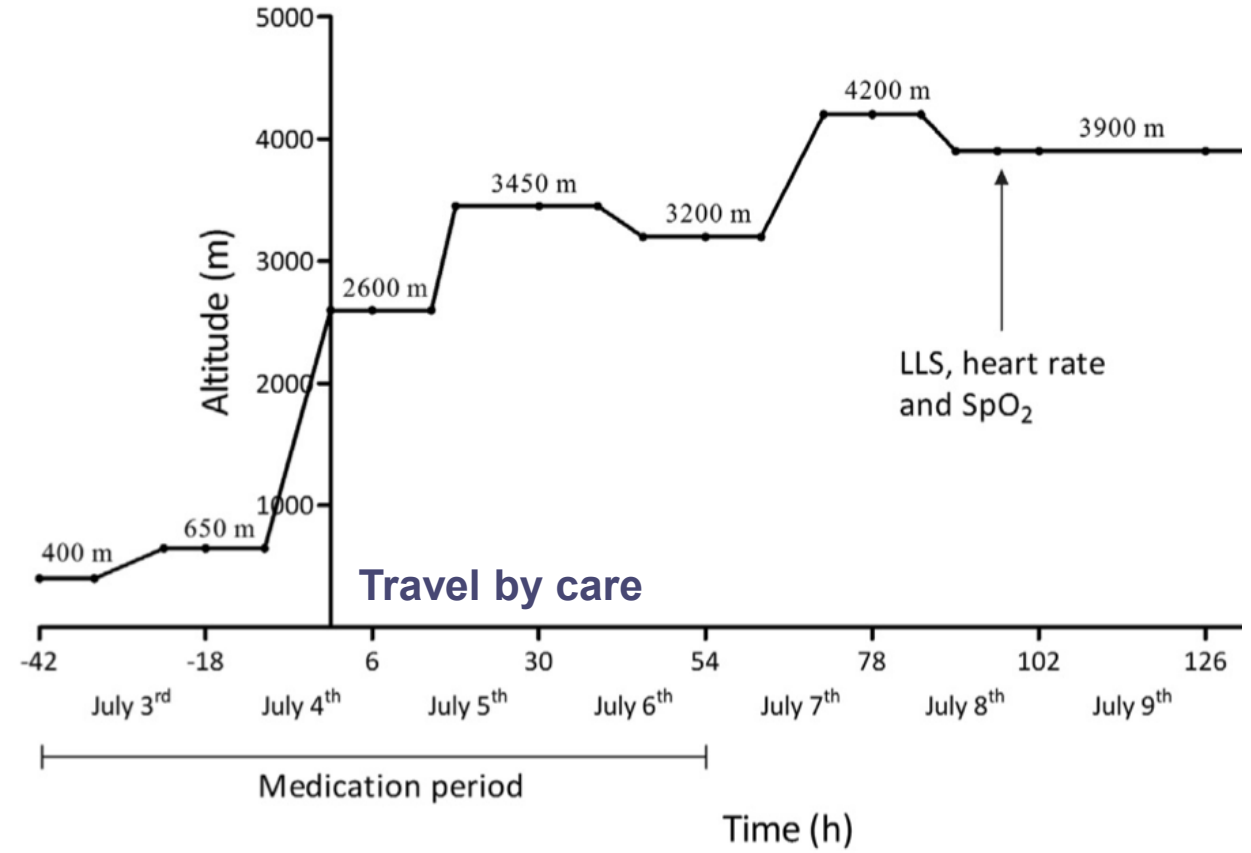
Inhaled Budesonide and Oral Dexamethasone Prevent Acute Mountain Sickness☆

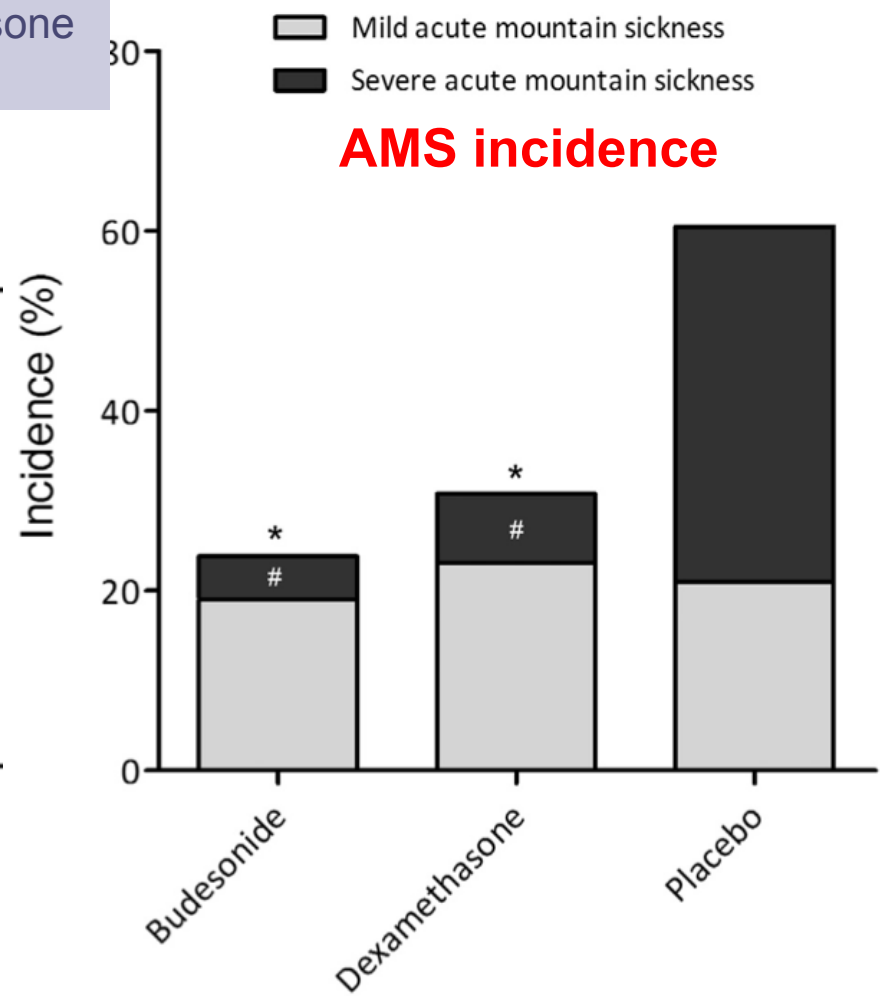
Cheng-Rong Zheng, MD,[a,*] Guo-Zhu Chen, PhD,[a,b,*] Jie Yu, PhD,[a,b] Jun Qin, PhD,[a,b] Pan Song, MM,[a] Shi-Zhu Bian, MD,[a,b] Bai-Da Xu, MM,[a] Xu-Gang Tang, PhD,[a] Yong-Tao Huang, MM,[a] Xiao Liang, MM,[a] Jie Yang, MM,[a] Lan Huang, MD, PhD[a,b]

[a]Institute of Cardiovascular Science, Xinqiao Hospital, Third Military Medical University, Chongqing, China; [b]PLA Institute of Cardiovascular Disease, Chongqing, China.

Am J Med 2014 127:1001-1009

Inhaled budesonide (200 mg, twice a day [bid]), oral dexamethasone (4 mg, bid), or placebo (46 in each group).

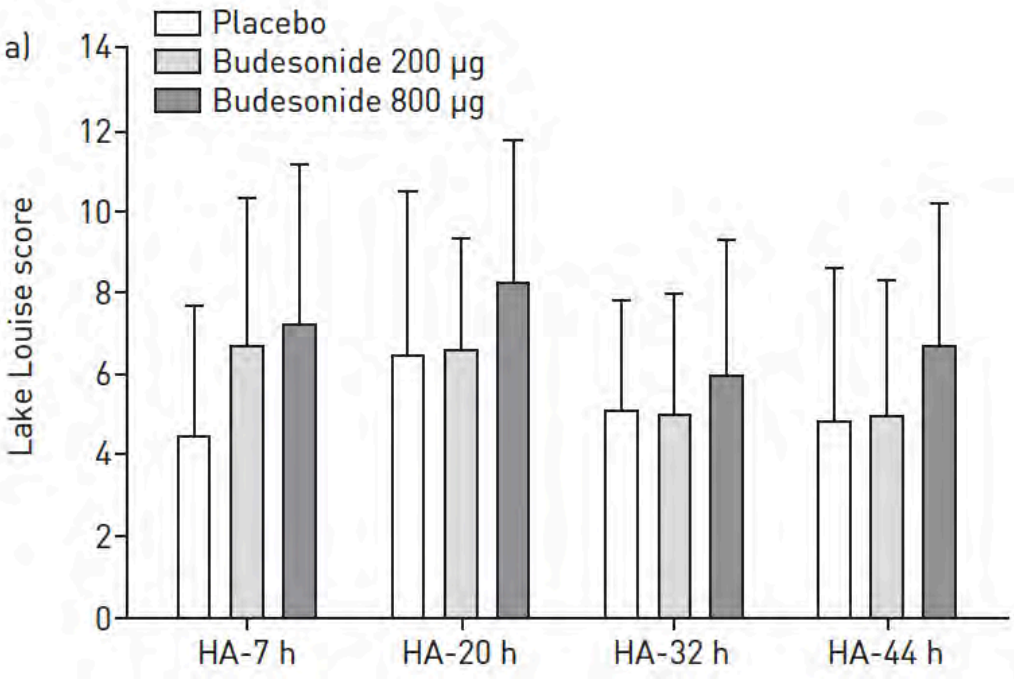




Inhaled budesonide does not prevent acute mountain sickness after rapid ascent to 4559 m

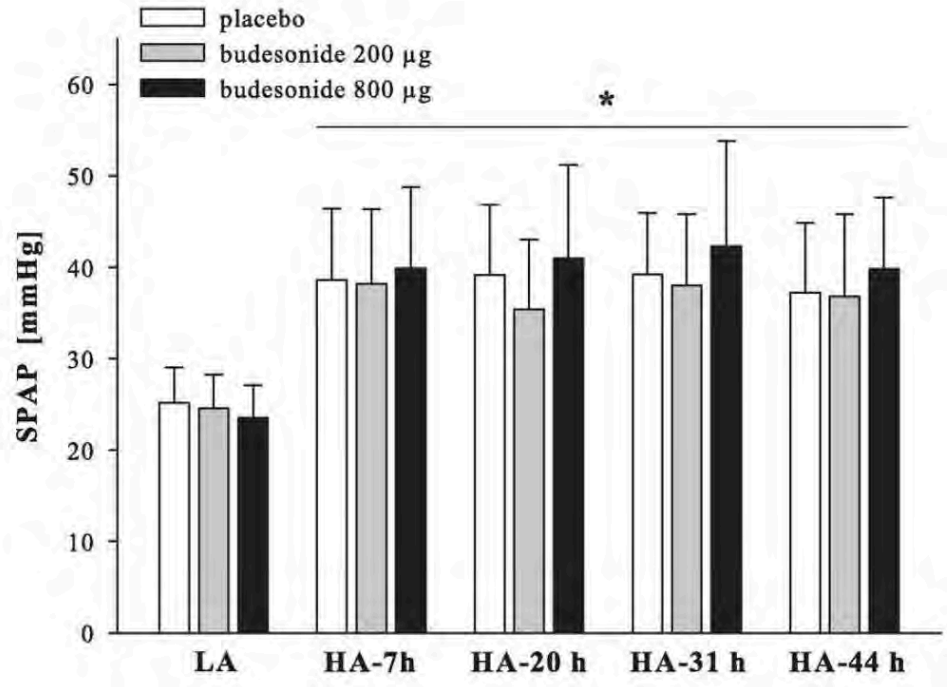
Inhaled budesonide 200 mg (16) or 800 mg (17) bid, or placebo (16) started 24h prior to ascent

AMS score



Berger et al. ERJ 2017

Systolic Pulmonary Artery Pressure



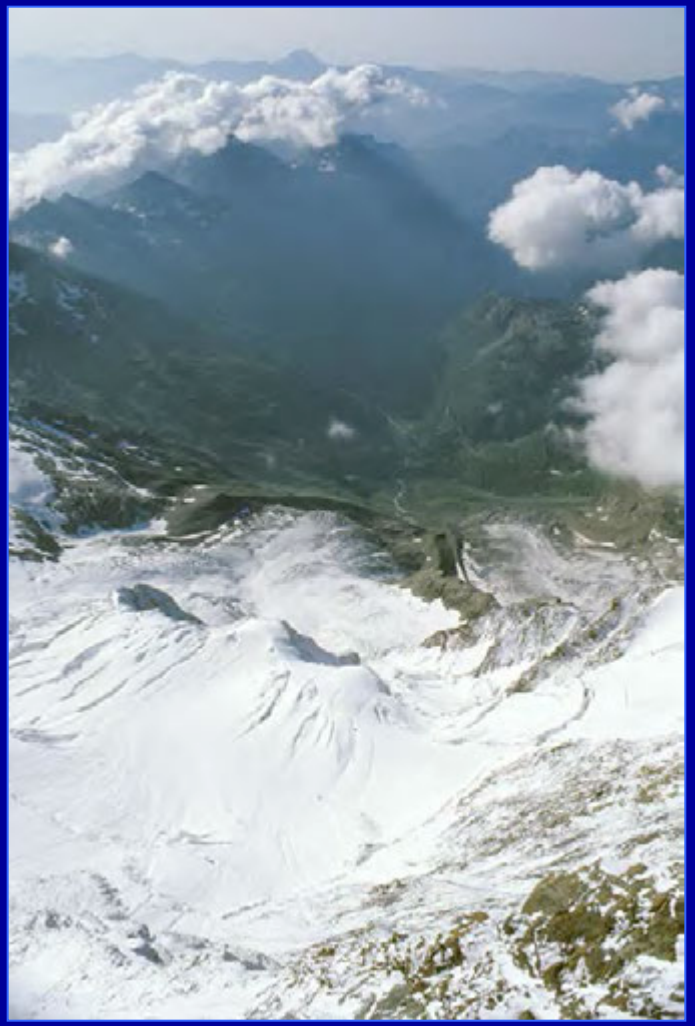
Berger et al. High Alt Med Biol 2017

Inhaled budesonide does not prevent acute mountain sickness after rapid ascent to 4559 m

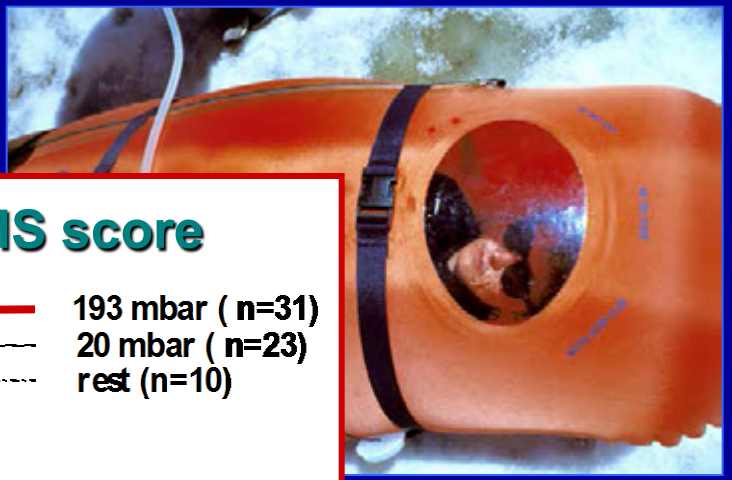
Berger et al. ERJ 2017

	LA	HA-7 h	HA-20 h	HA-32 h	HA-44 h	p-value (t)	p-value (group)	p-value (x group)
S_{pO_2} %								
Placebo	97±1	79±7	82±6	81±10	83±7			
B200	97±1	77±8	81±8	79±9	82±9	<0.001	0.467	0.657
B800	98±1	75±7	80±5	80±6	80±6			
Capillary P_{O_2} mmHg								
Placebo	84±7	46±4	48±5	47±6	49±5			
B200	85±8	47±5	48±5	48±6	50±6	<0.001	0.072	0.885
B800	82±6	43±4	48±3	47±4	46±3			
Capillary P_{CO_2} mmHg								
Placebo	35±3	27±2	26±2	27±2	25±2			
B200	34±3	28±3	26±2	27±2	25±2	<0.001	0.710	0.484
B800	36±3	28±3	27±2	27±2	26±2			
Plasma ACTH pg·mL^{-1}								
Placebo	14.8±7.2	15.1±12.0	24.8±14.2	17.1±12.5	26.8±16.2			
B200	20.5±10.6	21.1±25.7	37.7±26.9	15.0±8.5	30.7±11.9	<0.001	0.276	0.647
B800	20.8±17.0	28.0±30.4	29.3±18.5	18.8±28.9	31.7±19.5			
Plasma cortisol ng·mL^{-1}								
Placebo	136±50	118±83	201±64	122±69	173±32			
B200	148±62	122±74	221±76	96±71	176±56	<0.001	0.944	0.578
B800	140±55	150±105	220±52	92±67	175±55			
Urine cortisol µg per 24 h								
Placebo	43.3±15.7				73.6±52.0			
B200	47.2±14.0				64.4±24.4	<0.001	0.958	0.667
B800	47.6±25.2				67.9±48.7			

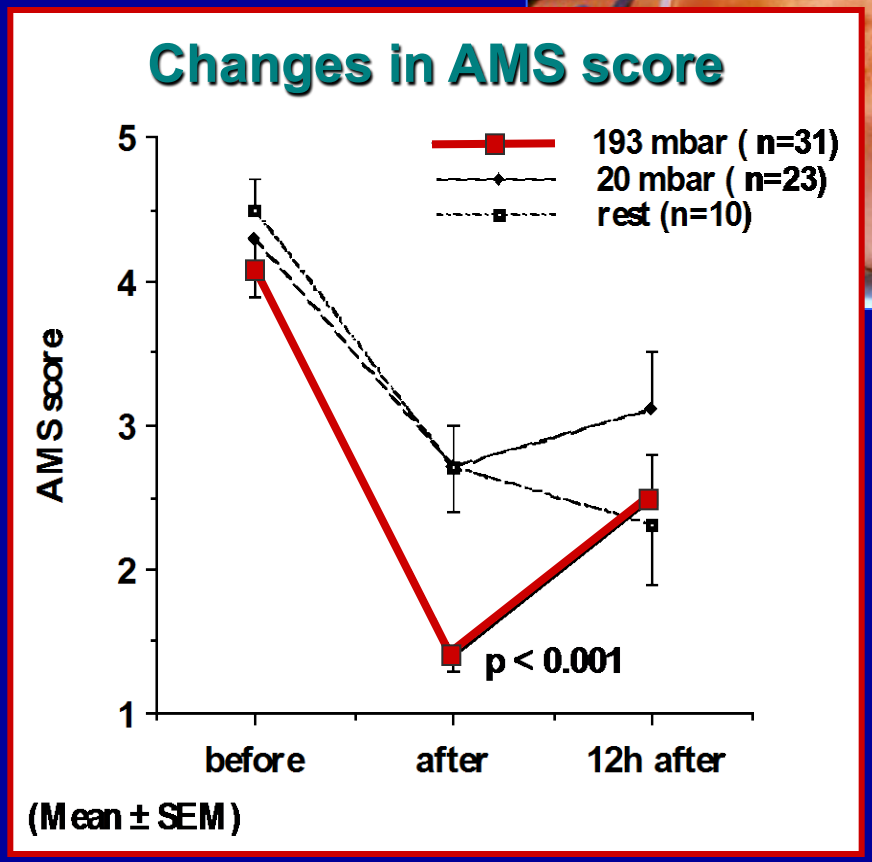
Rapid descent and bed-rest for the treatment of AMS



4500m
SpO2 70-75%



2200m
SpO2 90%



Bärtsch P et al.
Br Med J 1993,
306: 1098-1101

Treatment of acute mountain sickness

Excessive fatigue
Lassitude

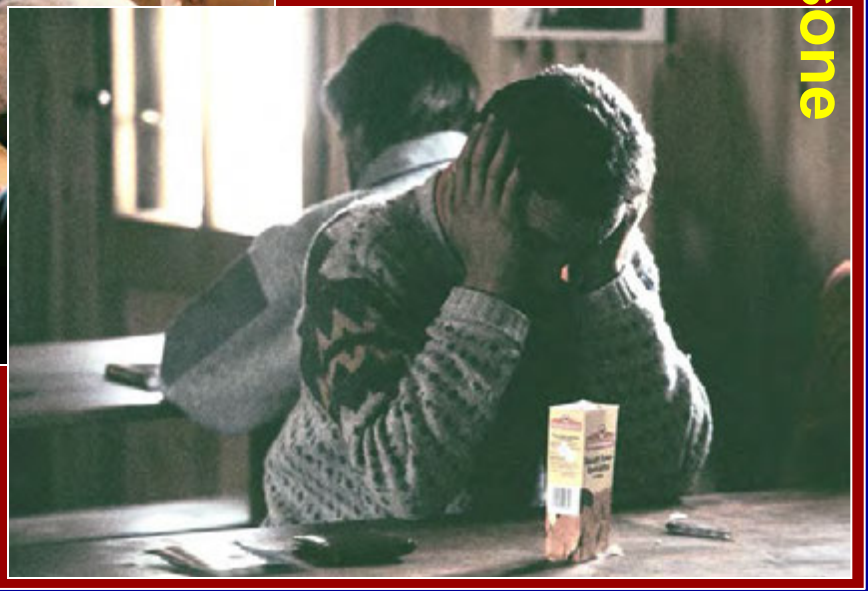
Acetazolamide

Headache, Nausea

Acetaminophen resistant headache, Vomiting

Dexamethasone

Altered mental status, Ataxia



Successful treatment of acute mountain sickness with dexamethasone

GIANMARIO FERRAZZINI, MARCO MAGGIORINI, SUSI KRIEMLER, PETER BÄRTSCH, OSWALD OELZ

Abstract

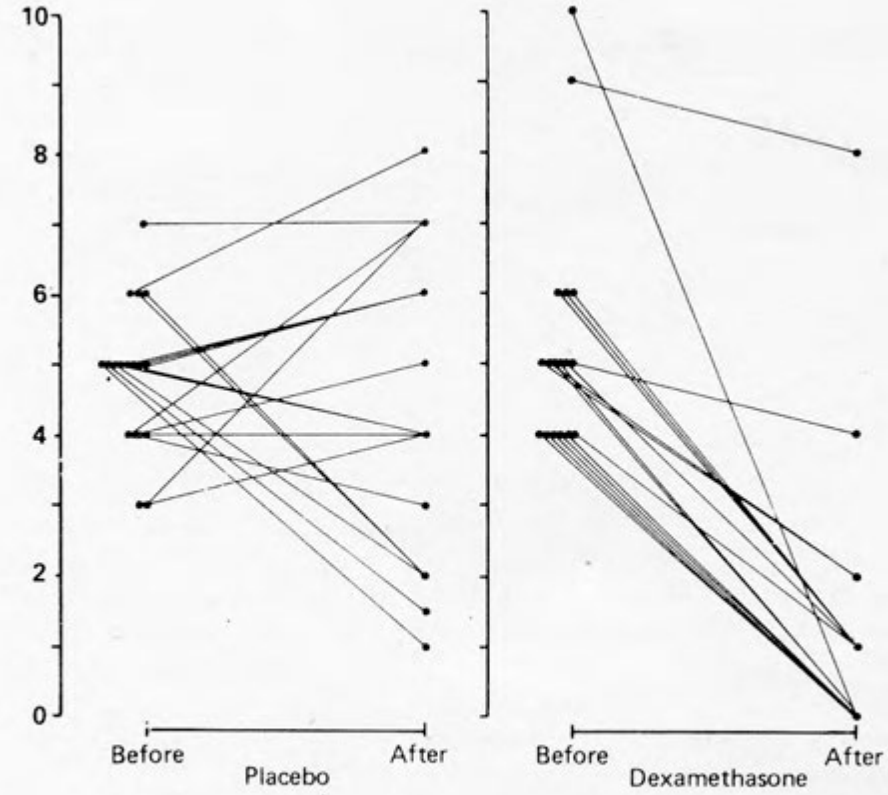
A double blind, randomised, placebo controlled trial of treatment with dexamethasone for acute mountain sickness was performed in the Capanna "Regina Margherita" at an altitude of 4559 m in the Alps Valais. After 12-16 hours of treatment (8 mg dexamethasone initially, followed by 4 mg every six hours) the mean acute mountain sickness score decreased significantly from 5·4 to 1·3, and eight of 17 patients became totally asymptomatic. Mean arterial oxygen saturation rose from 75·5% to 82·0%, and there

Department of Medicine, University Hospital, CH-8091 Zürich, Switzerland
GIANMARIO FERRAZZINI, MD, house officer in medicine
SUSI KRIEMLER, medical student
OSWALD OELZ, MD, lecturer in medicine

Ospedale la Carita, Locarno, Switzerland
MARCO MAGGIORINI, MD, house officer in medicine

Department of Medicine, University of Berne, Switzerland
PETER BÄRTSCH, MD, senior house officer in medicine

Correspondence to: Dr Oelz.



Acute mountain sickness score of mountaineers before and after 12-16 hours of treatment with placebo or dexamethasone.

British Medical Journal, Volume 294, 30 May 1987

Effects of acetazolamide and dexamethasone in subjects with AMS

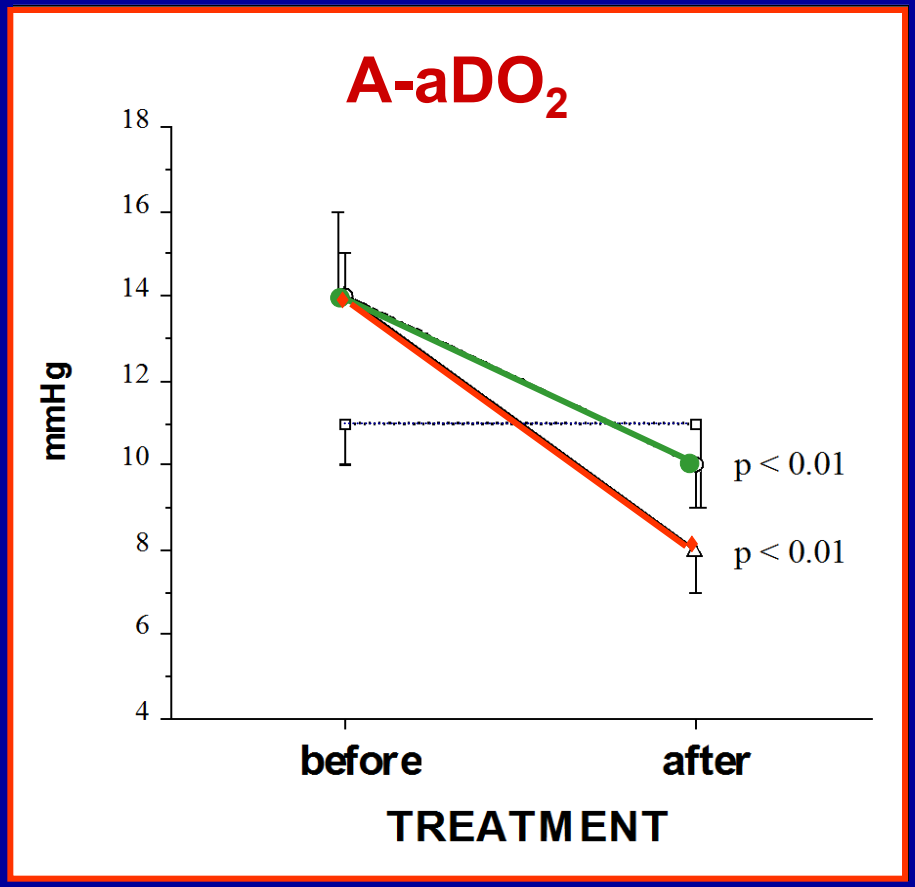
Randomized placebo controlled trial for AMS treatment

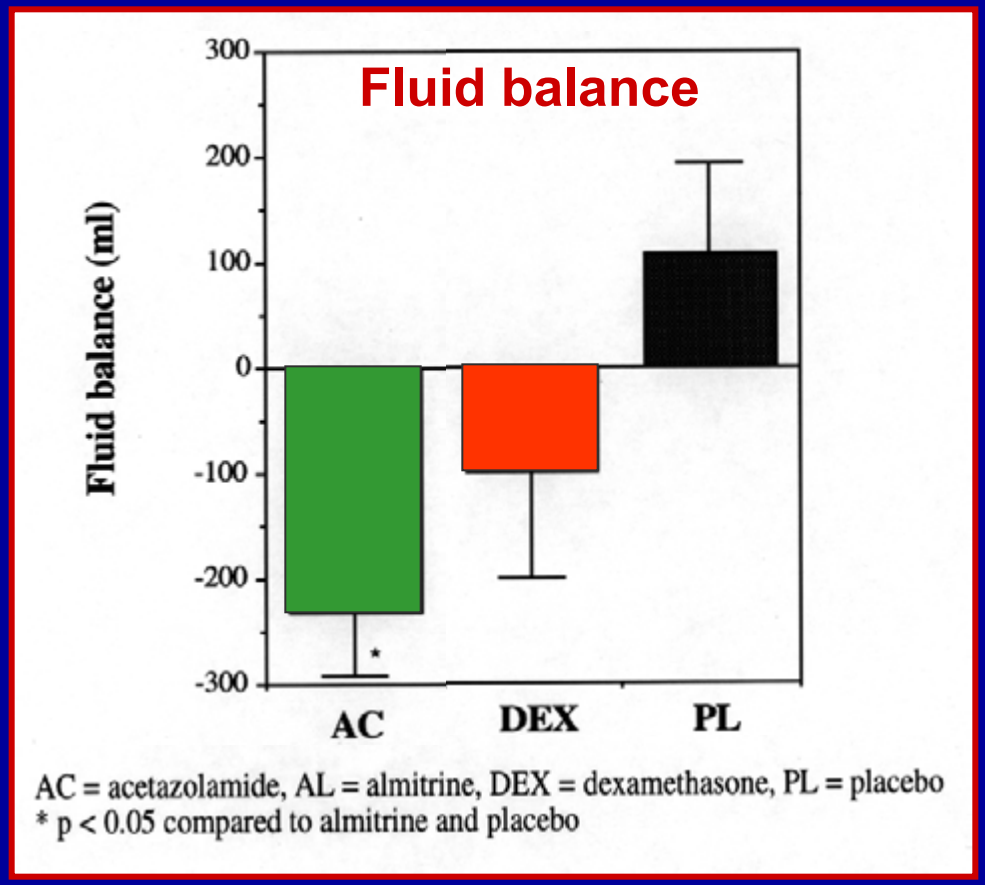
		AC	DEX	PL
n		12	13	10
AMS-C score (°C)	before	1.7 ± 0.1	1.4 ± 0.2	1.3 ± 0.2
	after	1.2 ± 0.2 **	0.7 ± 0.2 **	1.5 ± 0.3
BT (°C)	before	37.3 ± 0.2	37.4 ± 0.2	37.2 ± 0.2
	after	37.0 ± 0.1	36.8 ± 0.1 *	37.3 ± 0.2
PaO_2 (mmHg)	before	35 ± 1	35 ± 1	36 ± 1
	after	41 ± 1 **	43 ± 1 **	38 ± 2
pH	before	7.48 ± 0.01	7.48 ± 0.01	7.47 ± 0.01
	after	7.43 ± 0.01**	7.47 ± 0.01	7.48 ± 0.01

* P < 0.05, ** p < 0.01

Pallavicini E, unpublished

Effects of acetazolamide and dexamethasone on fluid homeostasis



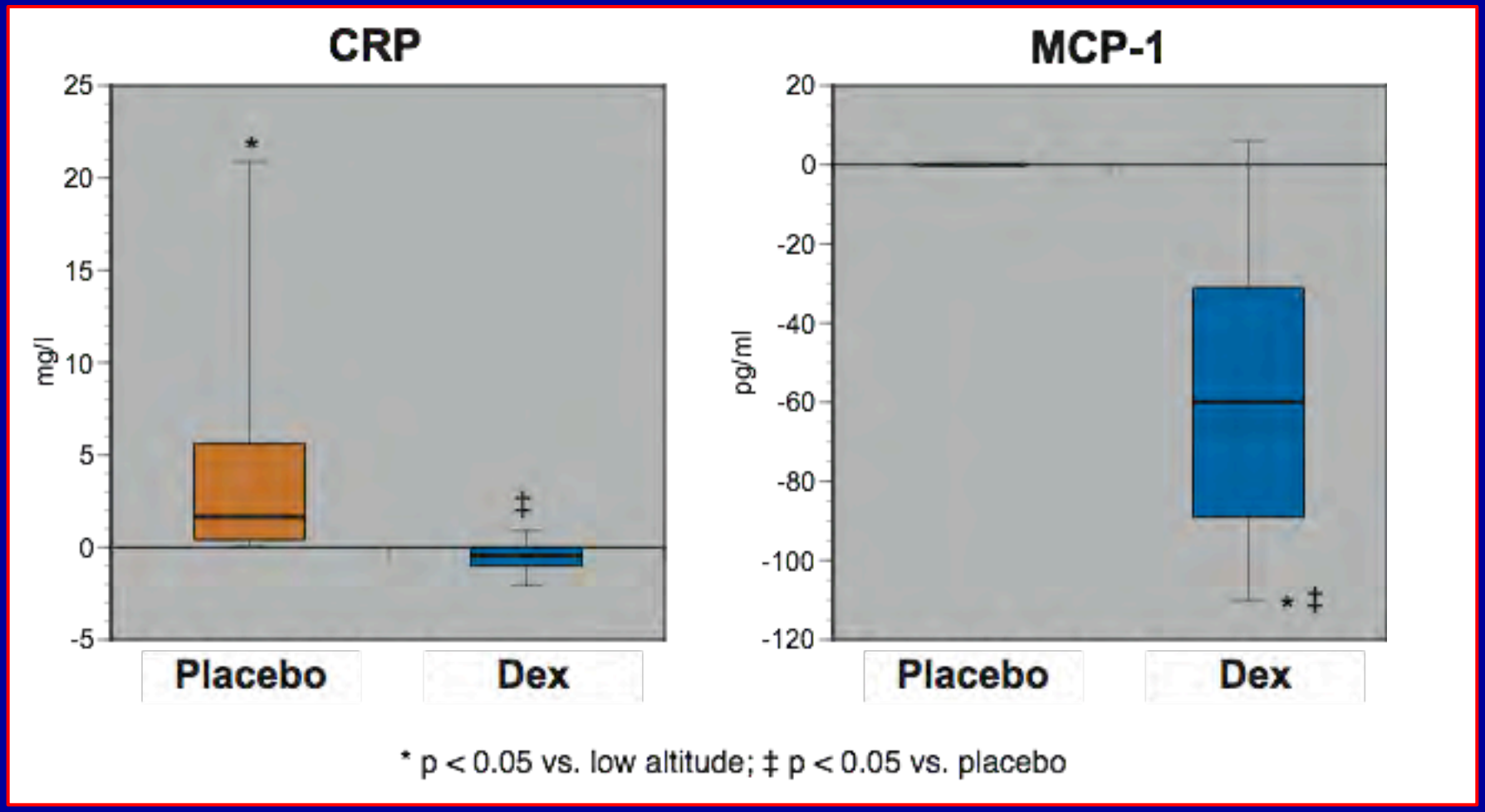


Placebo — Acetazolamide — Dexamethasone

Pallavicini E, unpublished

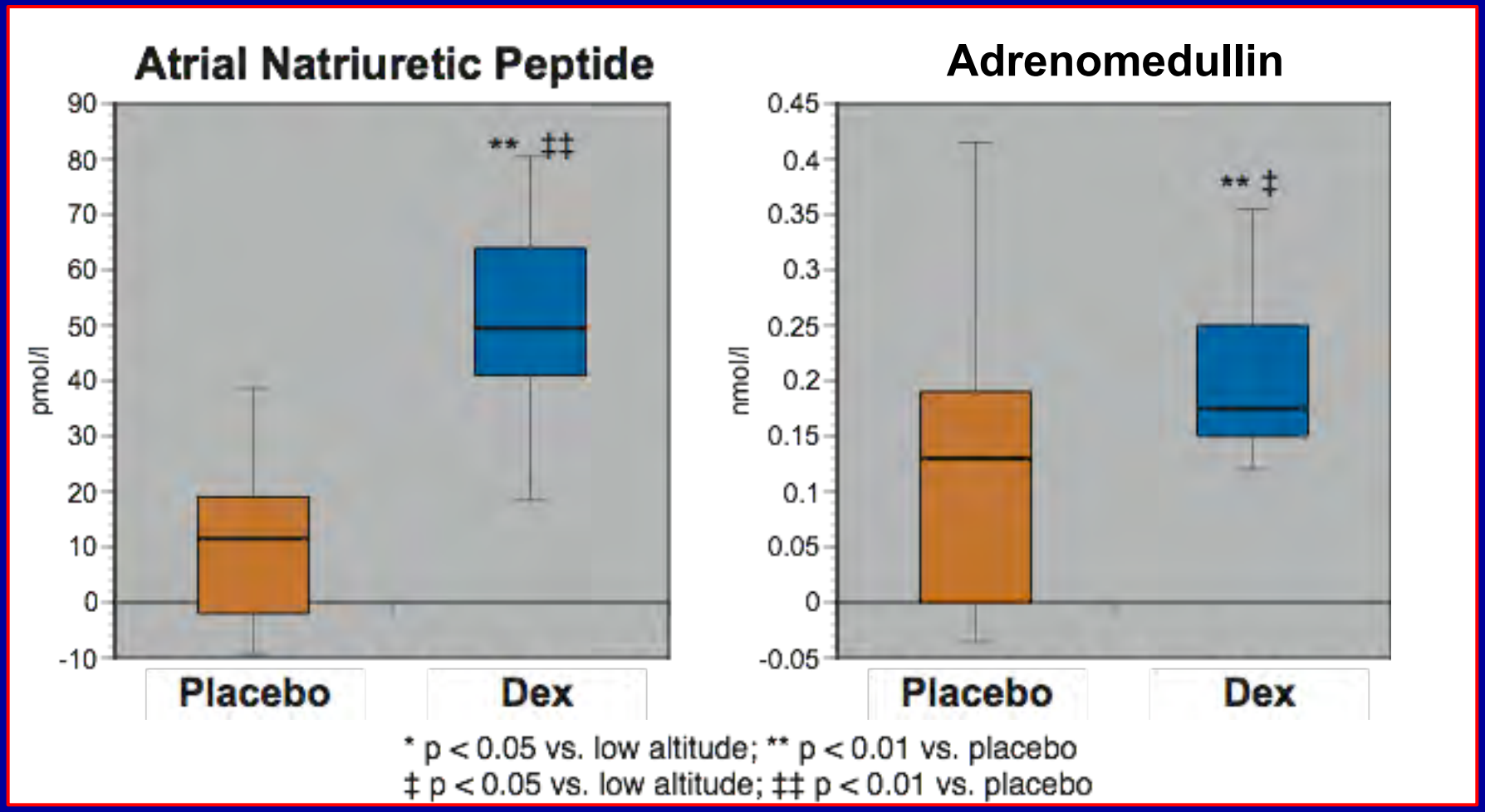
Effect of dexamethasone early prophylaxis on inflammation

Change from low to high altitude day 2

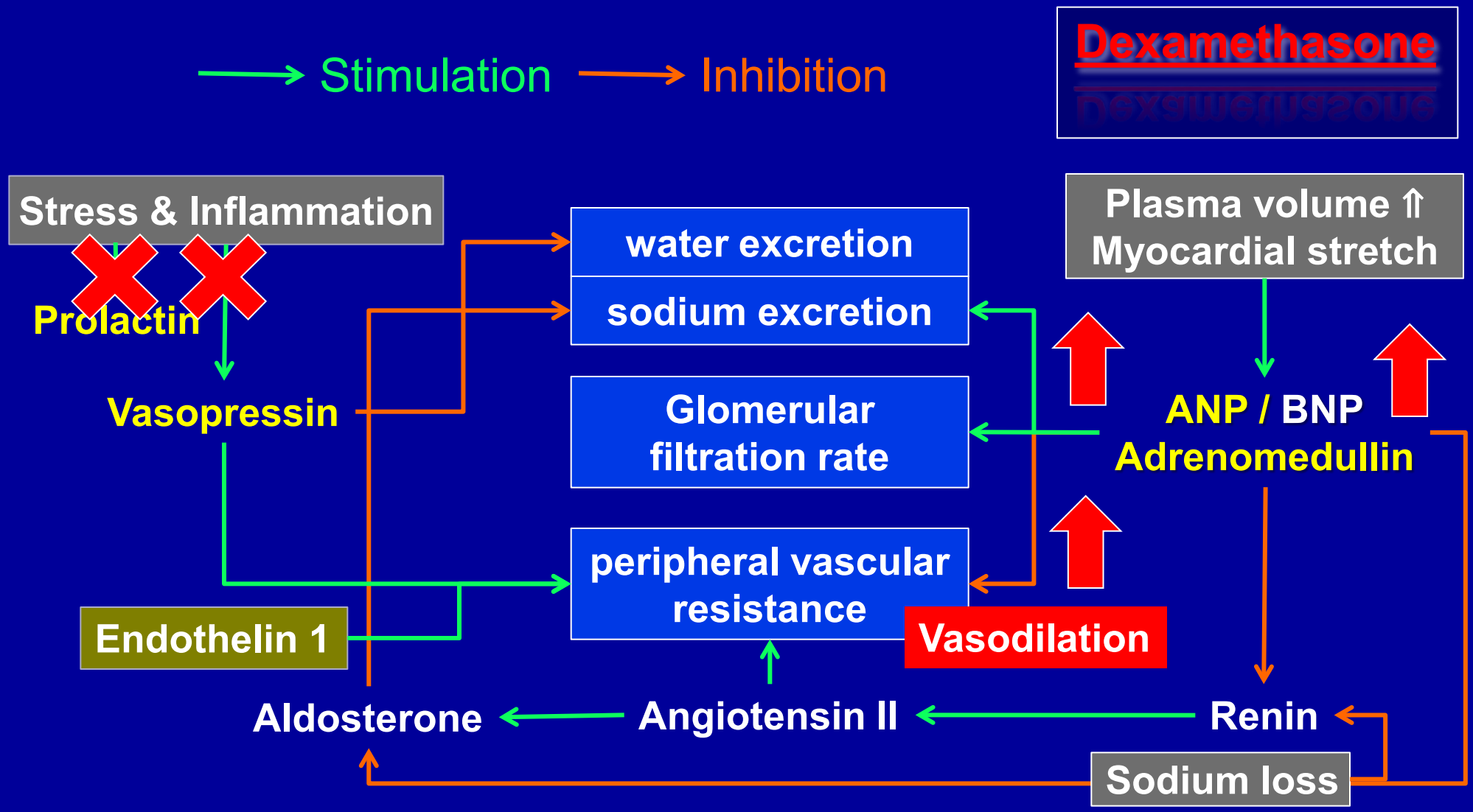


Effect of dexamethasone early prophylaxis on neurohormons

Change from low to high altitude day 2



Cardiovascular and Fluid Homeostasis



Dexamethasone for the treatment of acute mountain sikness

Mechanism

- ⇩ Cytoxines synthesis
- ⇧ Cellular Na+-Transport

Effect

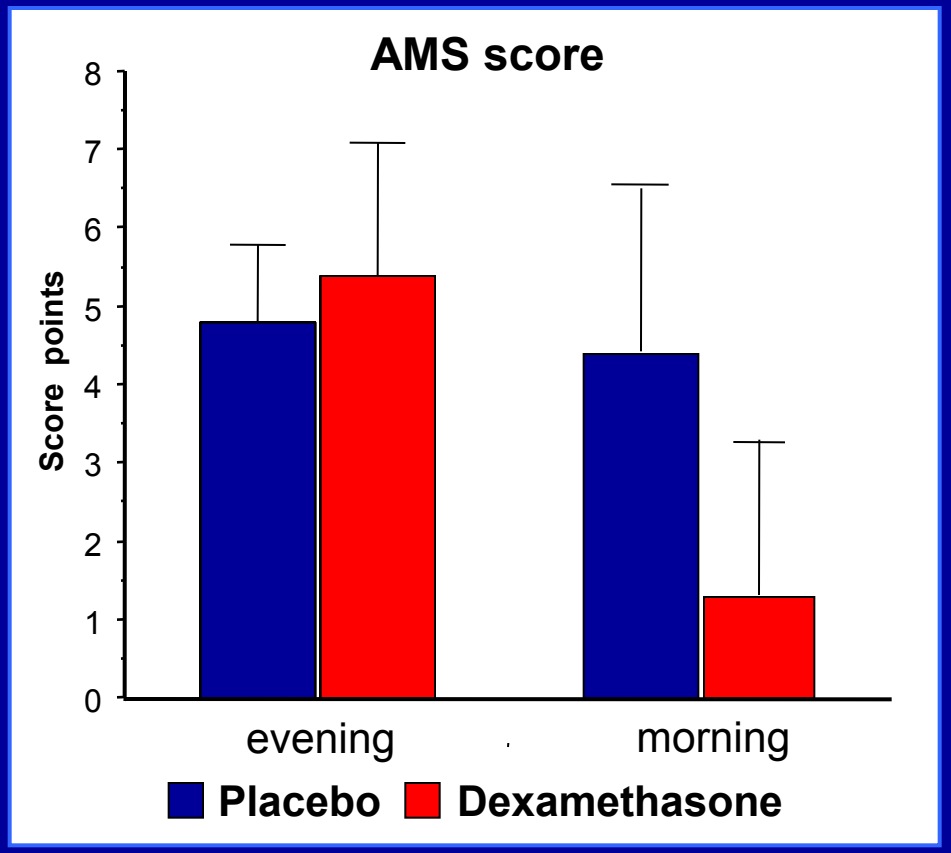
- ⇩ capillary leak
- ⇧ diureses (Kidney tubuli)
- ⇧ Water reabsorption (Alv. space)

⇒ ⇩ Central dysfunction

⇒ ⇧ PaO_2

Dosage

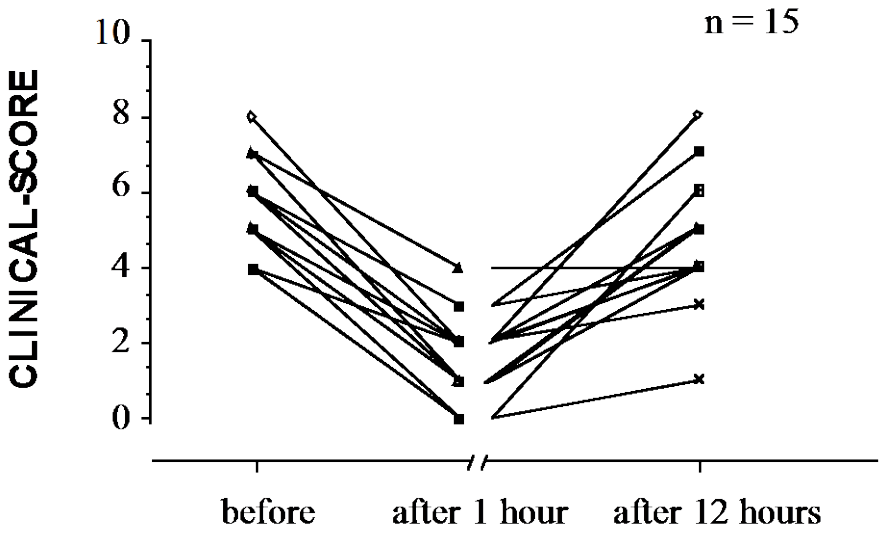
- 8 - 16 mg per day
- Therapy of moderate to severe AMS



Ferrazzini Br Med J 1987, 294: 1380-1382

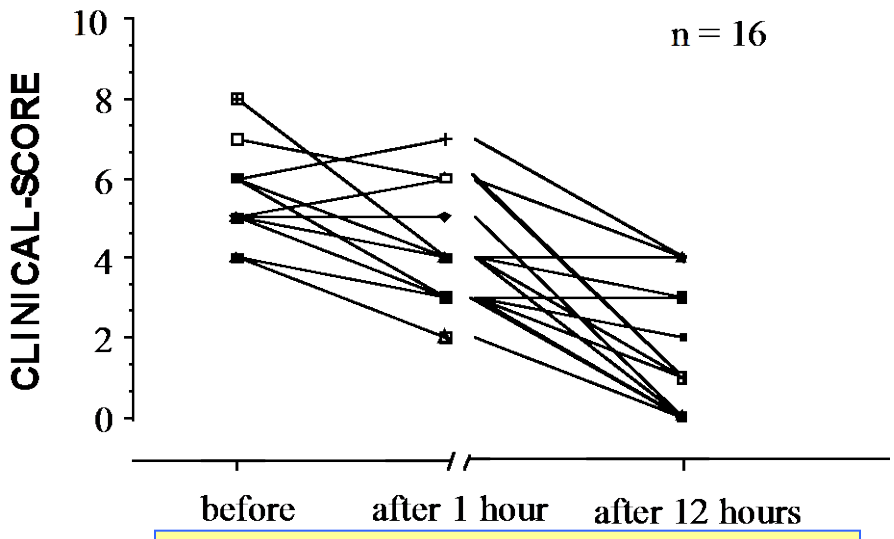
Combined AMS treatment strategy

Hyperbaric treatment



193 mbar

Medical treatment



Dexamethasone
8 mg initially, 4 mg every 6 h.

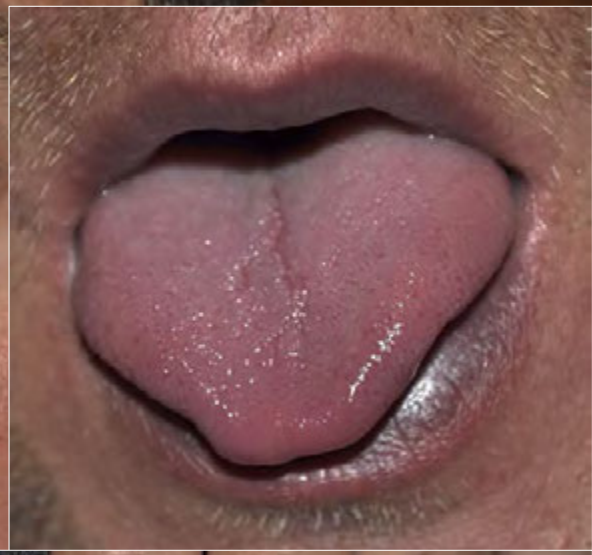
Keller H-R et al. BMJ 1995, 310: 1232-1235

High Altitude Pulmonary Edema (HAPE)

Central distributed infiltrates

Peripheral distributed infiltrates

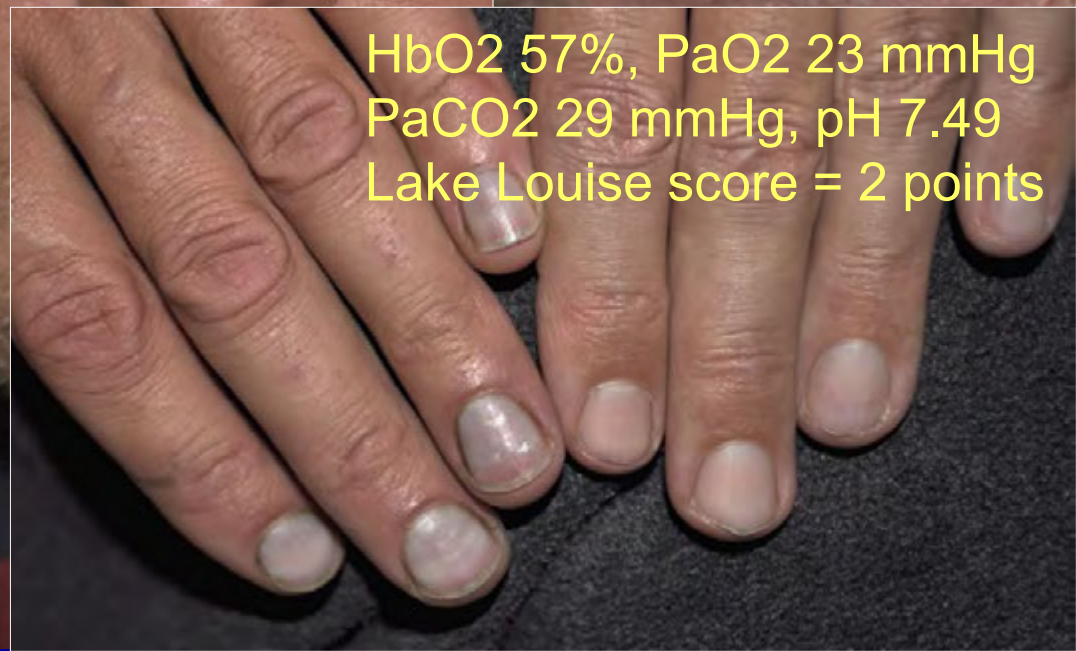
Clinical Presentation of HAPE



Symptoms and Signs

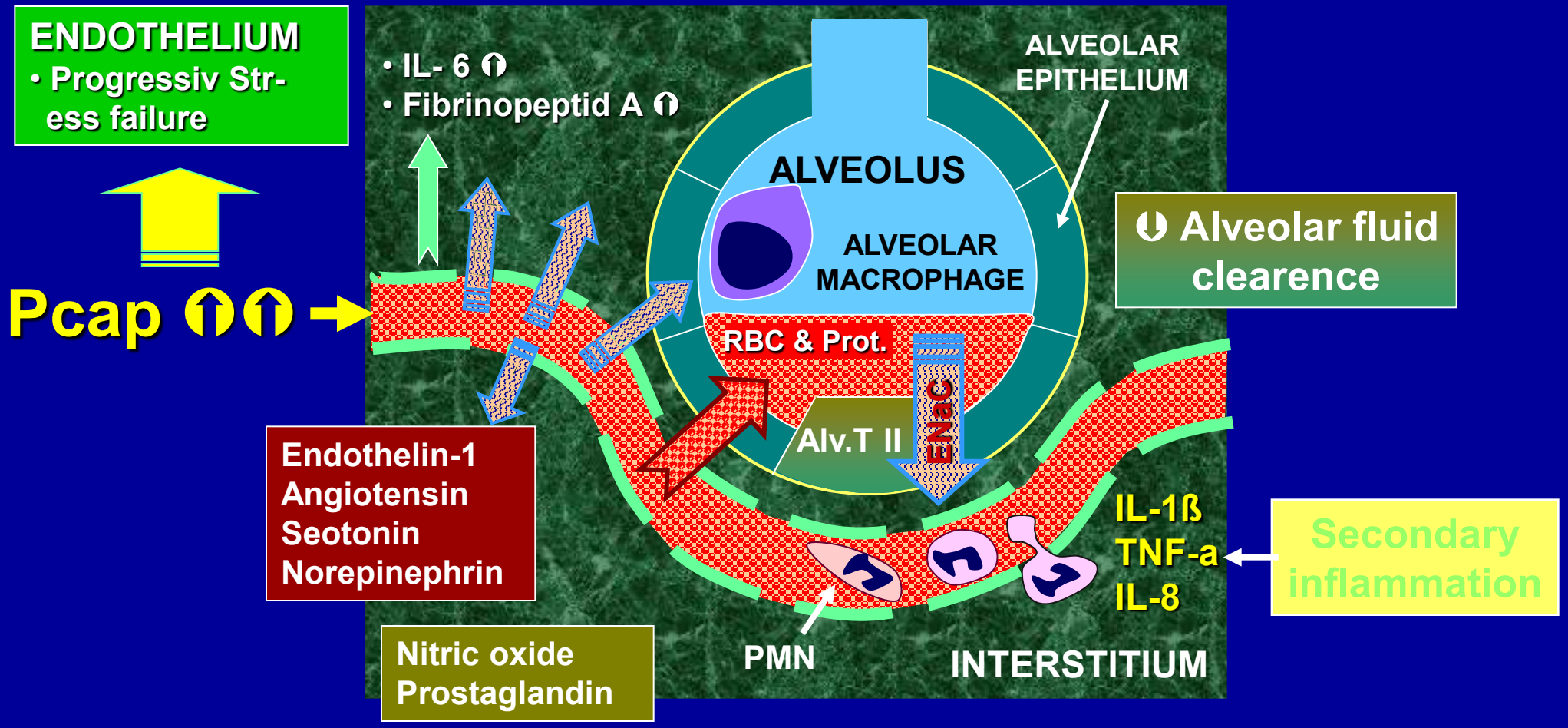
- Weakness / Decreased Exercise Performance
- Dyspnoe at Rest, Othopnoe
- Cough, Cracels bloody sputum
- Chest tightness or congestion

- Tachycarda > 90/min
- Tachypnoe > 25/min
- Cyanosis, SpO2 < 70% (4500m)
- Lung: Rales or wheezing
- Body Temperature > 37.4 ° C



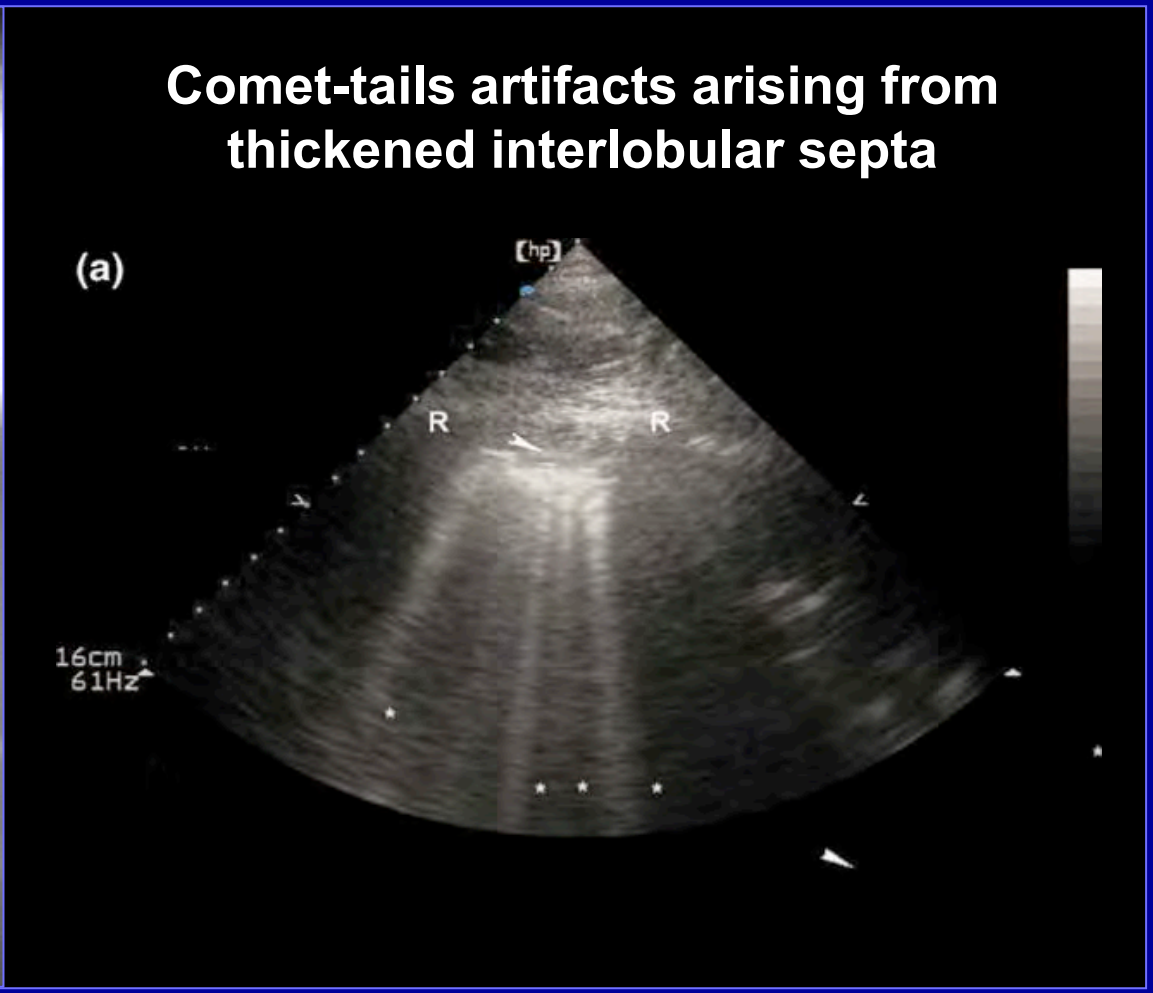
HbO2 57%, PaO2 23 mmHg
PaCO2 29 mmHg, pH 7.49
Lake Louise score = 2 points

Pathophysiology of high altitude pulmonary edema



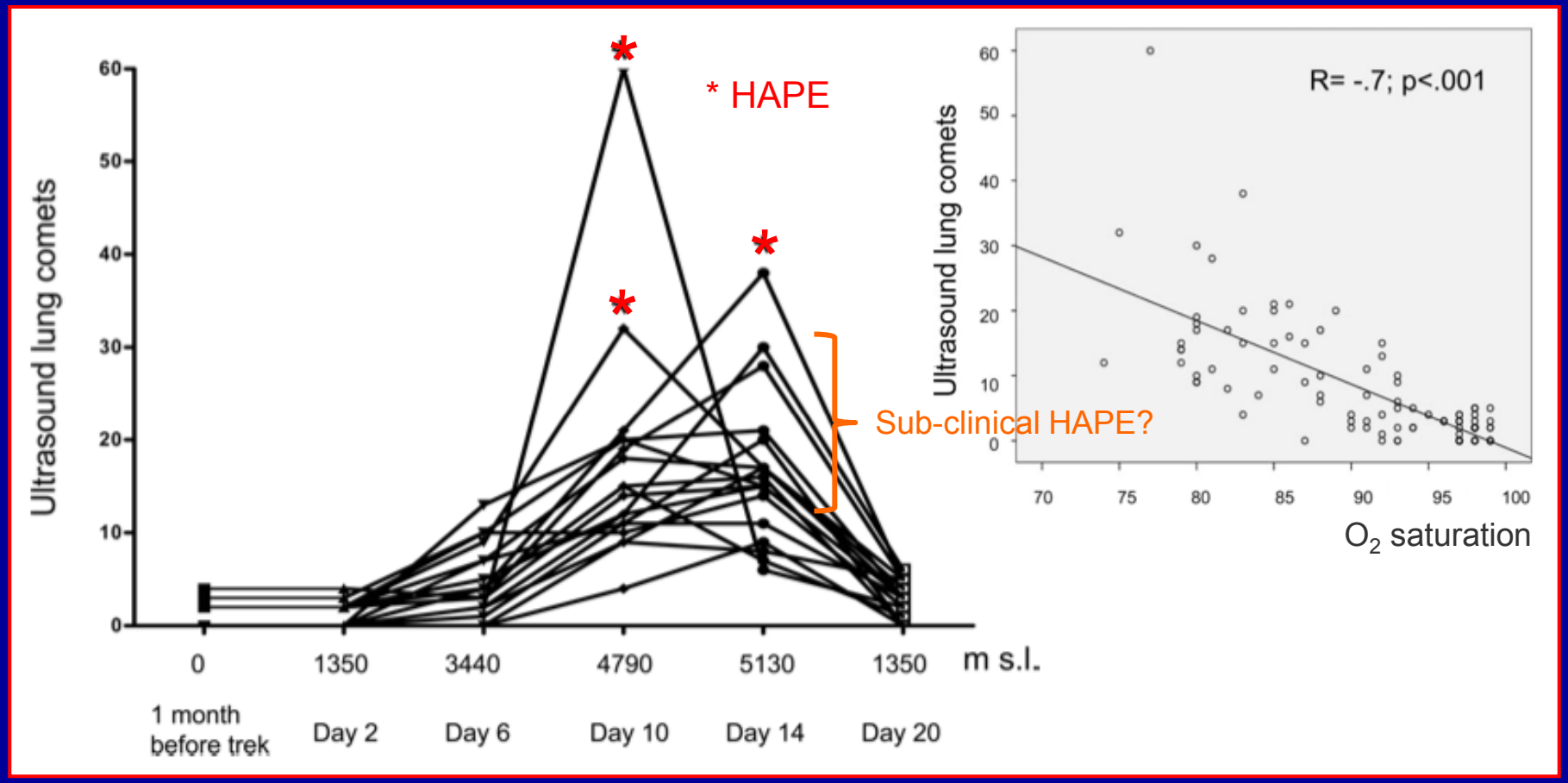
Chest ultrasound for monitoring of extravascular lung water in HAPE

Comet-tails artifacts arising from thickened interlobular septa



Monitoring comet-tails during ascent

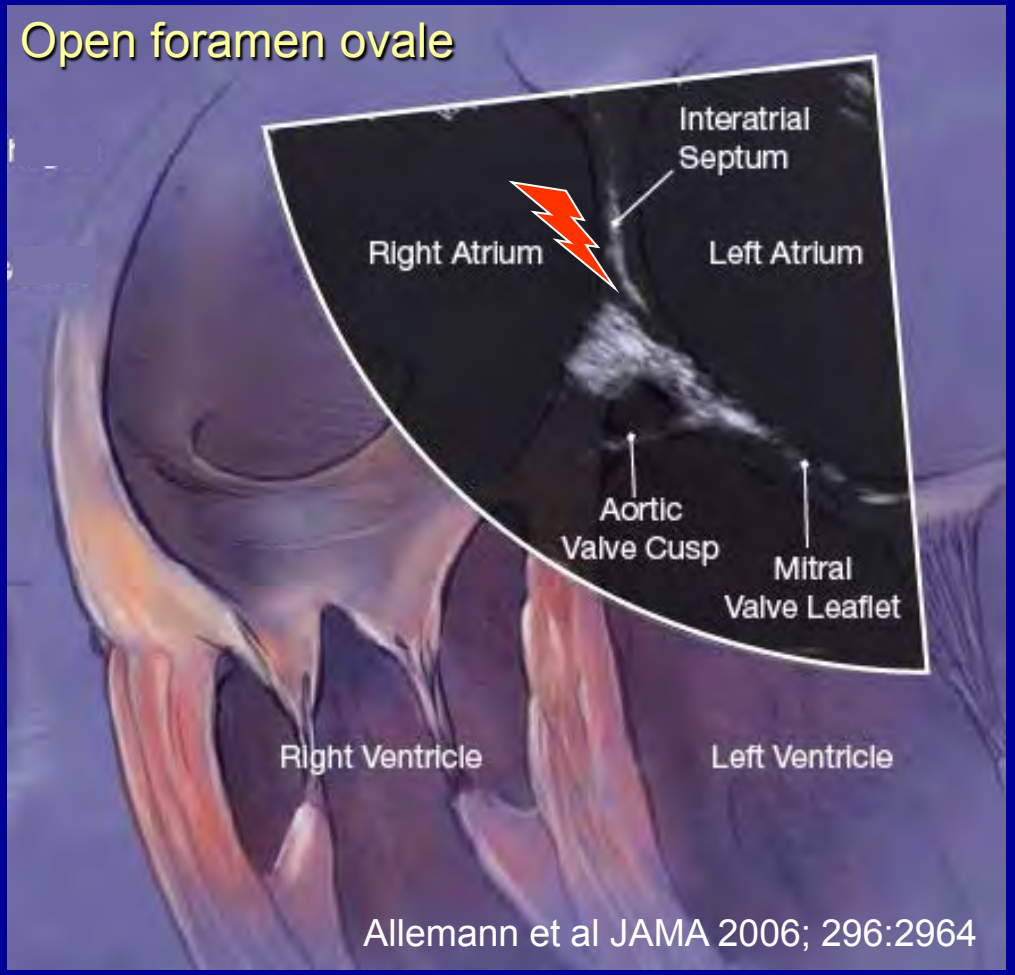
Monitoring comet-tails score during ascent to 5130 m (* subjects with HAPE)



Pratali L. et al. Crit Care Med 2010, 38 Epub

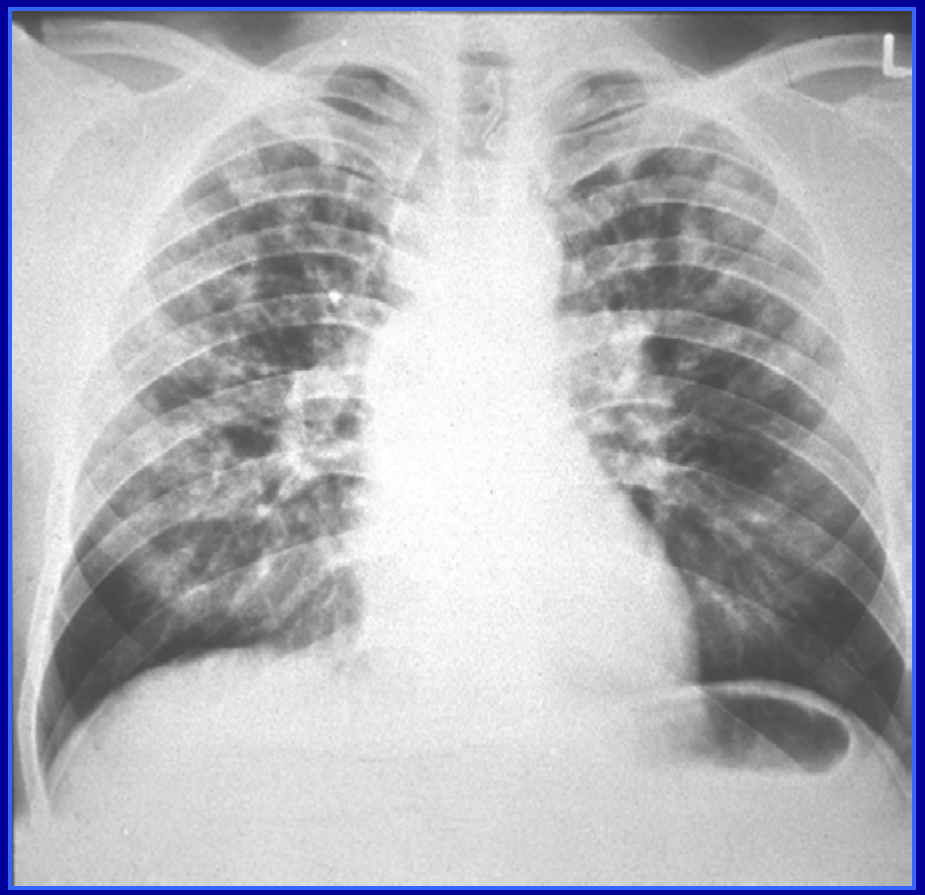
Factors known to be associated with an increased risk of HAPE

- **Individual susceptibility**
- Open foramen ovale
- Congenital atresia/hypoplasia of a pulmonary artery
- Pulmonary hypertension at low altitude
- Pulmonary embolism
- Systemic inflammation decreasing pulmonary capillaries edema formation threshold



Rationale for Prevention and Treatment Based on Pathophysiology

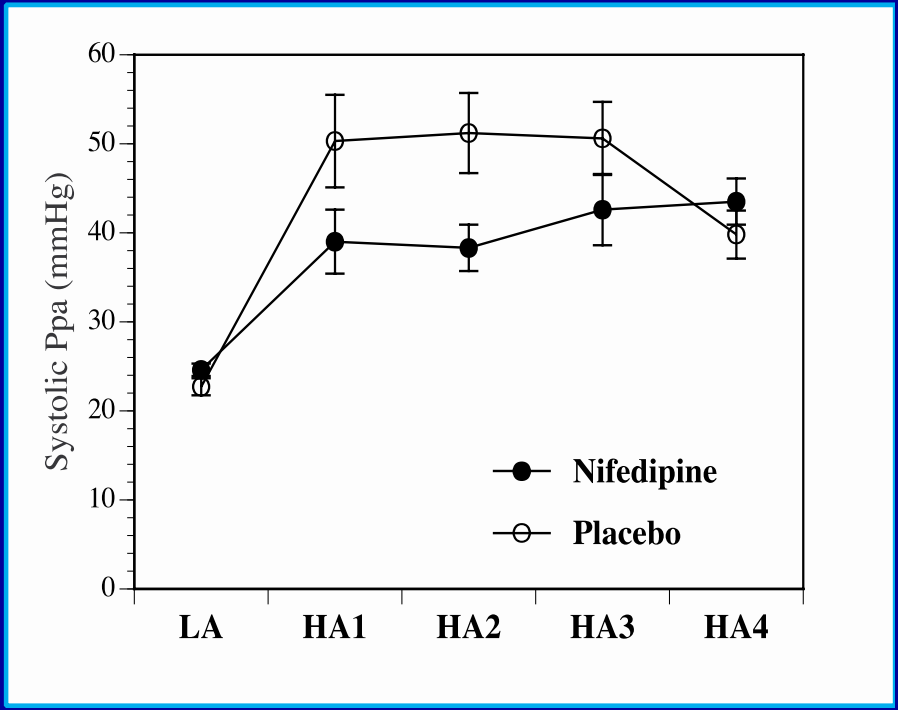
High Altitude Pulmonary edema



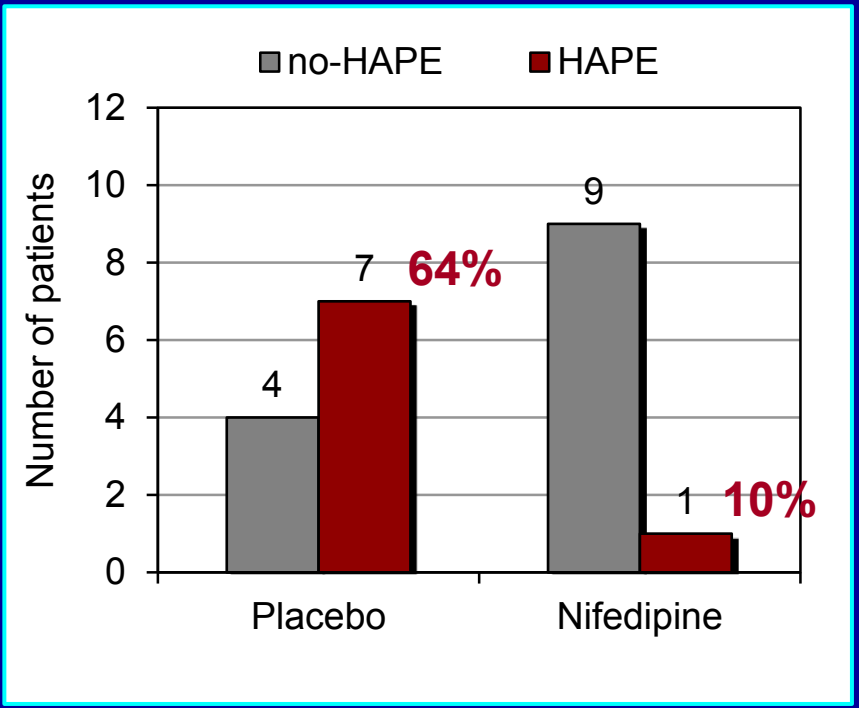
- **Inhibition of excessive hypoxic pulmonary vasoconstriction**
  - **Vasodilators**
    - **Calcium channel blokers**
    - **Phosphodiestherase 5 inhibitors**
  - **Improve nitric oxide availability**
    - **Phosphodiestherase 5 inhibitors**
    - **Glucocorticoids**
- **Improve water reabsorption**
  - **Beta-2-agonists**
  - **Glucocorticoids**

Prevention of high altitude pulmonary edema by nifedipine

Systolic pulmonary artery pressure

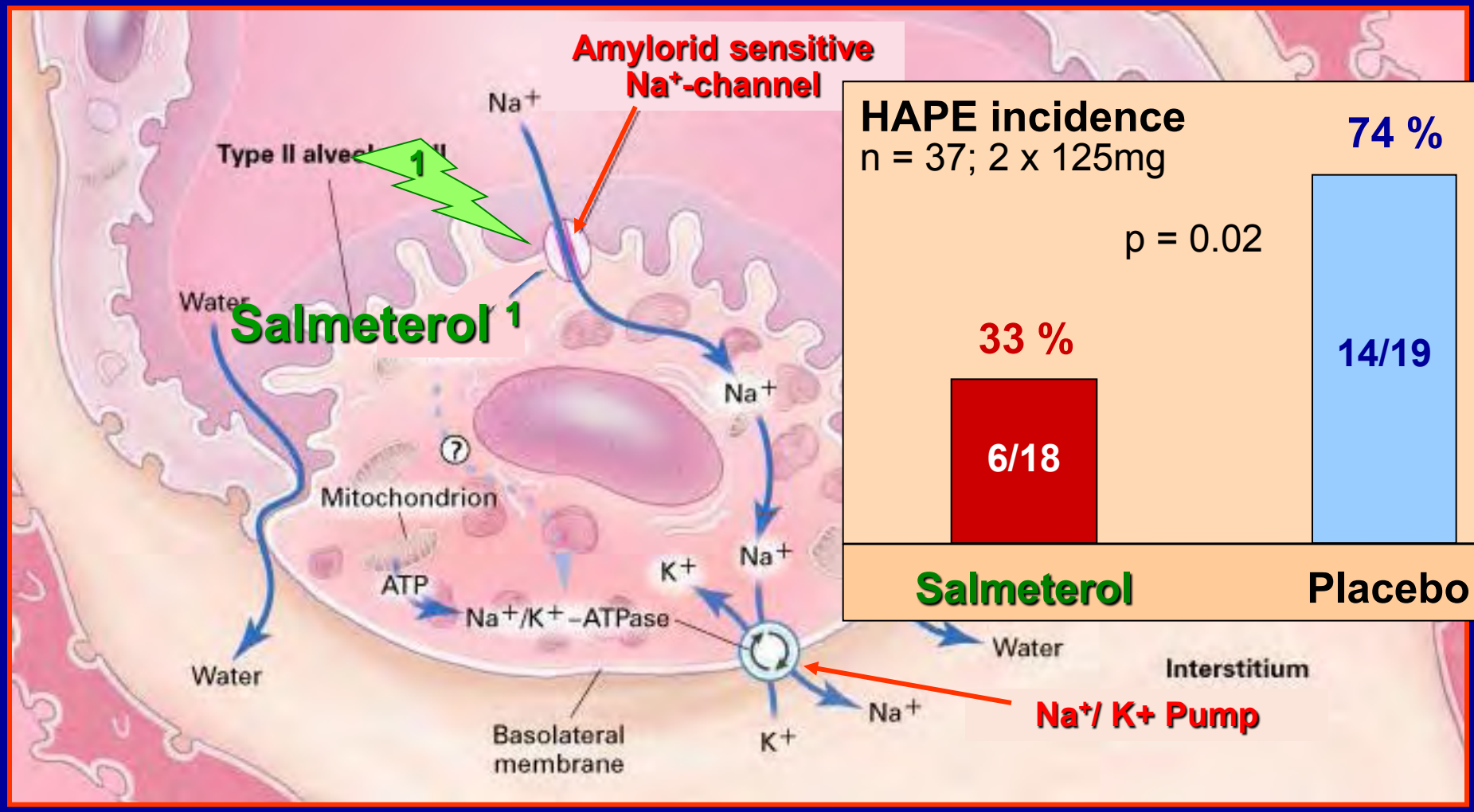


Incidence of HAPE

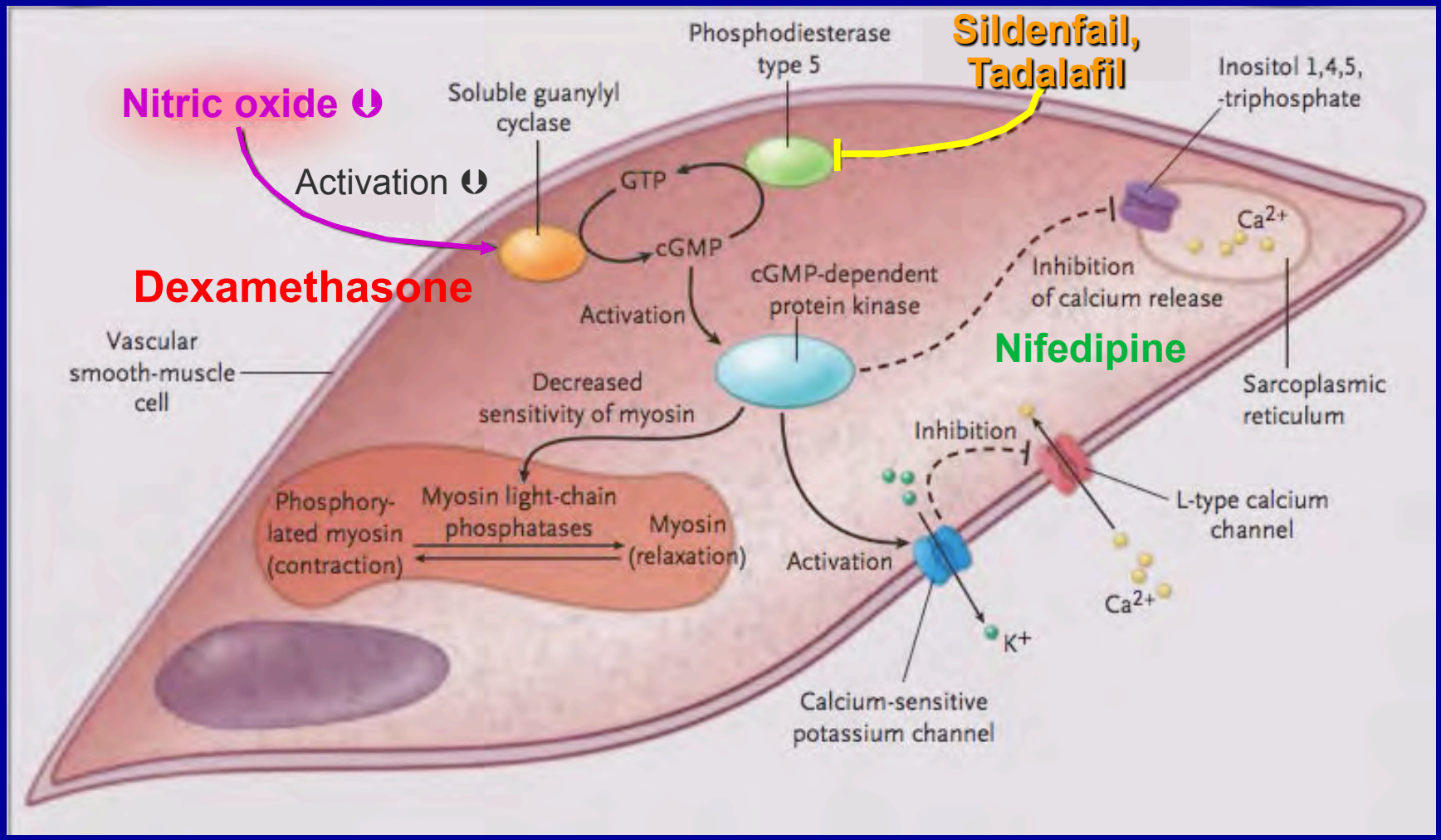


Bärtsch et al. NEJM 1991 325: 1284-9

Non-hemodynamic contribution to HAPE:
Improvement of alveolar water clearence



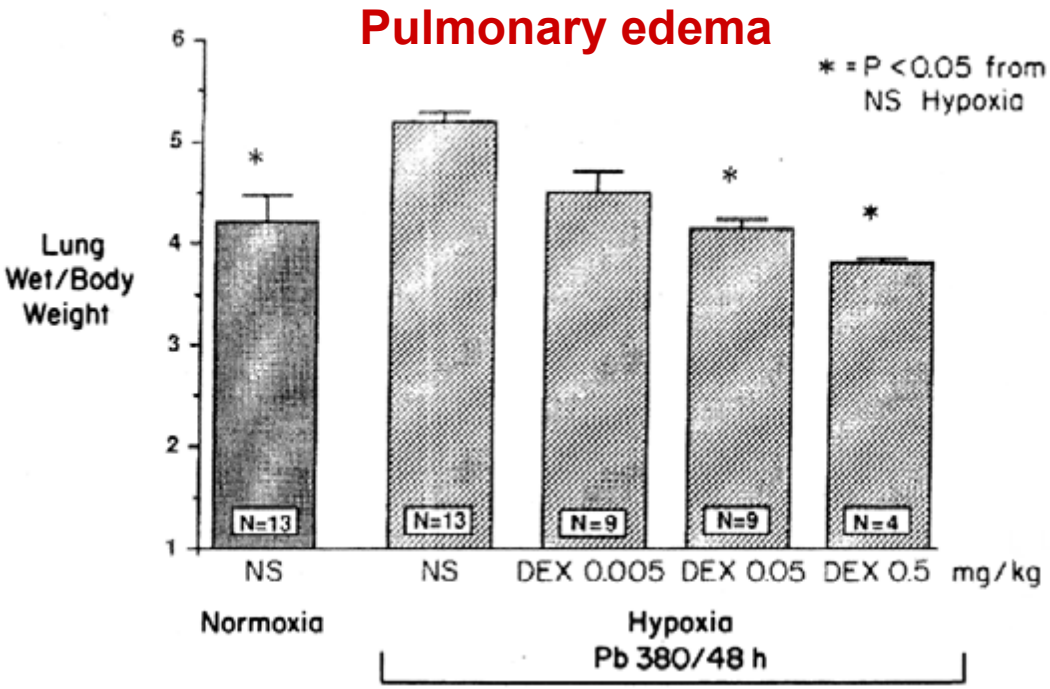
Phosphodiesterase 5-inhibitors to compensate decreased nitric oxide availability

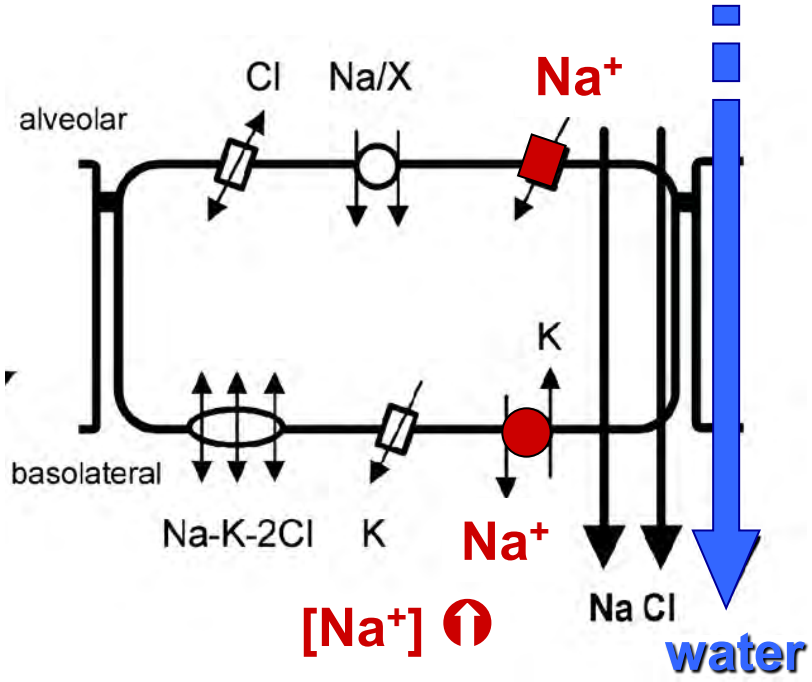


Possible mechanisms for the dexamethasone effect on gas exchange

Anti-inflammatory effect

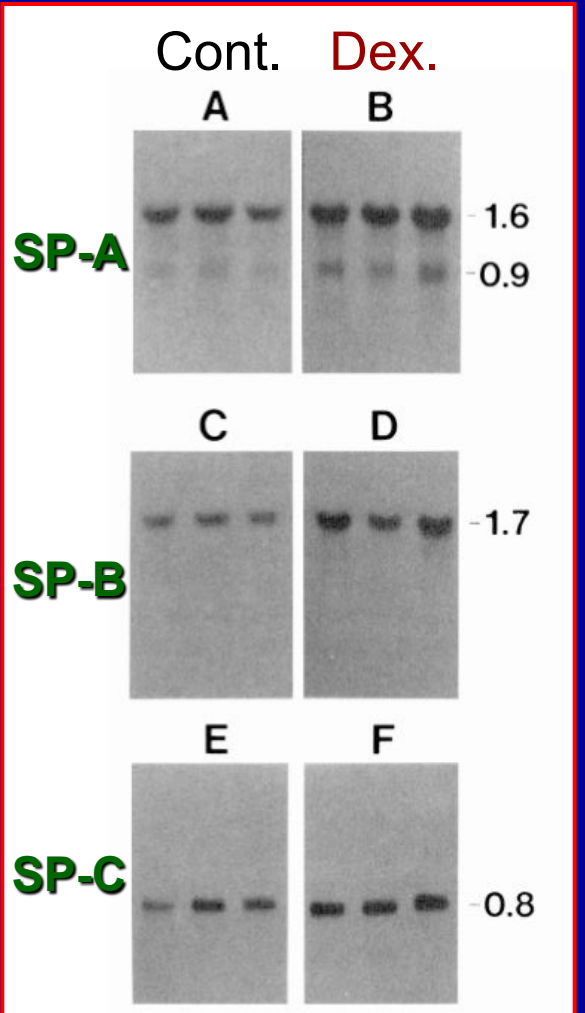
- suppression cytokines synthesis, reduction of the capillary leak
- enhancement of Na^+ transport in renal tubular and alveolar type II cells

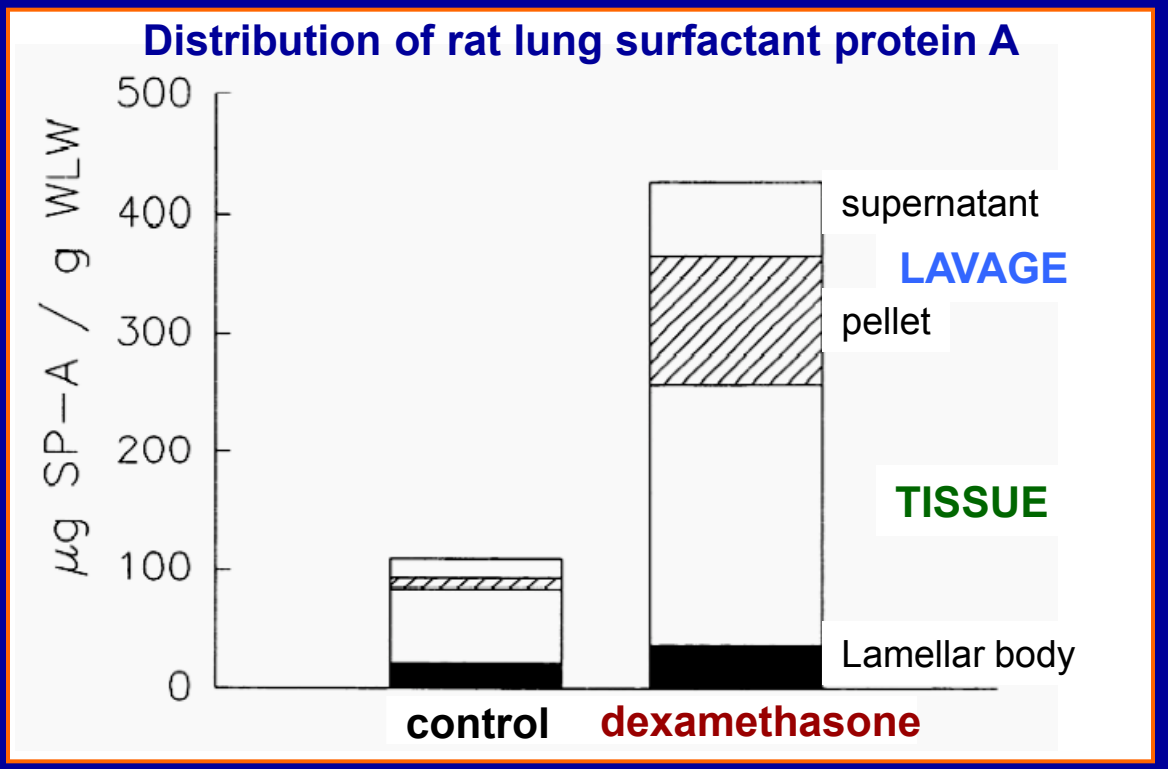




Seltzner et al. J Clin Invest 1988, 82:1840

Dexamethasone increase surfactant protein content in the rat lung





Lung mRNA

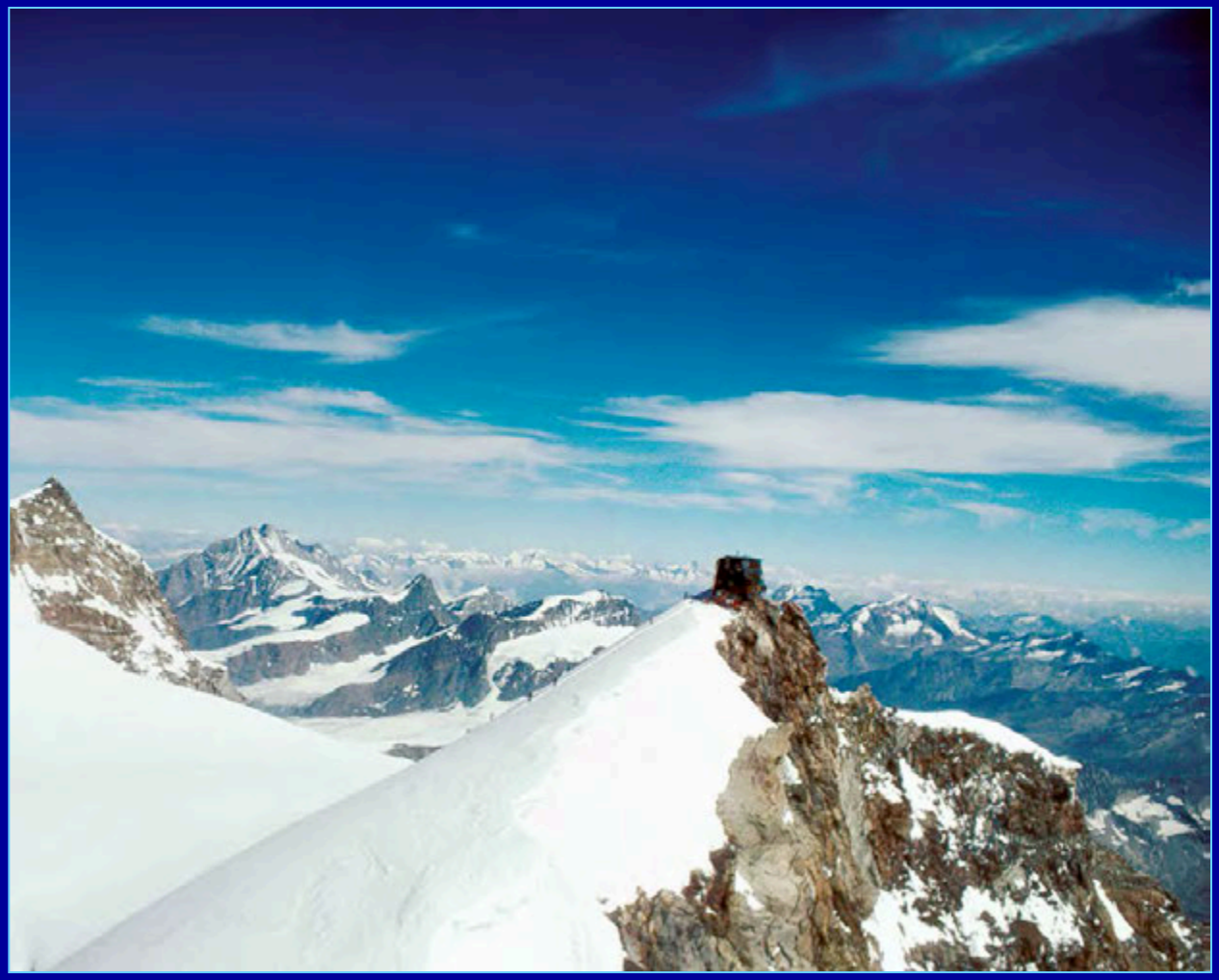
	SP-A	SP-B	SP-C
Cont	1.5±0.1	4.3±0.1	2.2±0.4
Dex	2.2±0.4	8.3±1	5.0±0.5

Young et al. Am J Physiol 1991, 260:L161

Dexamethasone or tadalafil for HAPE prophylaxis during stay at 4559m

Double blind randomized controlled trial

- **Dexamethasone 2 x 8 mg**
- **Tadalafil 2 x 10mg**
- **Placebo**



Maggiorini et et al.
Ann Inter Med 2006
145:497

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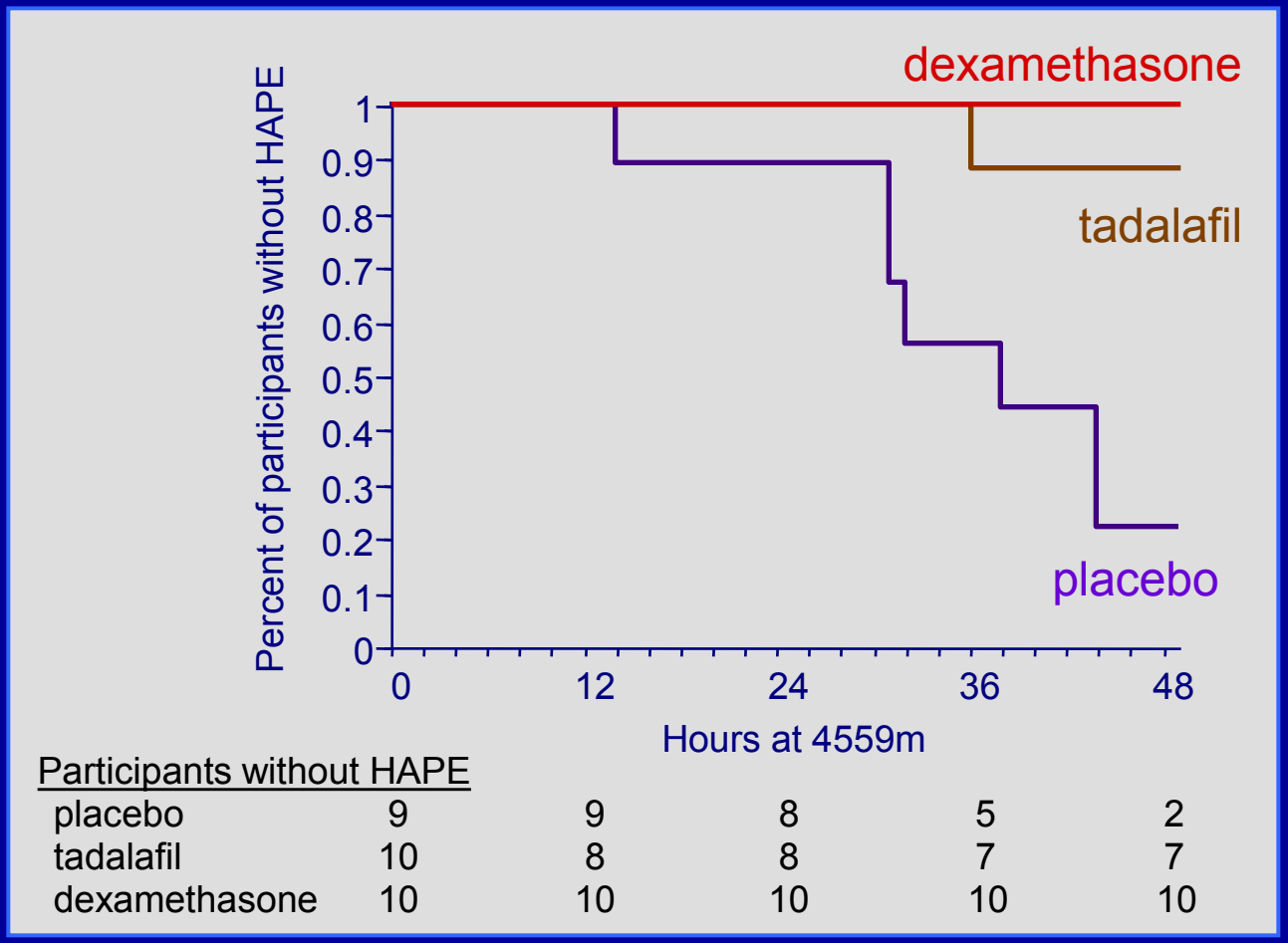
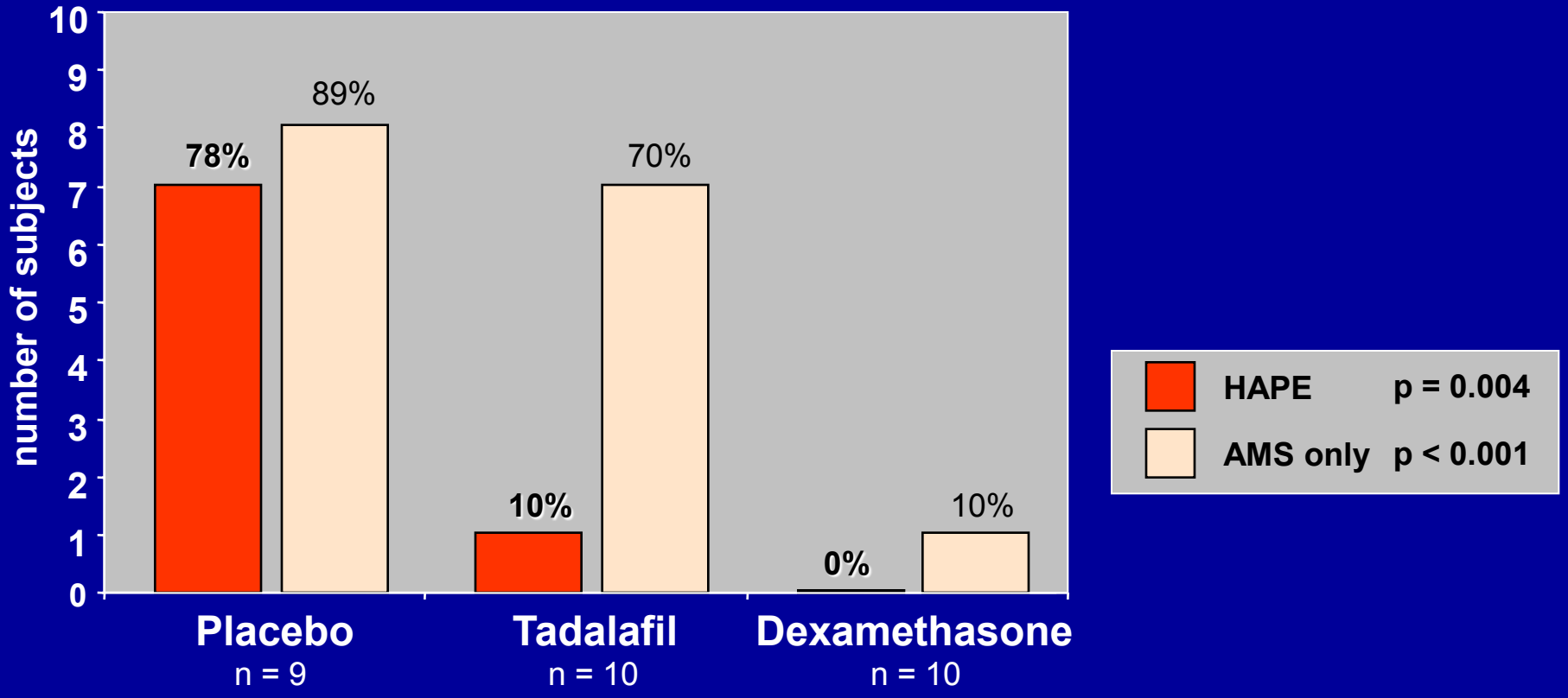


Participants without HAPE					
placebo	9	9	8	5	2
tadalafil	10	8	8	7	7
dexamethasone	10	10	10	10	10

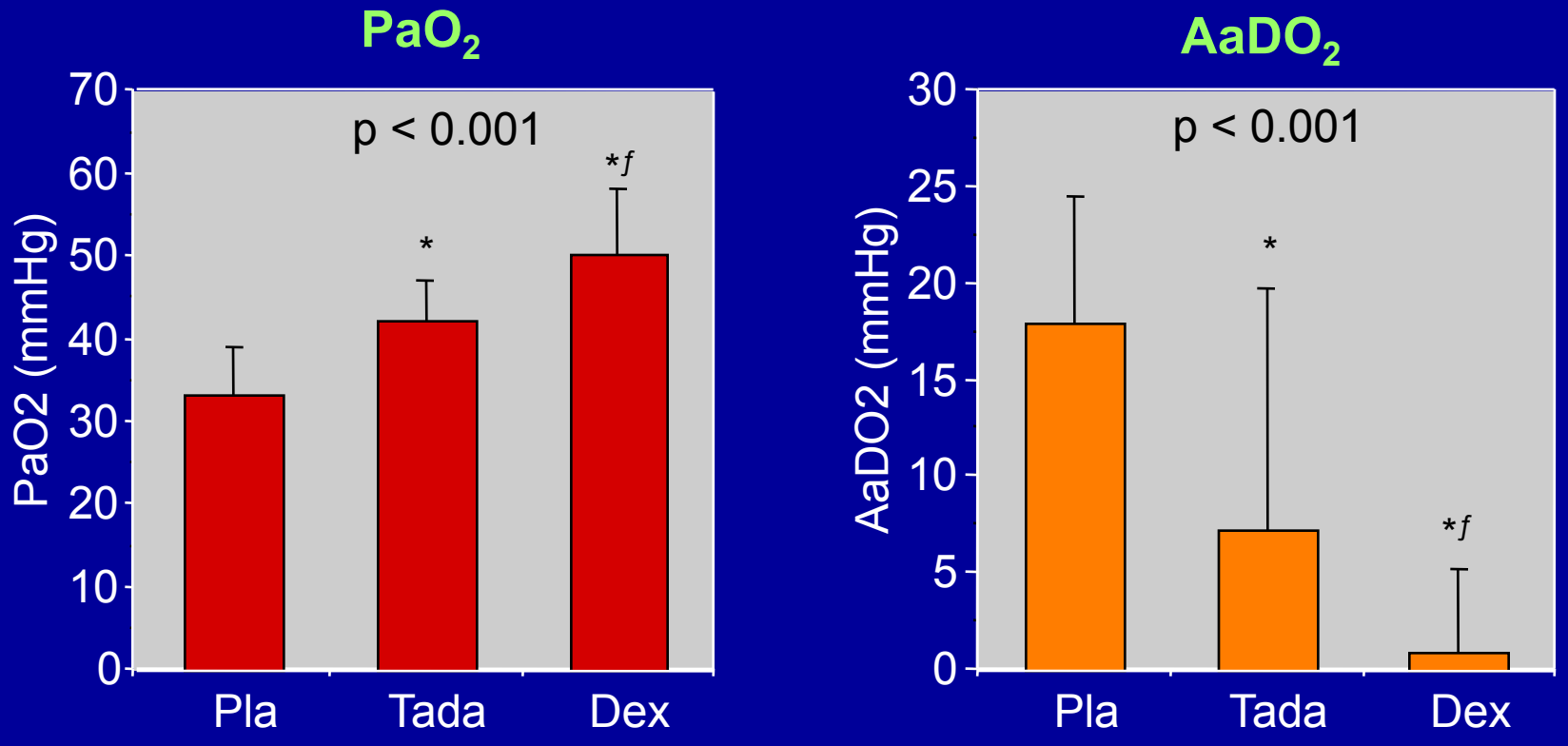
Maggiorini et et al.
Ann Inter Med 2006
145:497

Incidence of High Altitude Pulmonary Edema in Susceptible Subjects



Maggiorini et et al.
Ann Inter Med 2006 145:497

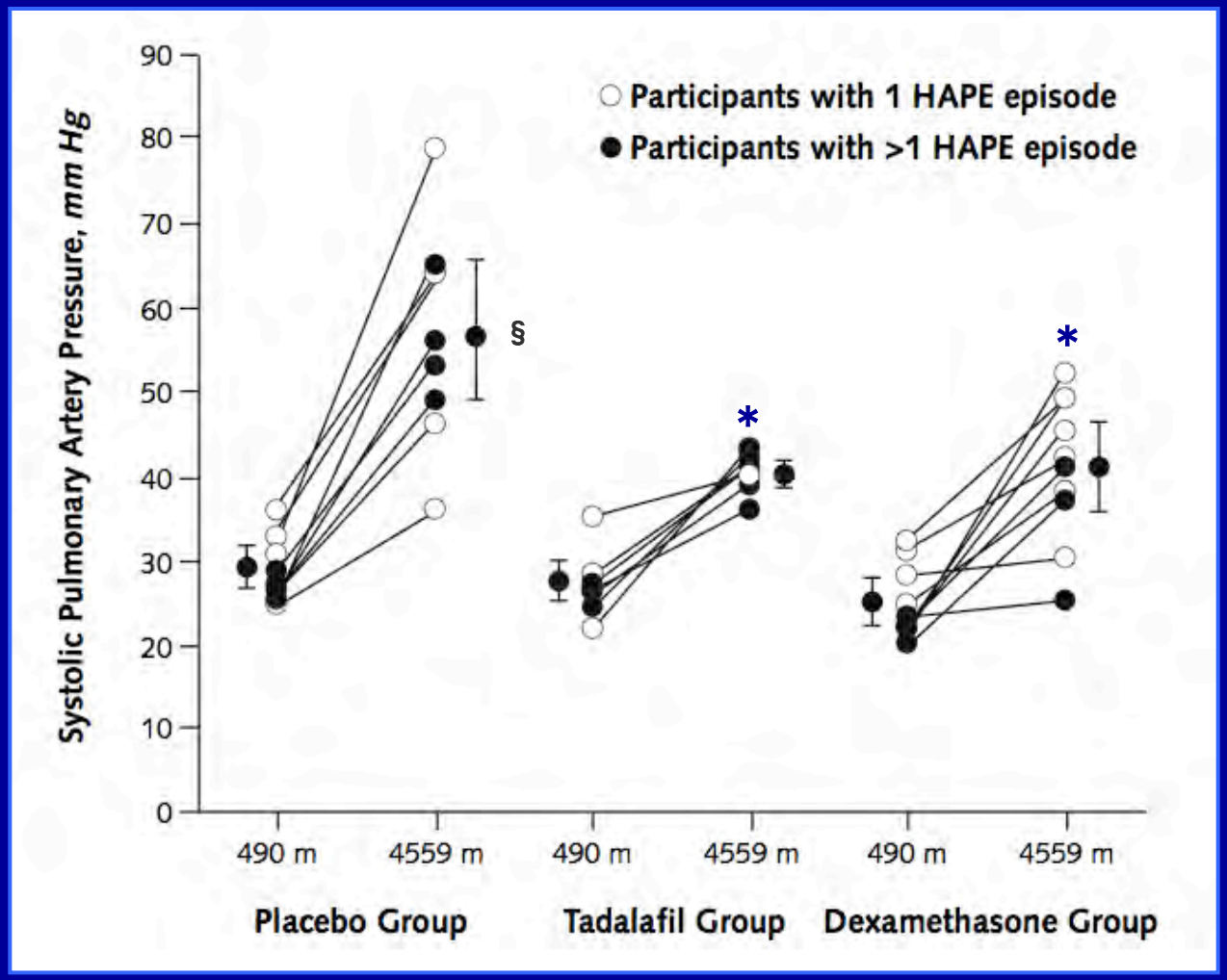
Effects of Tadalafil and Dexamethasone on arterial oxygenation



*** at least p < 0.05 vs placebo; *ƒ* vs. tadalfil**

Maggiorini et et al.
Ann Inter Med 2006 145:497

Effects of Tadalafil and Dexamethasone on pulmonary artery pressure



§ mean systolic pulmonary artery pressure Mean with 95% CI

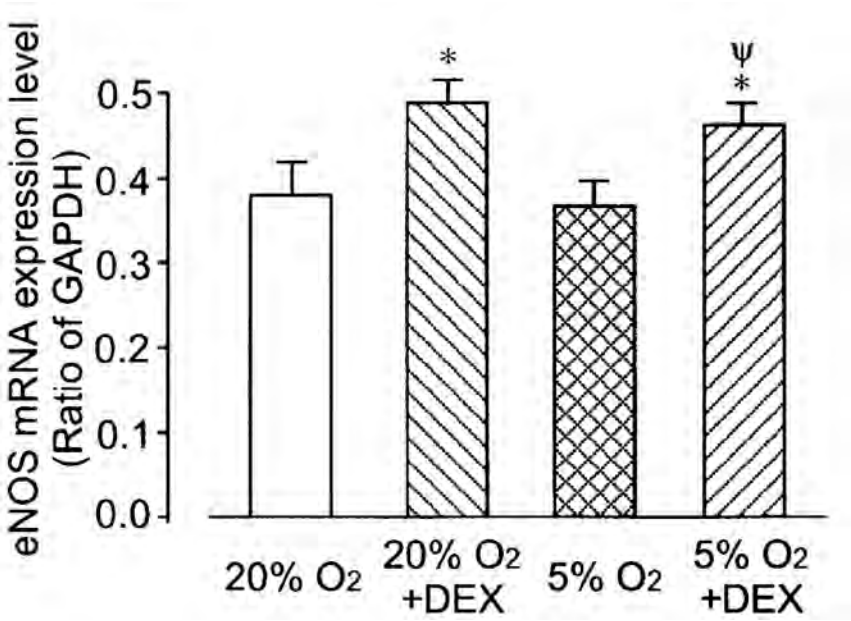
* $p < 0.01$ vs control

Maggiorini et et al.
Ann Inter Med 2006 145:497

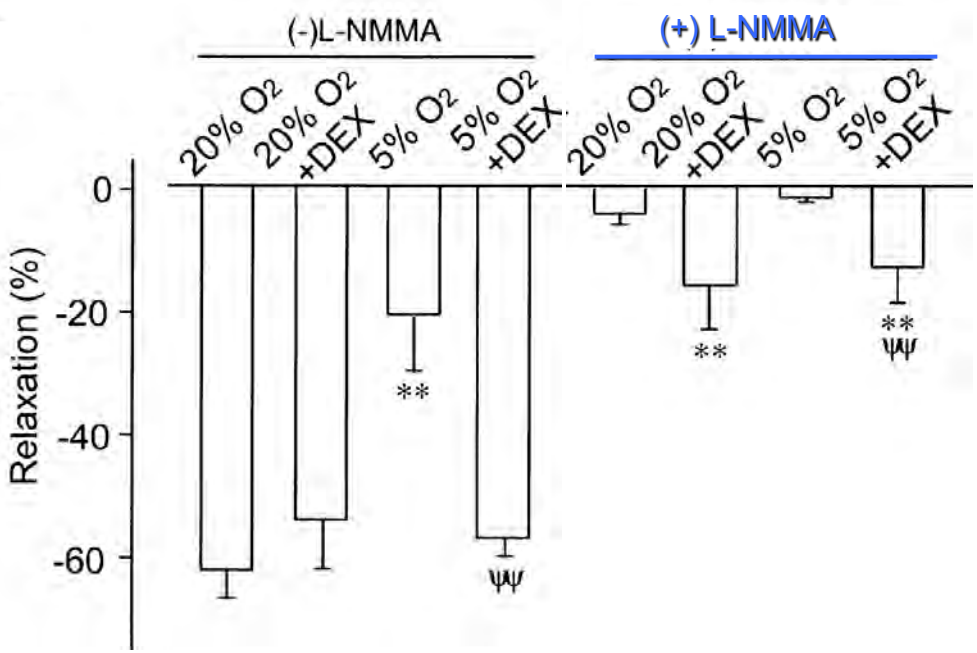
Dexamethasone inhibition of hypoxic pulmonary vasoconstriction in the rabbit

Dexamethasone increases nitric oxyde availability in rabbit intrapulmonary arteries leading to vasorelaxation

eNOS mRNA expression



Vasorelaxation



Murata et al AJRCCM 2004, 170:647

Prophylaxis of High Altitude Pulmonary Edema (HAPE)

HAPE

Trekking/climbing above 2500m

Slow ascent
300 m/day
+

Nifedipine
CR30-60 every 24 h
Start
24h before ascent

or

Tadalafil
20 mg every 24 h
Start
24h before ascent

+ AMS > 2 AMS Symptoms

Azetazolamide
125 mg every 12 h

HAPE & AMS

Busienesstrip above 2500m

Rapid ascent with a short sojourn
1000 m/day + < 5 days above 2500m

Dexamethasone
4-8mg every 12 h
Start
24 h before ascent

Treatment of High Altitude Pulmonary Edema

Non medial treatment

- Bed rest
- Oxygen / Hyperbaric Bag
- Descent

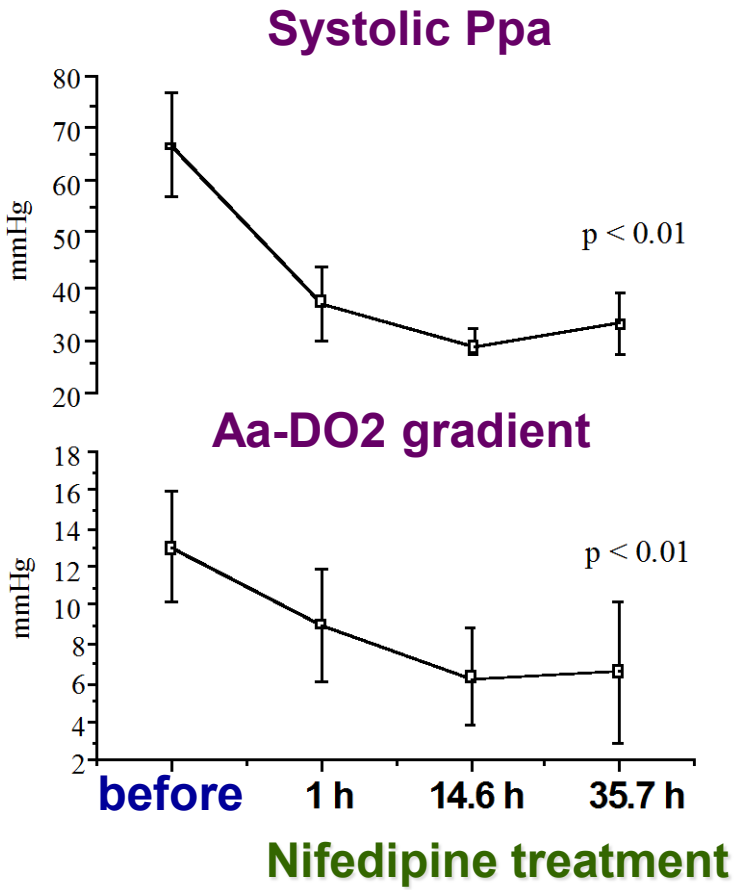
Medical treatment options

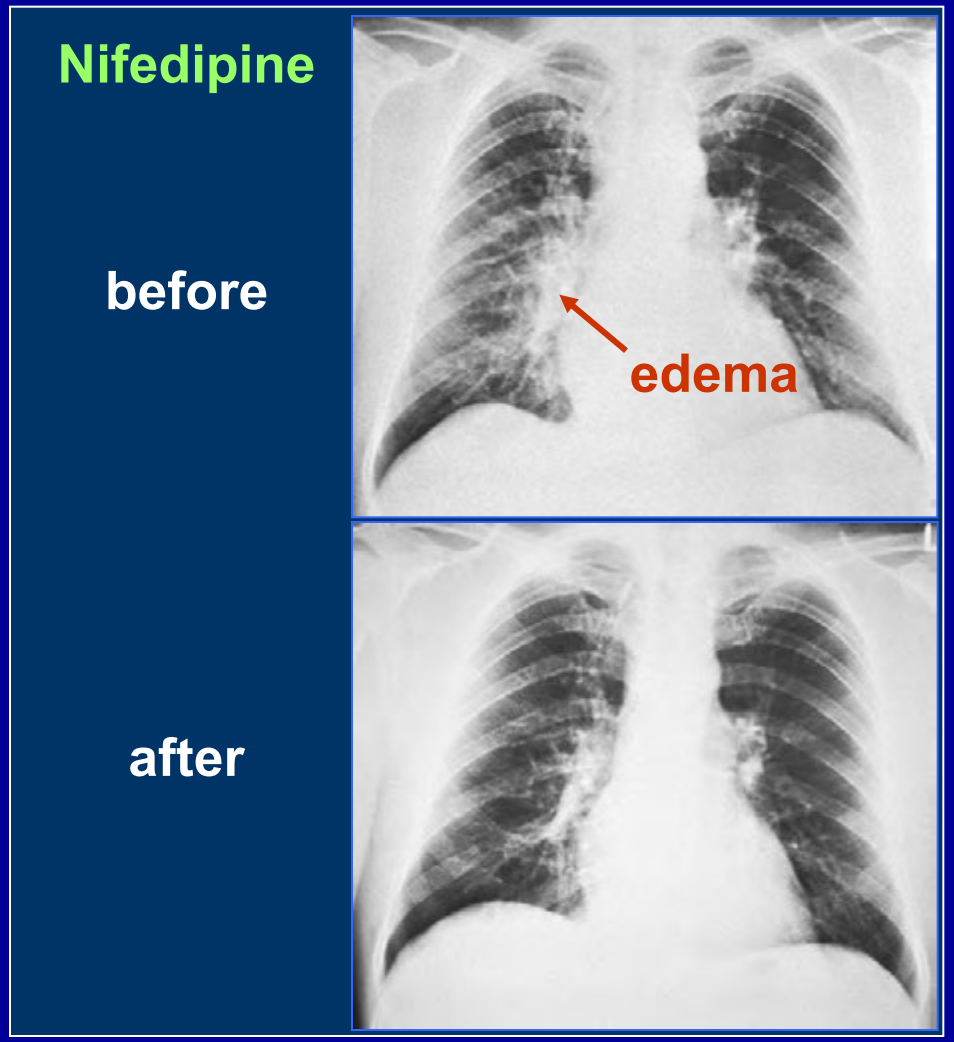
- Nifedipine 3 x 20mg sr
- Sildenafil 3 x 25 mg
- Tadalafil 1 x 20 mg

Medical supportive treatment

- Dexamethosone 2 x 8 mg
- Acetazolamide 2 x 250 mg

Pulmonary artery pressure is crucial for the development of HAPE

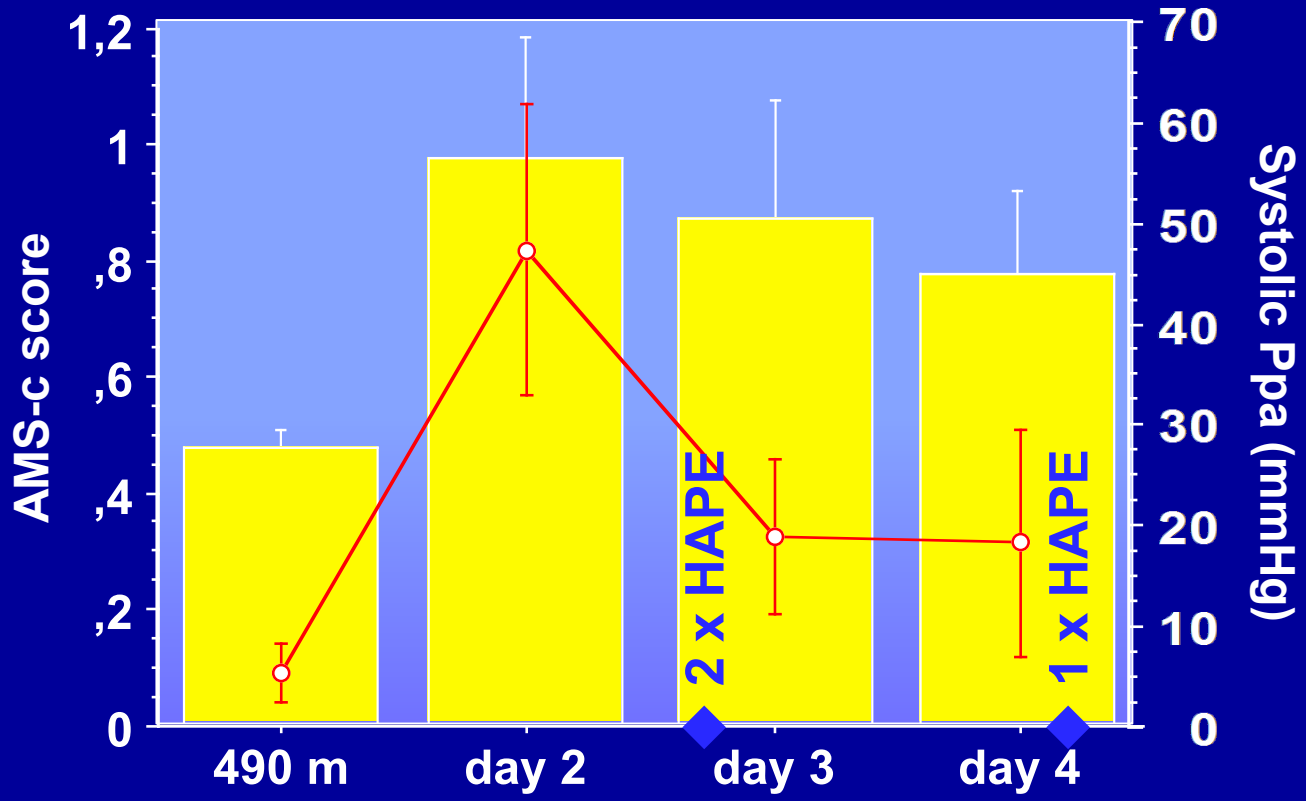




Oelz et al. Lancet 1989

Dexamethasone treatment in HAPE susceptible persons

14 HAPE susceptible persons receiving 2 x 8 mg dexamethasone for AMS at high altitude day 2 after rapid ascent to 4559m



Maggiorini et al.
unpublished

Treatment of High Altitude Pulmonary Edema (HAPE)

HAPE

Mild-AMS
≤ 2 AMS Symptoms

Azetazolamide
125 mg every 12 h

4-6 l/min O_2
+
Nifedipin 20 mg
or
Sildenafil 50mg
every 8 h

Descent > 1000m

Mild/Severe AMS
> 2 AMS Symptoms

Dexamethasone
8 mg loading dose
4 mg every 6 h

Thank you Margherita researcher and hut keepers team!

Thank you for your attention