# High Altitude


**Tom DeLoughery, MD MACP FAWM @bloodman**

**Oregon Health &Sciences University**

GENERAL HEMATOLOGY

OHSU

# DISCLOSURE

**<u>Relevant Financial Relationship(s)</u>**

**Speaker Bureau - None**

**Consultant/Research – none**

# Overview

- Adapting to high altitude
- High altitude illnesses
  - Acute mountain sickness
  - High altitude cerebral edema
  - High altitude pulmonary edema

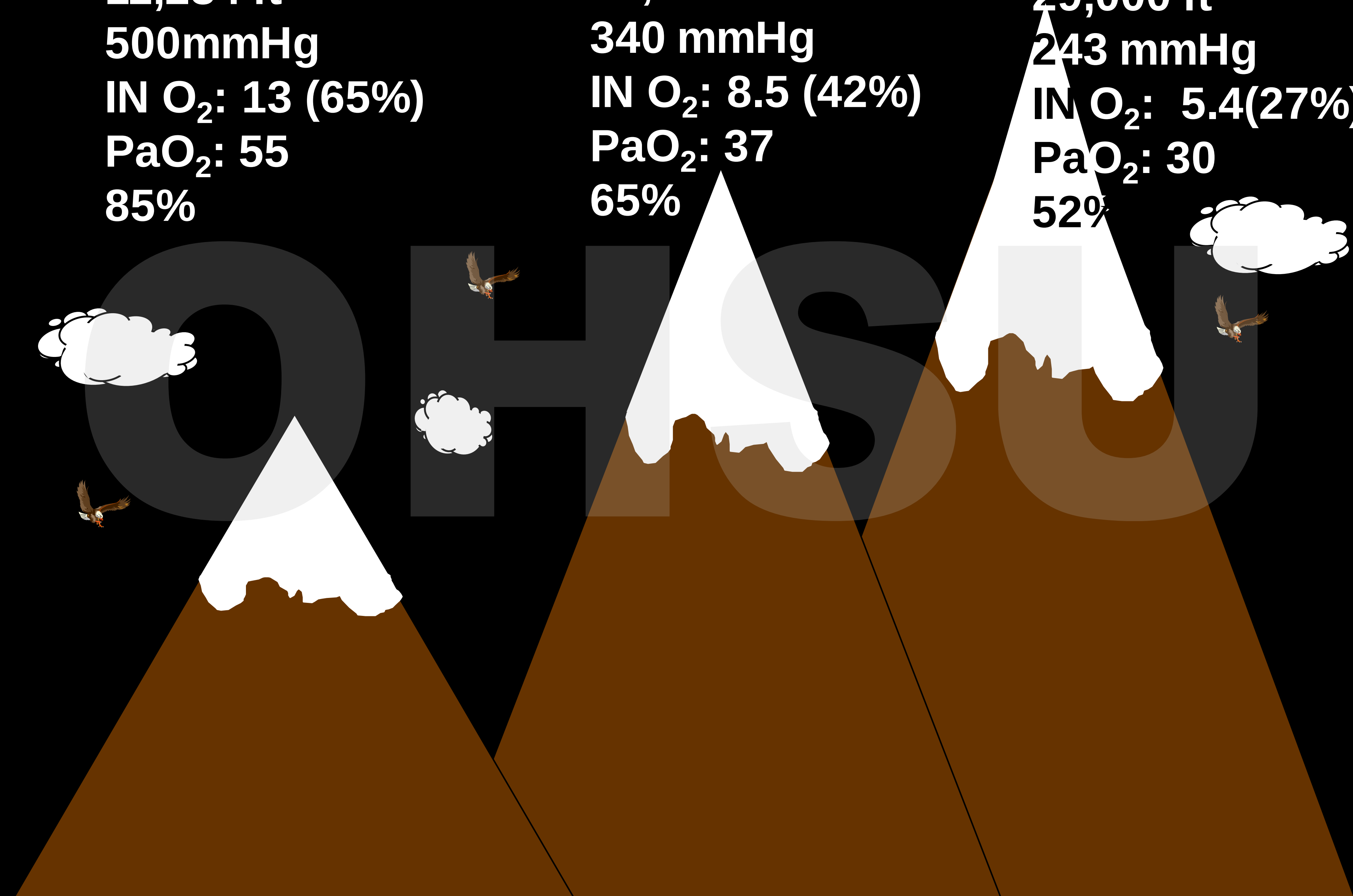
# High Altitude Medicine

- 30,000,000 people live above 9000 ft
- Unique physiologic changes

**MT HOOD**
**11,234 ft**
**500mmHg**
**IN $O_2$: 13 (65%)**
**$PaO_2$: 55**
**85%**

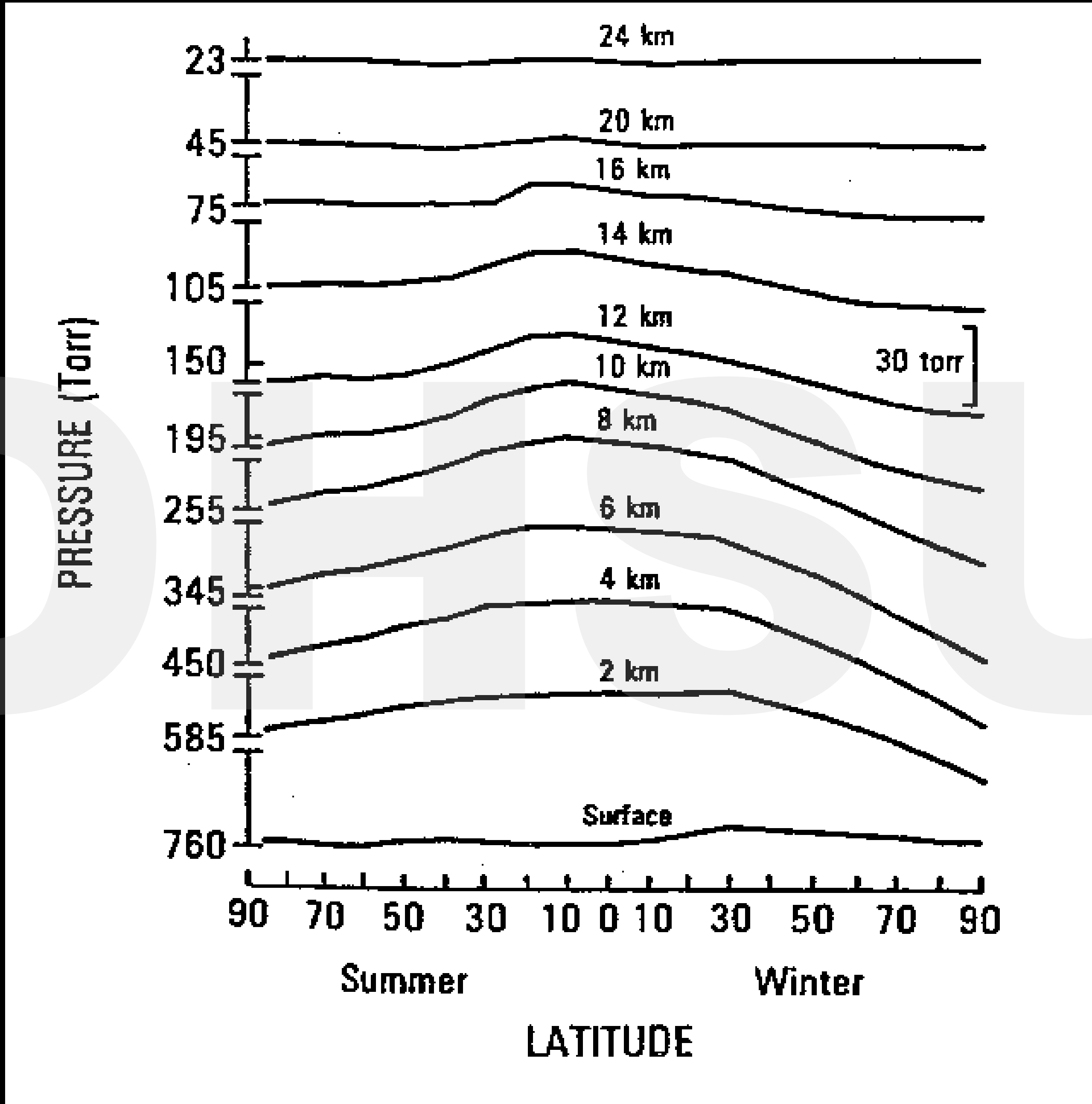
**DENALI**
**20,325 ft**
**340 mmHg**
**IN $O_2$: 8.5 (42%)**
**$PaO_2$: 37**
**65%**

**EVEREST**
**29,000 ft**
**243 mmHg**
**IN $O_2$: 5.4(27%)**
**$PaO_2$: 30**
**52%**

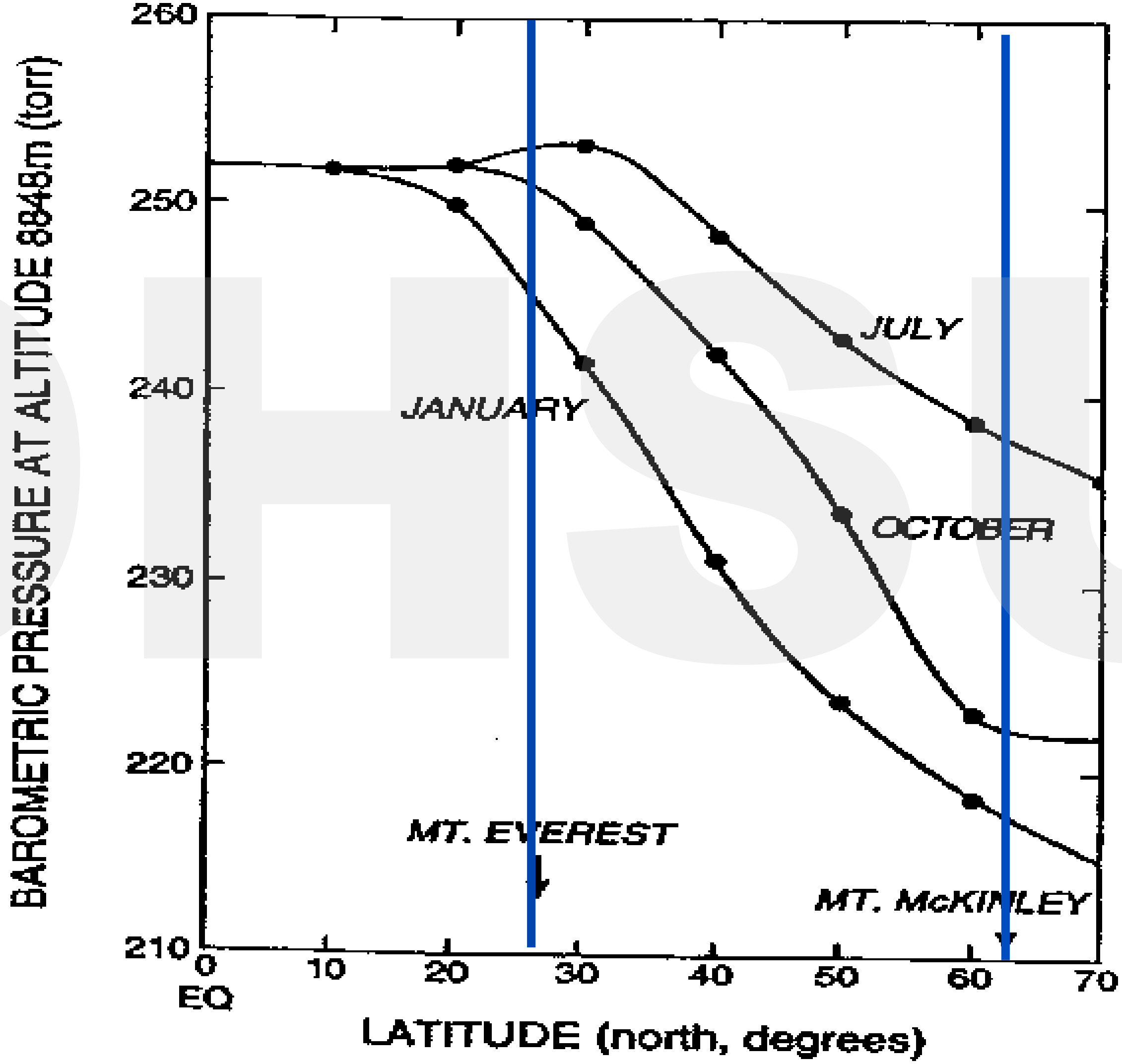


# High Altitude

- Decreased oxygen tension
- Decreased barometric pressure
  - Varies with latitude
  - If Everest was in Alaska, pressure = 222 mmHg not 243 mmHg



24 km
20 km
16 km
14 km
12 km
10 km
8 km
6 km
4 km
2 km
Surface
30 torr
PRESSURE (Torr)
23
45
75
105
150
195
255
345
450
585
760
90 70 50 30 10 0 10 30 50 70 90
Summer
Winter
LATITUDE


BAROMETRIC PRESSURE AT ALTITUDE 8848m (torr)
260
250
240
230
220
210
0
EQ
10
20
30
40
50
60
70
LATITUDE (north, degrees)
JULY
JANUARY
OCTOBER
MT. EVEREST
MT. McKINLEY


CHINA
AIRLINES
CARGO

Table 2-5: Time of Useful Consciousness (TUC) at Various Altitudes

| Altitude (ft) | Altitude (m) | Approximate TUC* (minutes) |
|---|---|---|
| 18 000 | 5 486 | 20–30 |
| 25 000 | 7 620 | 3–5 |
| 30 000 | 9 144 | 1.5 (90 seconds) |
| 40 000 | 12 192 | ≤0.25 (15 seconds or less) |

*Individual tolerance varies.

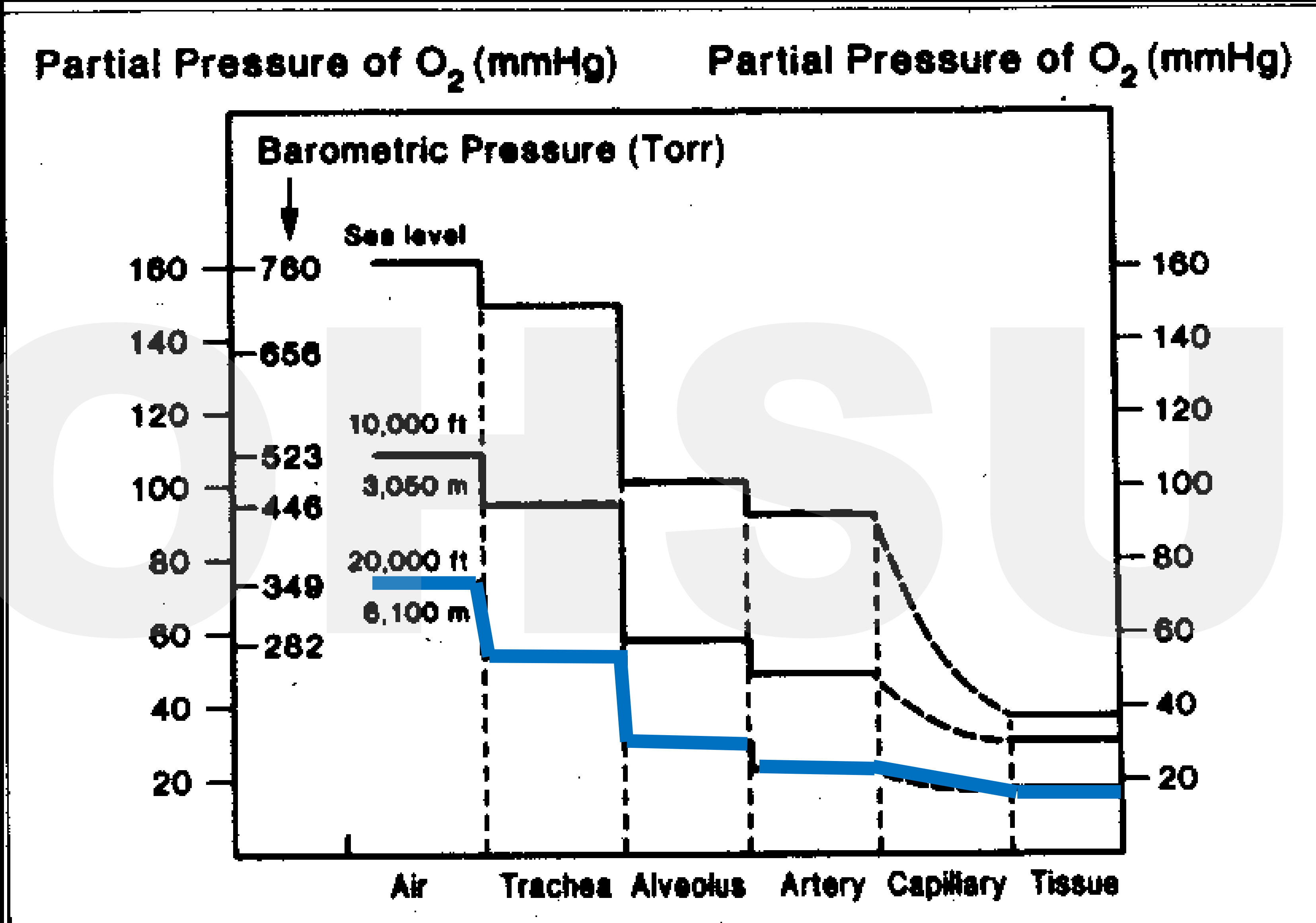
Photo: Lindsey Fell

# How do we Adapt to Hypoxia???

Increase oxygen delivery to tissues

# Chain of Oxygen

- Lungs
- Blood
- Tissue



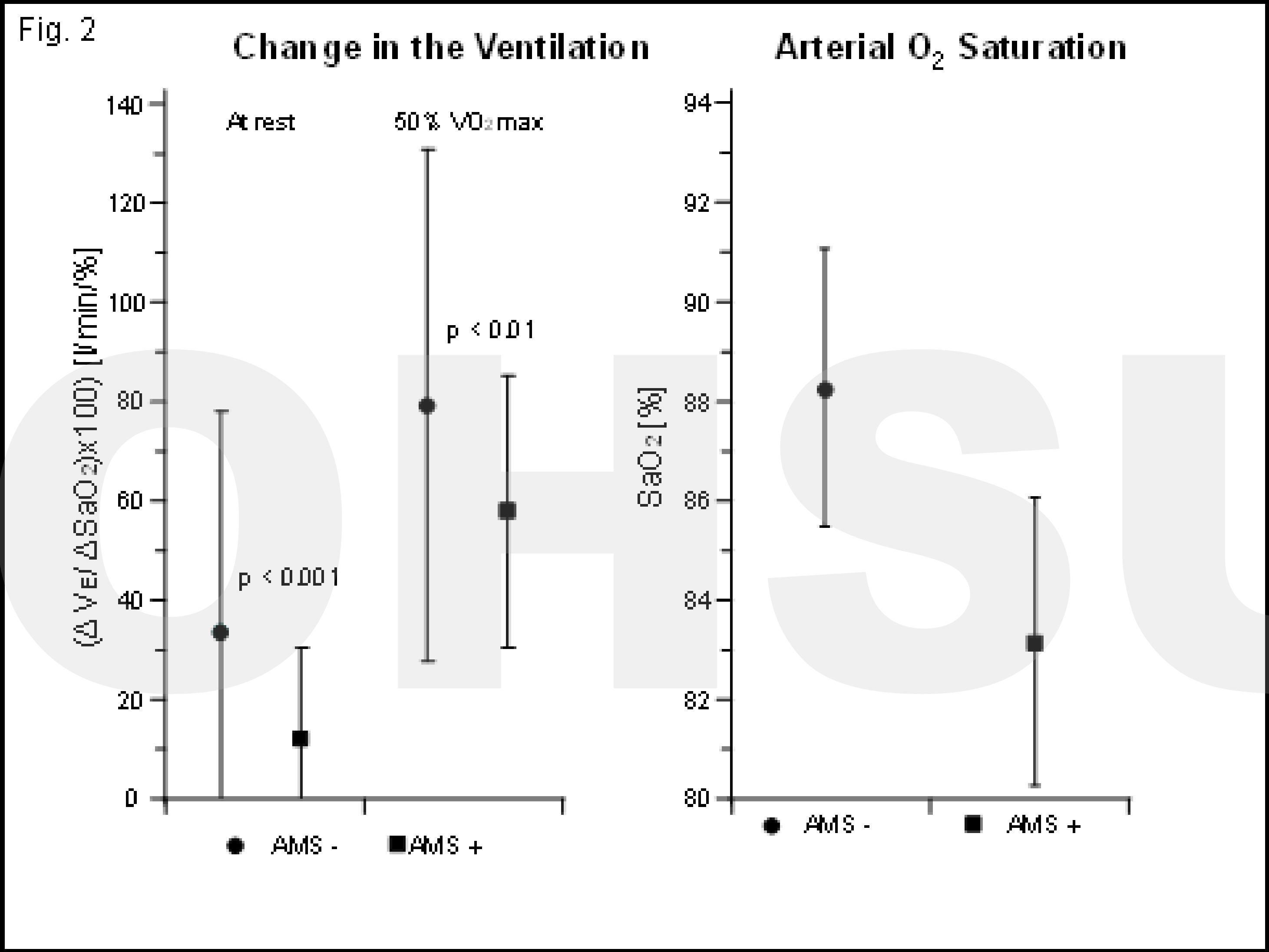
Partial Pressure of O2 (mmHg)
Partial Pressure of O2 (mmHg)
Barometric Pressure (Torr)
Sea level
10,000 ft
3,050 m
20,000 ft
6,100 m
160
140
120
100
80
60
40
20
760
656
523
446
349
282
Air
Trachea
Alveolus
Artery
Capillary
Tissue

# Lungs

1. Increase ventilation
   - Starts at $pO_2$ of 60 mmHG
   - With acclimatization increase sensitivity to $pCO_2$
2. Increased pulmonary artery pressure
   - ? Increase blood flow to all portions of lungs
   - ? Decrease V/Q mismatch
3. Decreased oxygen diffusion

# Hypoxic Ventilatory Response

- People vary in response to hypoxia
- Genetically determined
- People with greater HVR *tend* do better at altitude



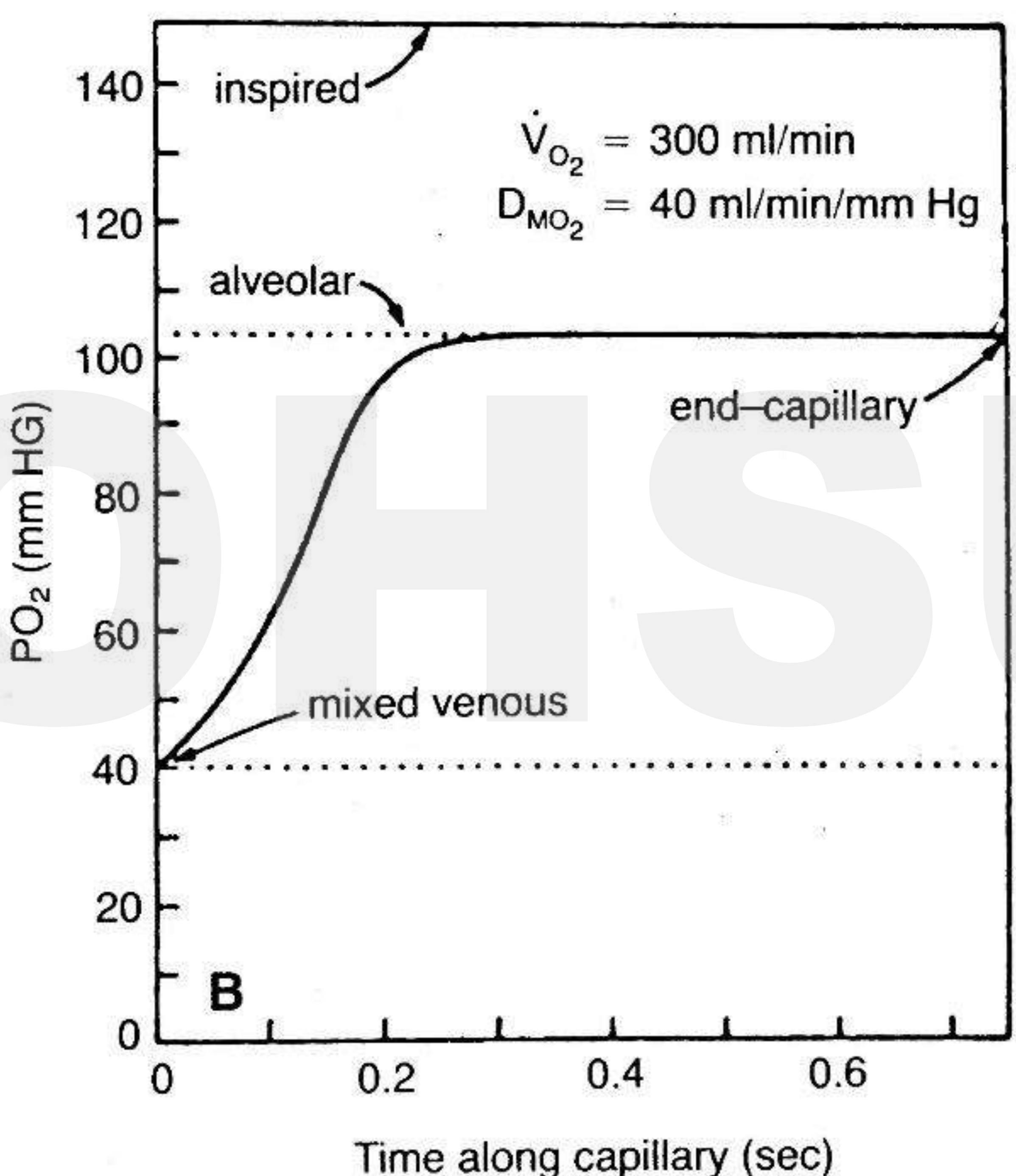

https://www.military-medicine.com/article/3332-who-gets-mountain-sickness.html

# Exception!

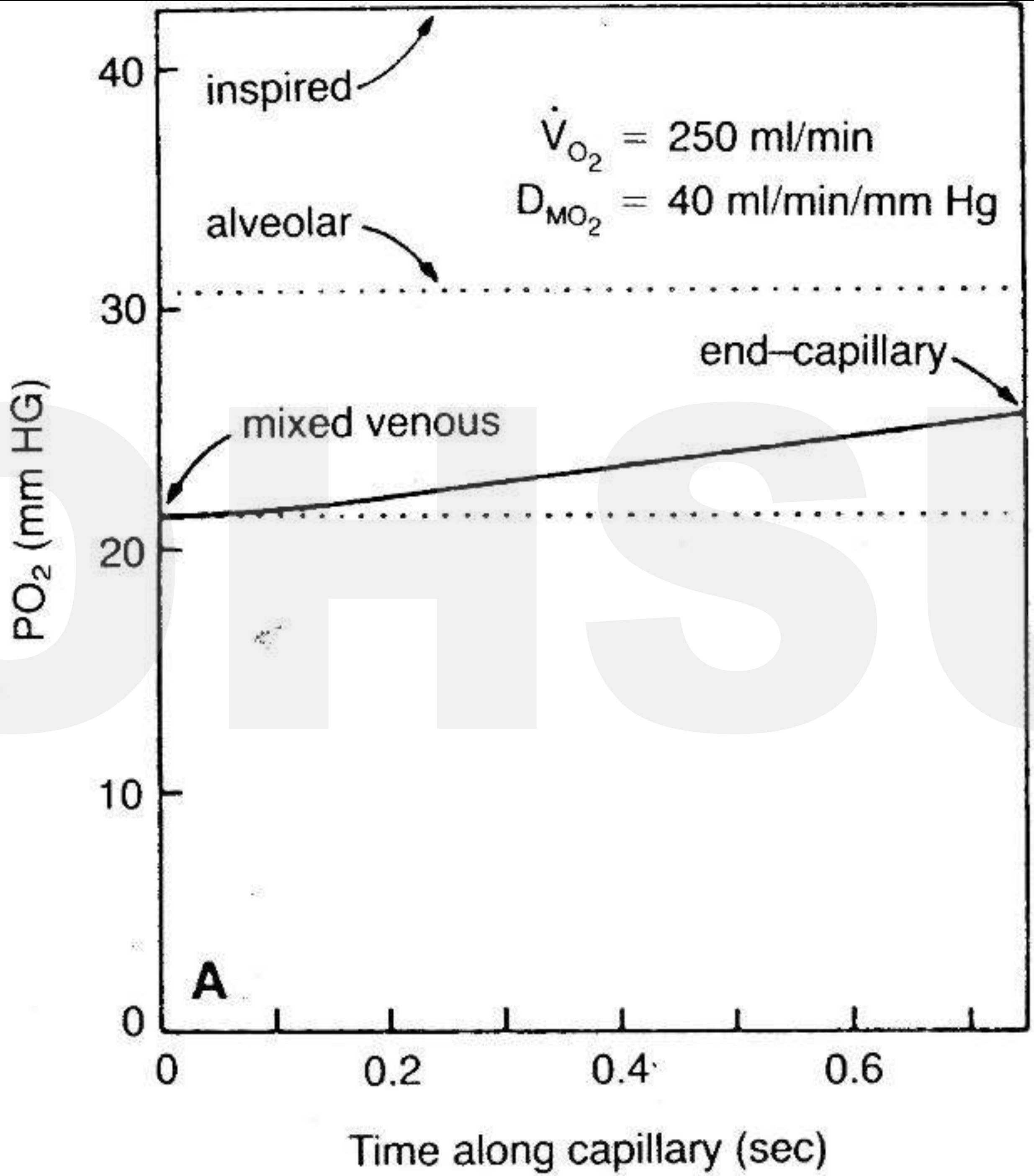
- Increasing data show that climbers who reach extreme altitude have lower HVR
- Greater “ventilatory reserve” at higher altitude?
- Less energy for breathing?

# Cardiac

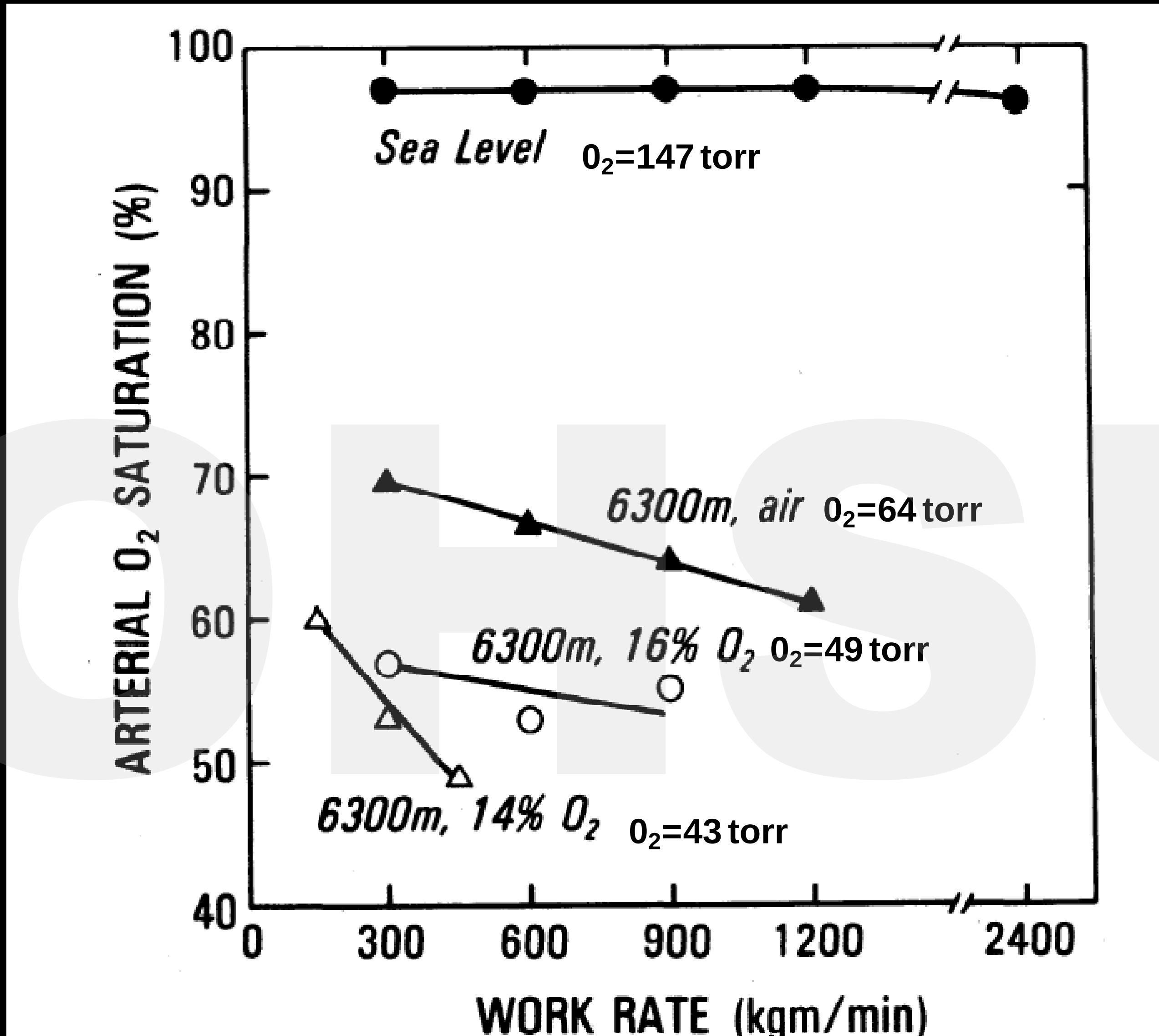
- Decreased cardiac output
  - Decreased stroke volume
    - Decreased plasma volume
    - Decreased heart rate
  - Protects against diffusion limitations?
- No ischemia
- Cardiac output **not** a limiting factor at altitude



inspired
$\dot{V}_{O_2}$ = 300 ml/min
$D_{MO_2}$ = 40 ml/min/mm Hg
alveolar
end–capillary
mixed venous
B
$PO_2$ (mm HG)
Time along capillary (sec)
0
20
40
60
80
100
120
140
0.2
0.4
0.6



inspired
$\dot{V}_{O_2}$ = 250 ml/min
$D_{MO_2}$ = 40 ml/min/mm Hg
alveolar
end–capillary
mixed venous
A
40
30
20
10
0
0
0.2
0.4
0.6
PO$_2$ (mm HG)
Time along capillary (sec)





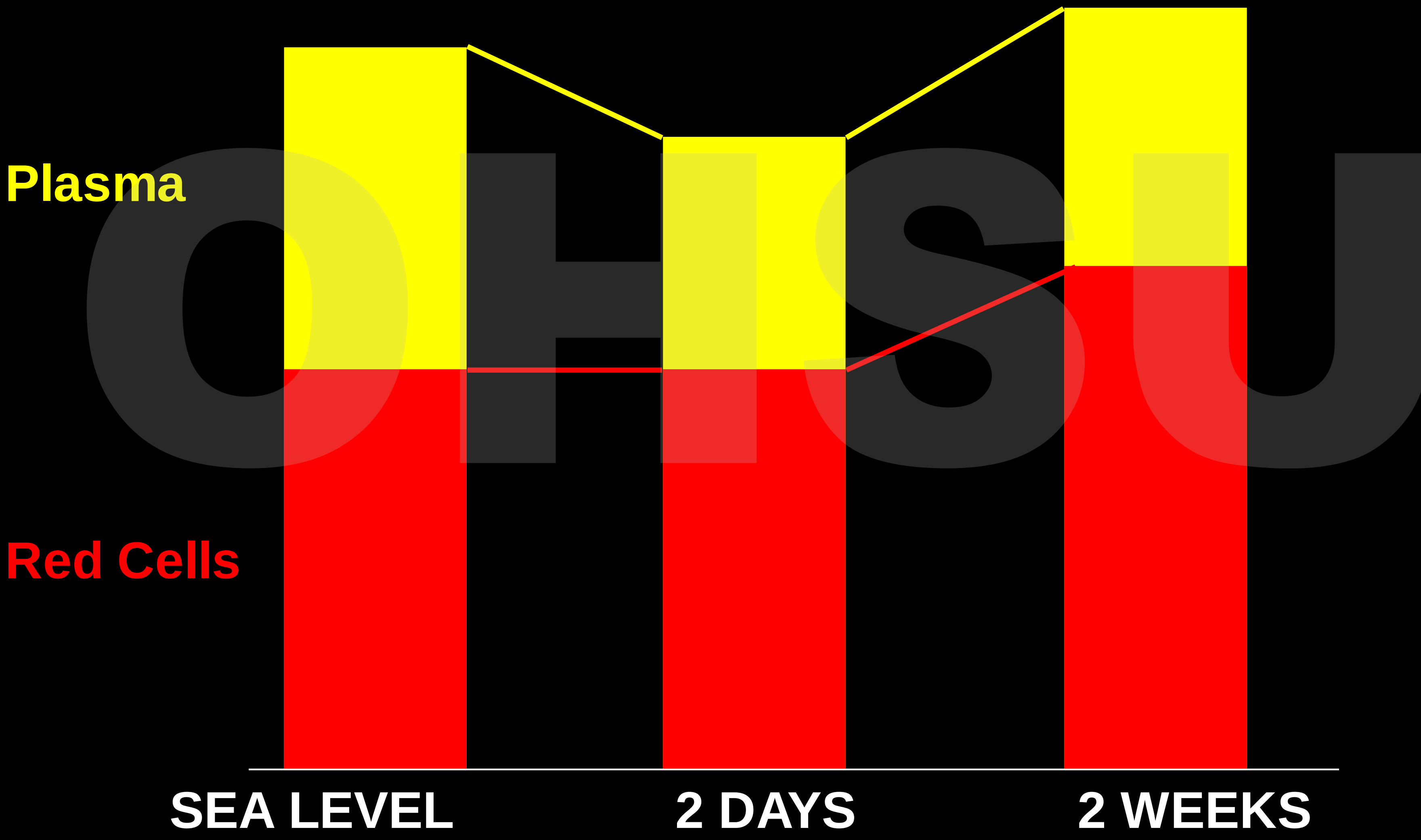

J. Appl. Physiol.: Respirat. Environ. Exercise Physiol.
55(3): 688–698, 1983.

# Blood

- Changes in hematocrit
- Changes in oxygen disassociation curve

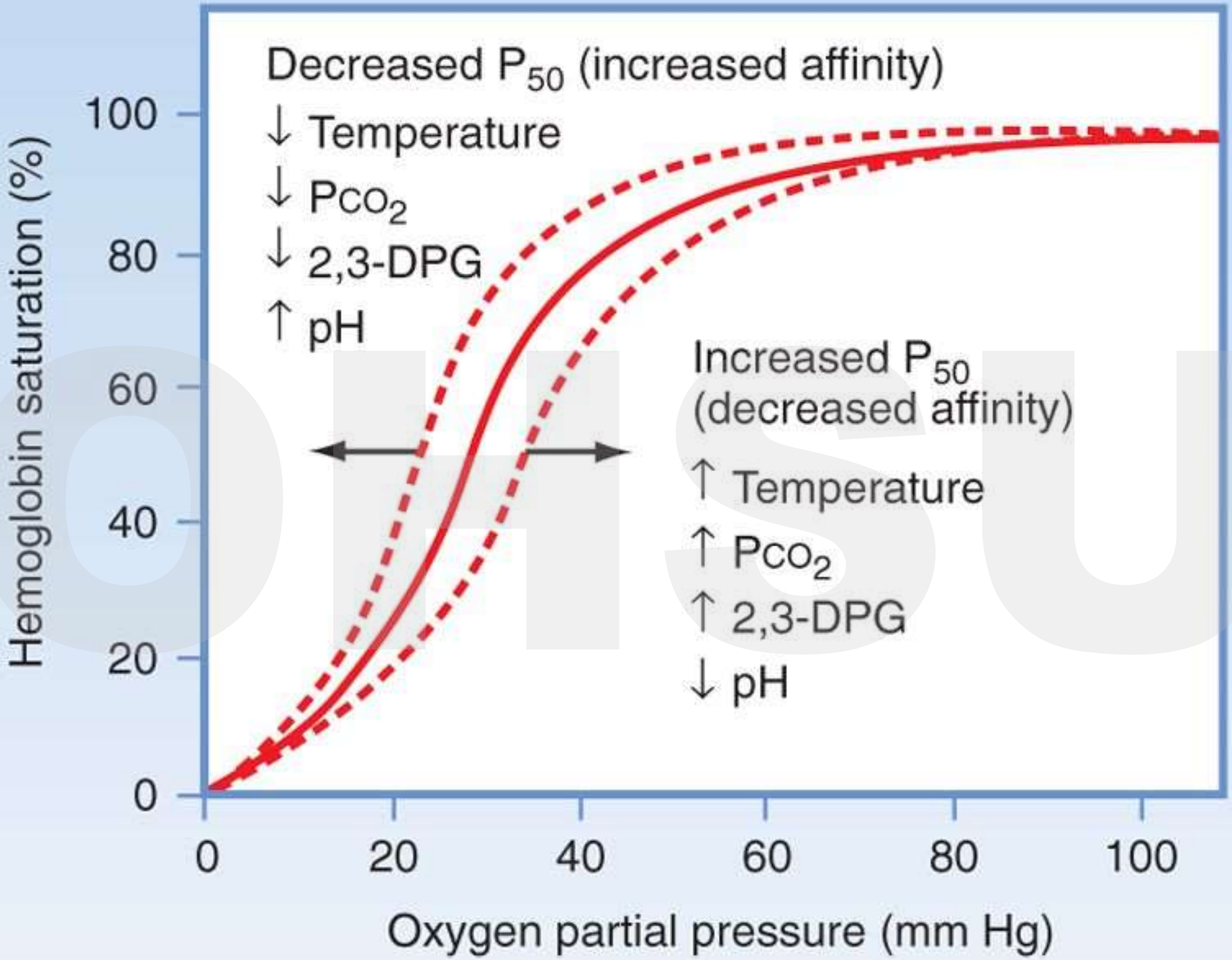
# Hematocrit

- Rises with exposure to high altitude
- 2 - phases
  - Dehydration (hours)
    - Drop in plasma volume of 25% in days
  - Increase red cell mass (days)
- Benefits of increased $O_2$ delivery by more red cells balance by decreased delivery due to increase viscosity


Plasma
Red Cells
SEA LEVEL
2 DAYS
2 WEEKS

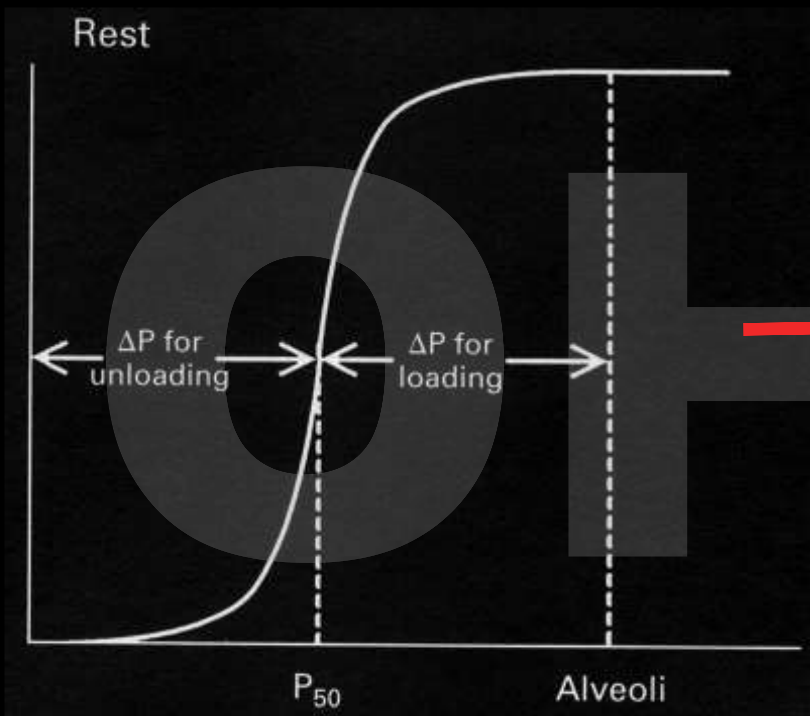
# Hematocrit at Heights

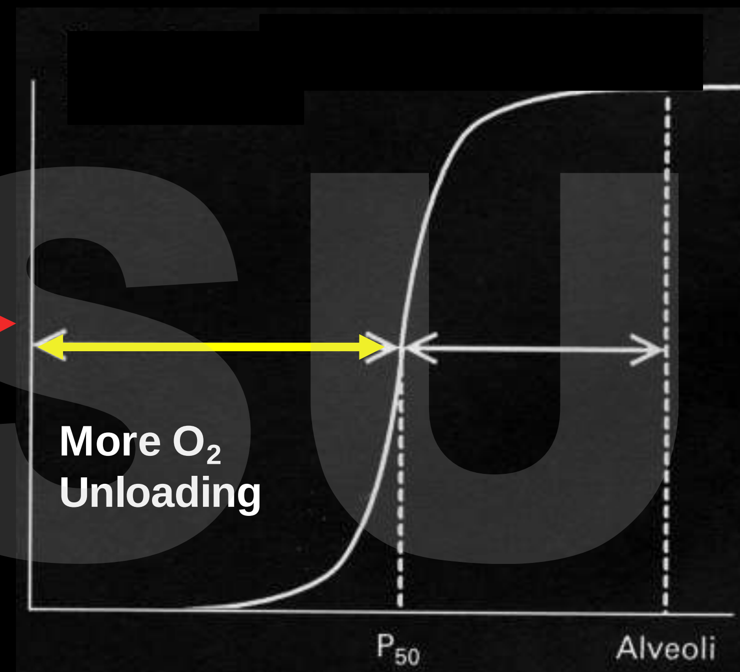
- Sea Level
  - 40-45%
- High altitude natives
  - Andes 55-60%
  - Sherpas 50-55%
- AMREE
  - 17,000 ft 50%
  - 21,000 ft 53%



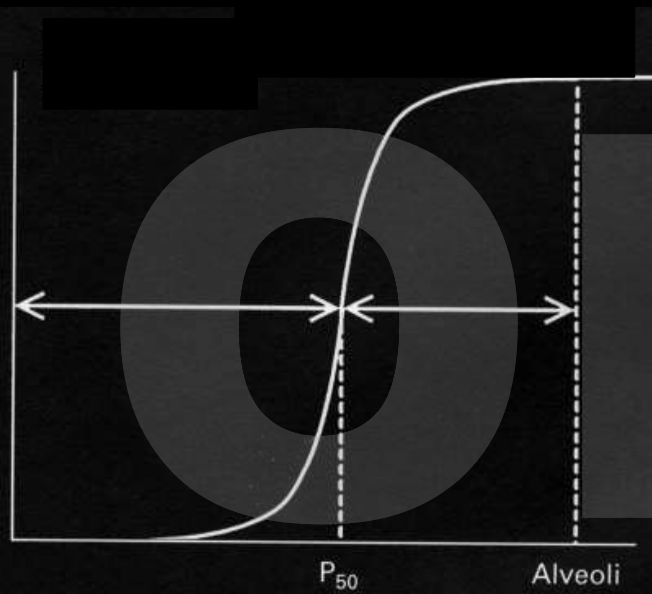

Koeppen & Stanton: Berne and Levy Physiology, 6th Edition.

# Modest Altitude (~ 10,000 ft)

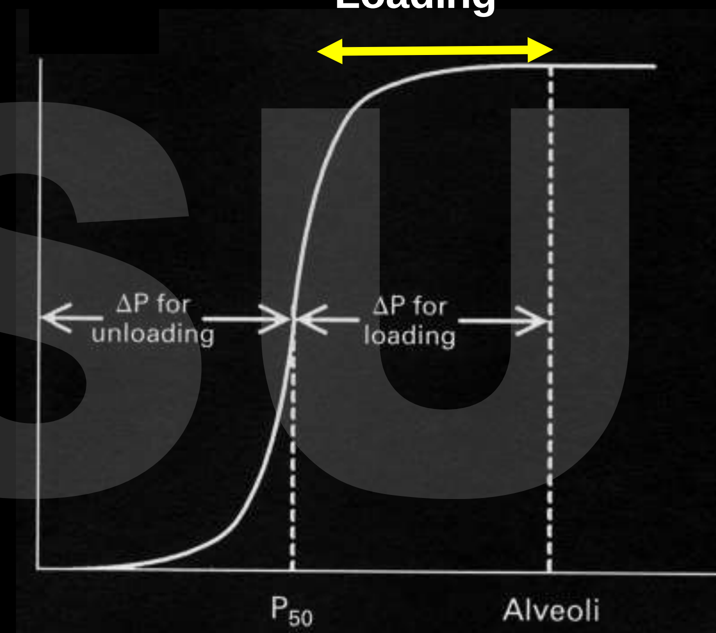


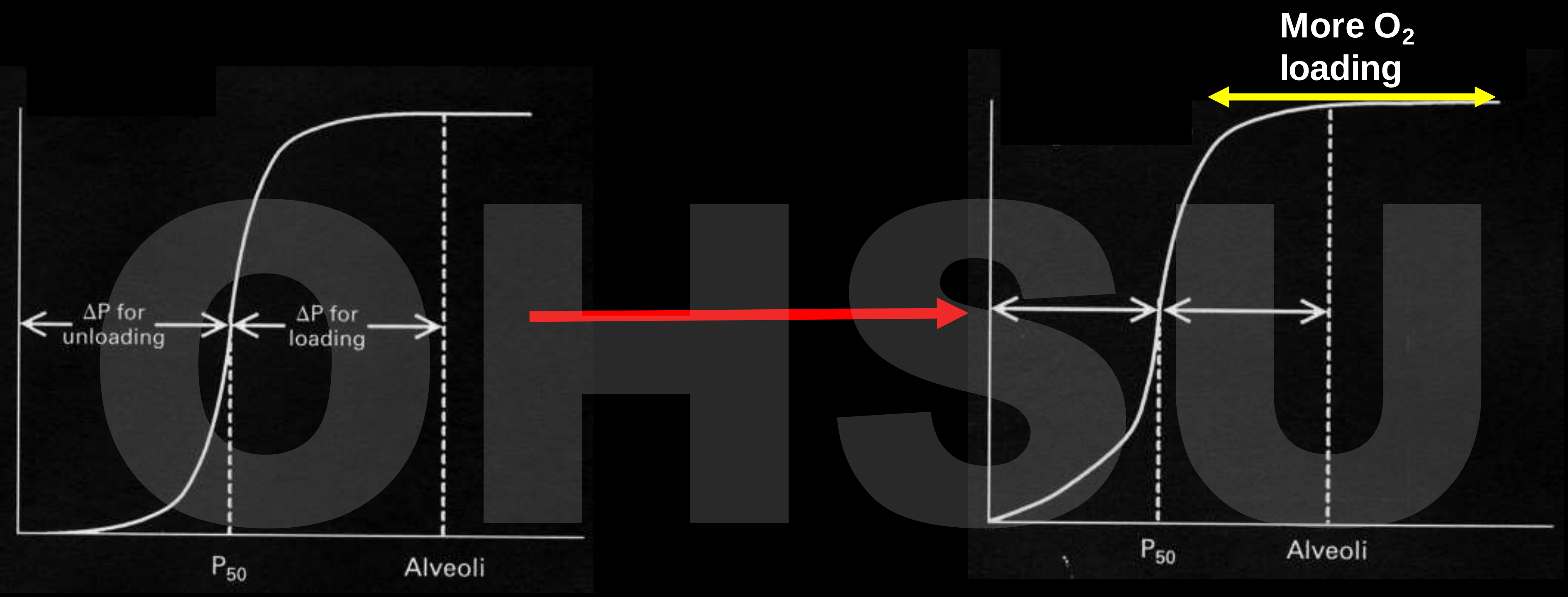
# Higher Altitude (~ 20,000 ft)




**More $O_2$ Loading**



# Extreme Altitude (~ 30,000 ft)



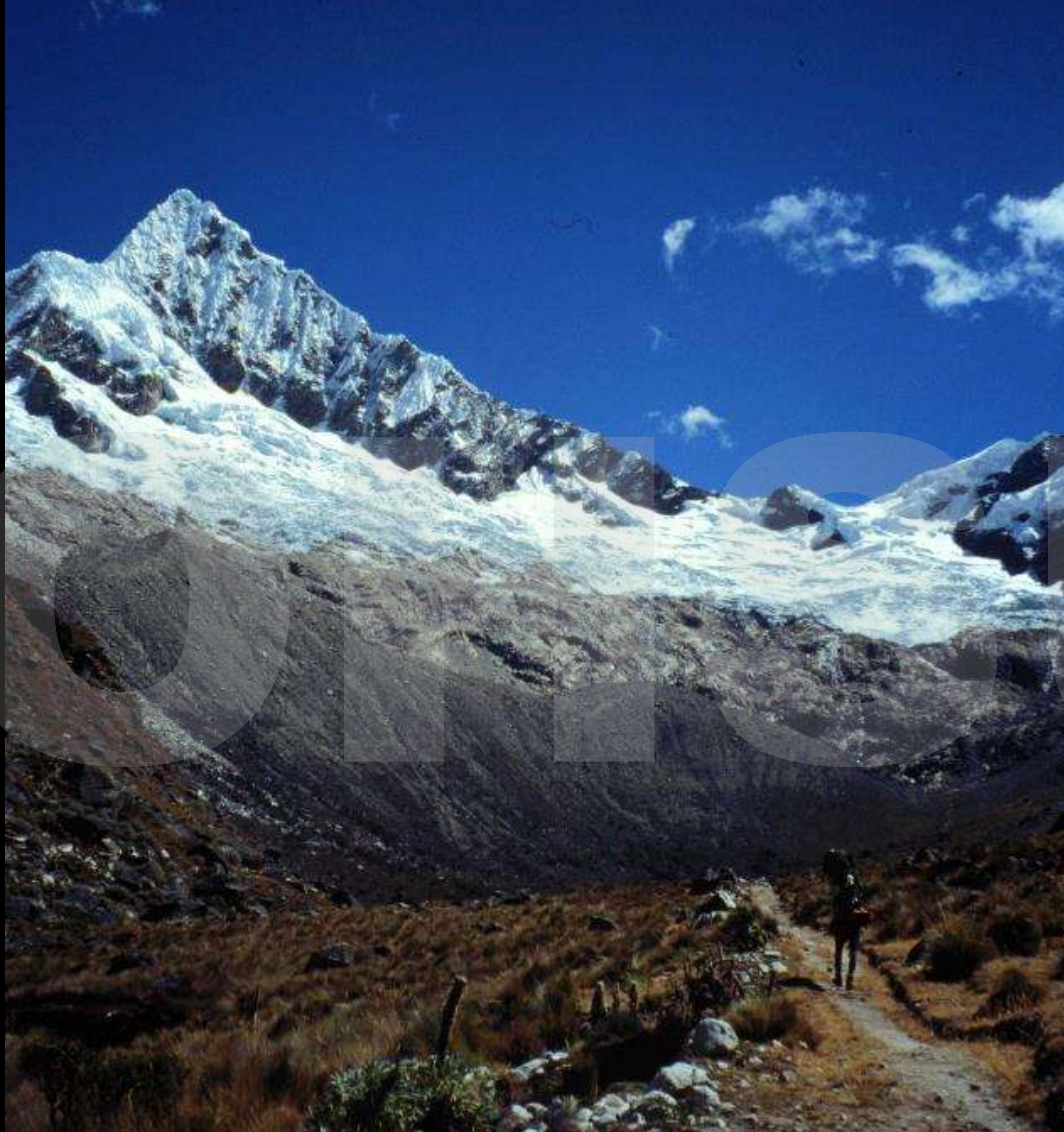


Photo: Deb Robertson

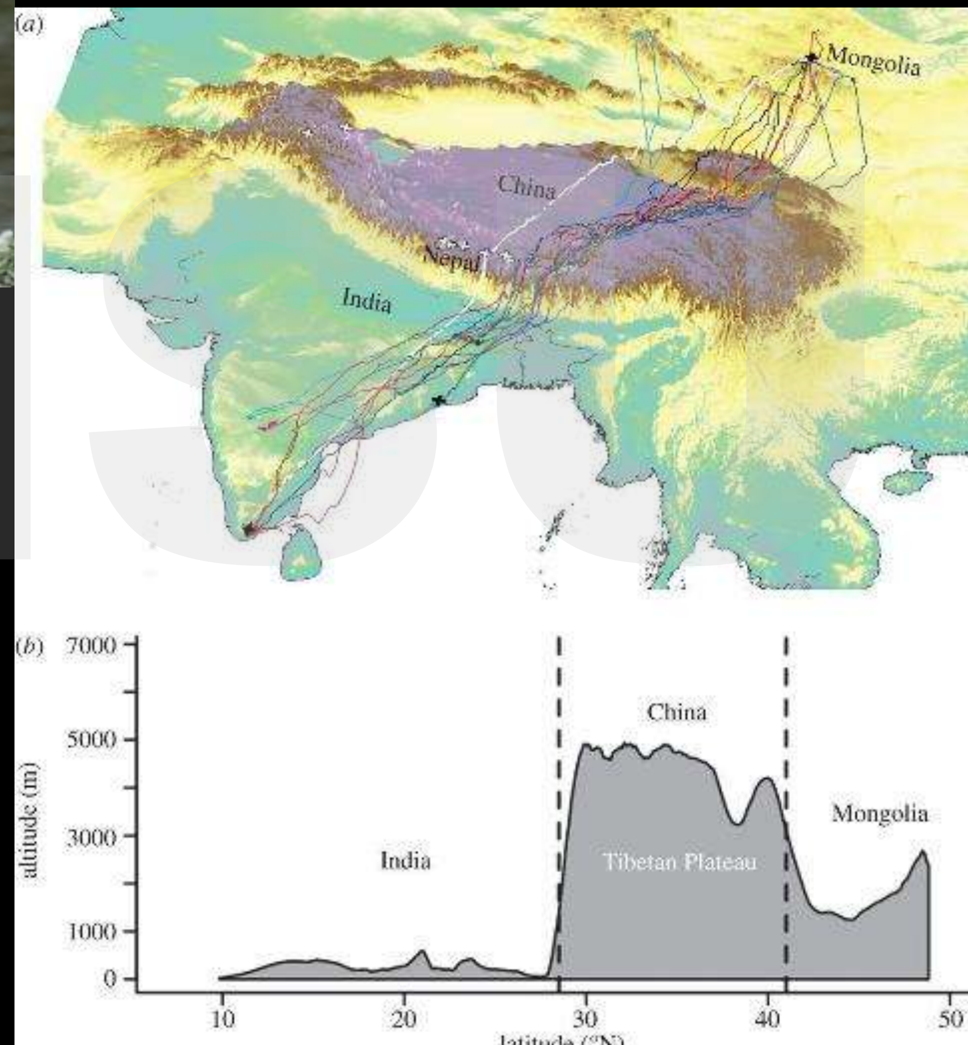
# Evidence Increase $O_2$ Affinity is Beneficial

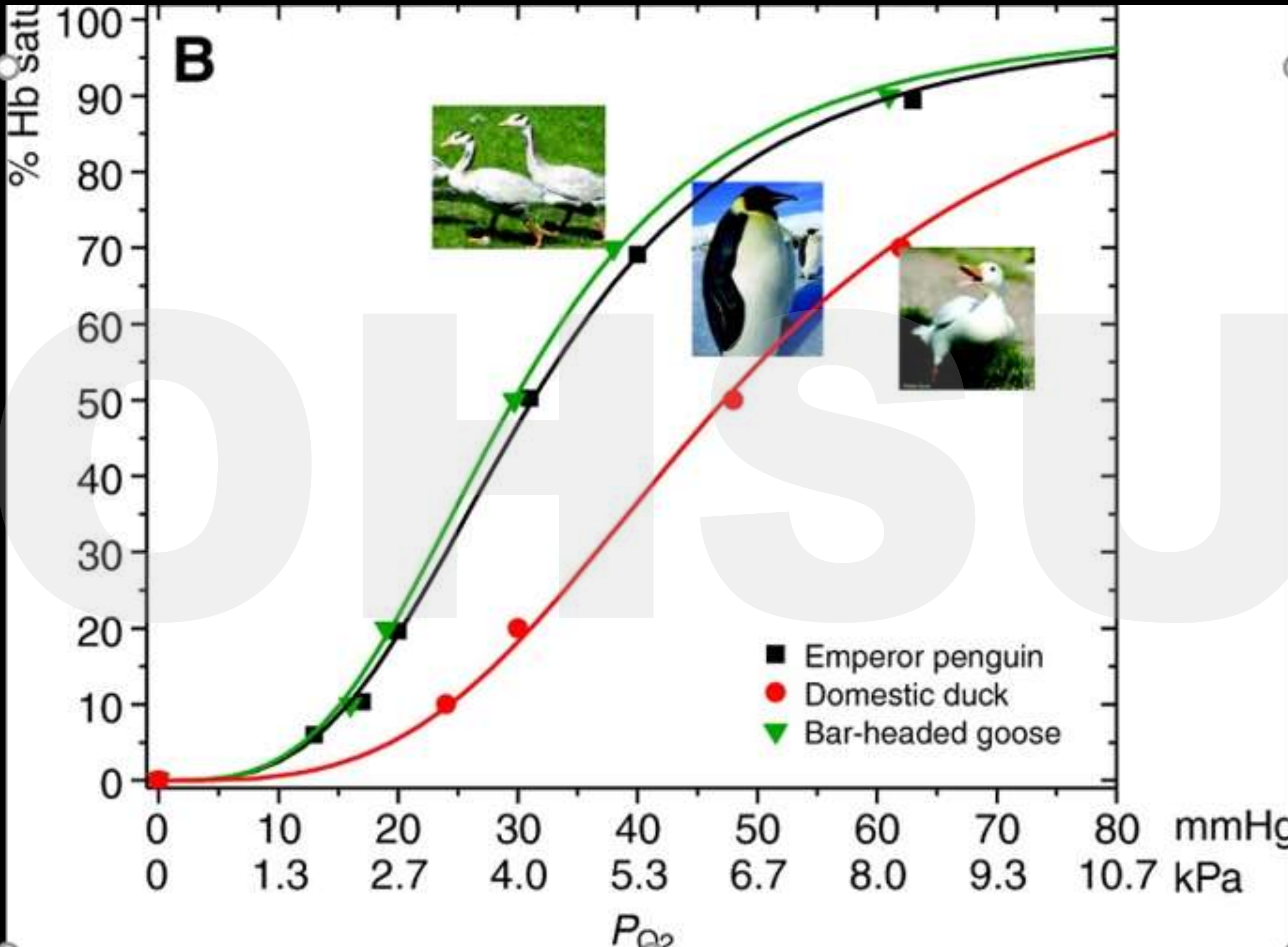
- High altitude animals
  - Sheep with high affinity polymorphism
- Human studies
- “Human llamas” study

# Human Llamas

- High affinity hemoglobin
- At altitude (14,000ft)
  - No change in EPO
  - No decrease in exercise ability

- J Clin Invest. 1978 Sep; 62(3): 593–600.


(a)
Mongolia
China
Nepal
India
(b)
7000
5000
3000
1000
0
altitude (m)
China
Mongolia
India
Tibetan Plateau
10
20
30
40
50
latitude (°N)



% Hb satu
B
100
90
80
70
60
50
40
30
20
10
0
Emperor penguin
Domestic duck
Bar-headed goose
0 10 20 30 40 50 60 70 80 mmHg
0 1.3 2.7 4.0 5.3 6.7 8.0 9.3 10.7 kPa
$P_{O2}$
OHSU

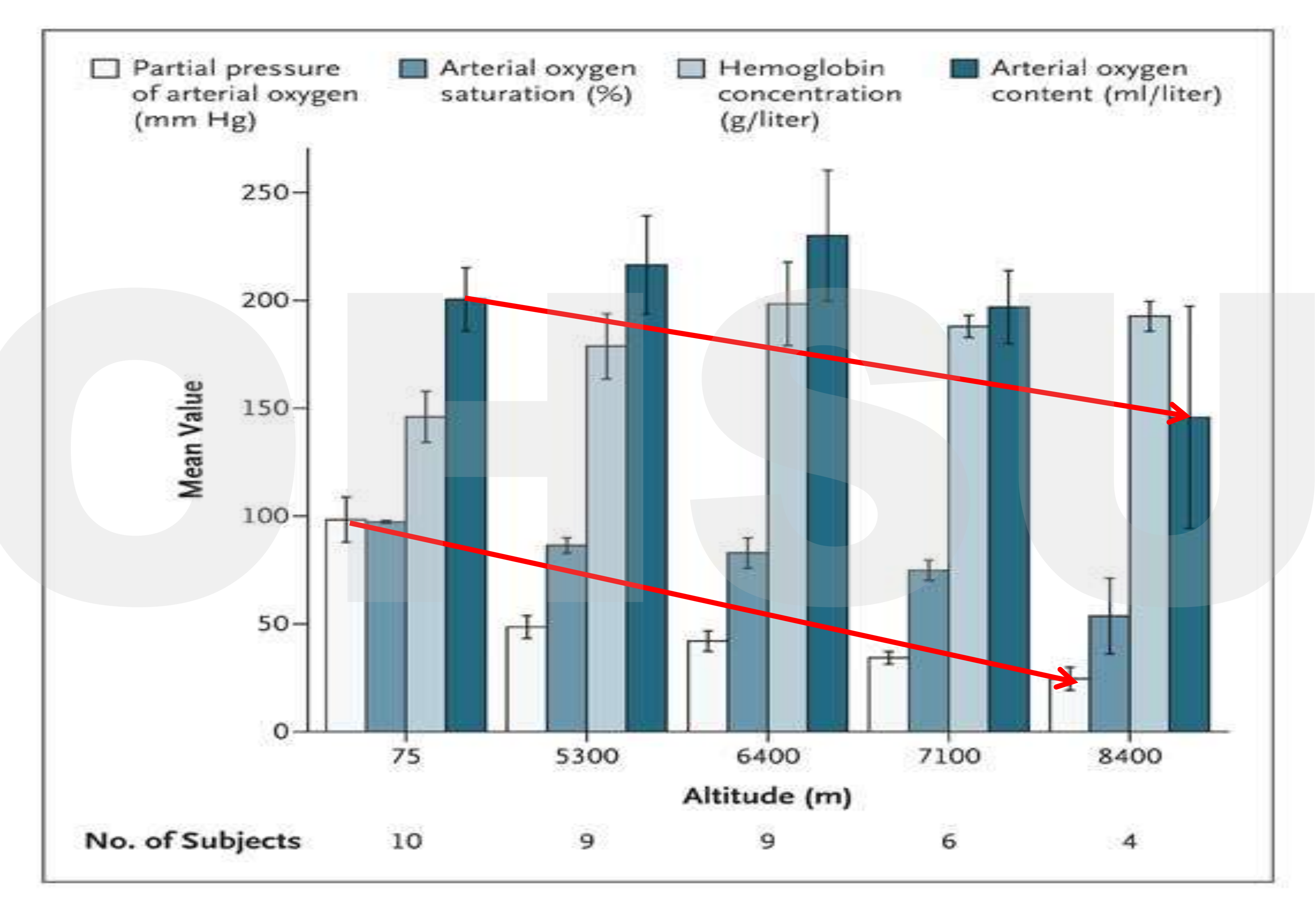
# Tibetans

- Evolved in high altitudes
- Tibetans
  - Less erythrocytosis
  - Lower P50
  - Altitude adaptation legendary

# Tissues

- Increase capillary density
- Decrease muscle mass

Photo: Lindsey Fell




N Engl J Med 2009; 360:140-149

**Table 2. Arterial Blood Gas Measurements and Calculated Values for Pulmonary Gas Exchange from Four Subjects at an Altitude of 8400 m, during Descent from the Summit of Mount Everest.***

| Variable | Subject No. | | | | Group Mean |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | |
| pH | 7.55 | 7.45 | 7.52 | 7.60 | 7.53 |
| $PaO_2$ (mm Hg)† | 29.5 | 19.1 | 21.0 | 28.7 | 24.6 |
| $PaCO_2$ (mm Hg)† | 12.3 | 15.7 | 15.0 | 10.3 | 13.3 |
| Bicarbonate (mmol/liter)‡ | 10.5 | 10.67 | 11.97 | 9.87 | 10.8 |
| Base excess of blood‡ | −6.3 | −9.16 | −6.39 | −5.71 | −6.9 |
| Lactate concentration (mmol/liter) | 2.0 | 2.0 | 2.9 | 1.8 | 2.2 |
| $SaO_2$ (%)‡ | 68.1 | 34.4 | 43.7 | 69.7 | 54.0 |
| Hemoglobin (g/dl)§ | 20.2 | 18.7 | 18.8 | 19.4 | 19.3 |
| Respiratory exchange ratio¶ | 0.81 | 0.74‖ | 0.72 | 0.70 | 0.74 |
| $P_AO_2$ — mm Hg†** | 32.4 | 26.9 | 27.4 | 33.2 | 30.0 |
| Alveolar–arterial oxygen difference — mm Hg† | 2.89 | 7.81 | 6.44 | 4.51 | 5.41 |

* $PaCO_2$ denotes partial pressure of arterial carbon dioxide, $P_AO_2$ partial pressure of alveolar oxygen, $PaO_2$ partial pressure of arterial oxygen, and $SaO_2$ calculated arterial oxygen saturation.

† To convert the values for $PaO_2$, $PaCO_2$, $P_AO_2$, and the alveolar–arterial oxygen difference to kilopascals, multiply by 0.1333.

‡ These values were calculated with the use of the algorithms currently approved by the Clinical Laboratory Standards Institute.[10]

§ The values for hemoglobin are the mean values of measurements obtained at 5300 m (17,388 ft) 9 days before and 8 days after the arterial blood sampling.

¶ The respiratory exchange ratio was measured at an elevation of 7950 m while the subject was resting.

‖ No measured respiratory exchange ratio was available for this subject; the value was derived from the mean values for the other three subjects.

** $P_AO_2$ was calculated with the use of the full alveolar gas equation.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# Diseases of High Altitude

- Acute mountain sickness (AMS)
- High altitude pulmonary edema (HAPE)
- High altitude cerebral edema (HACE)

# Epidemiology

| Group | Sleep | Max | Time | AMS | HAPE | Death |
|---|---|---|---|---|---|---|
| Skiers | 8,-10,000 | 11,000 | 1-2 | 15-40% | 0.1 | ? |
| Trekker | 10,-17,000 | 18,000 | 1-2 | 47% | 1.6 | 1:2500 |
| Trekker | 10,-17,000 | 18,000 | 10 | 23% | 0.05 | - |
| Denali | 10,-18,000 | 20,325 | 1-3 | 50% | 2-3 | 1:625 |
| Rainier | 10,000 | 14,409 | 1-2 | 67% | 0.1 | 1:10,000 |

# Acute Mountain Sickness

- Occurs in 6 - 24 hours of altitude
- Most common altitude problem
- Annoying, debilitating, and precursor of fatal syndromes

# Incidence Of AMS vs Altitude

| Height | %AMS | avg score |
|---|---|---|
| 2850m (9350ft) | 9% | 0.85 |
| 3050m (10,000ft) | 13% | 1.03 |
| 3650m (12,000ft) | 34% | 2.11 |
| 4559m (14,950ft) | 52% | 3.28 |

# AMS: Symptoms

- Headache:
  - Key symptom
  - Throbbing
  - Worse with valsalva
- Dizziness
- Lassitude
- Nausea/Vomiting
- Decreased urine output

# Grading of AMS

- Lake Louise criteria
  - Headache (0-3)*
  - GI symptoms (0-3)*
  - Fatigue (0-3)*
  - Dizziness (0-3)*
  - Sleep difficulty (0-3)*
  - Change in mental status
  - Ataxia (0-4)
  - Peripheral edema (0-2)

**AMS:**

Headache plus:

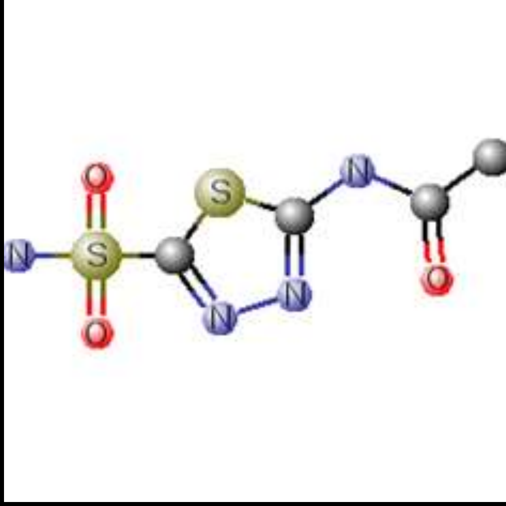
Self-reported $\geq$ 4

Total > 5

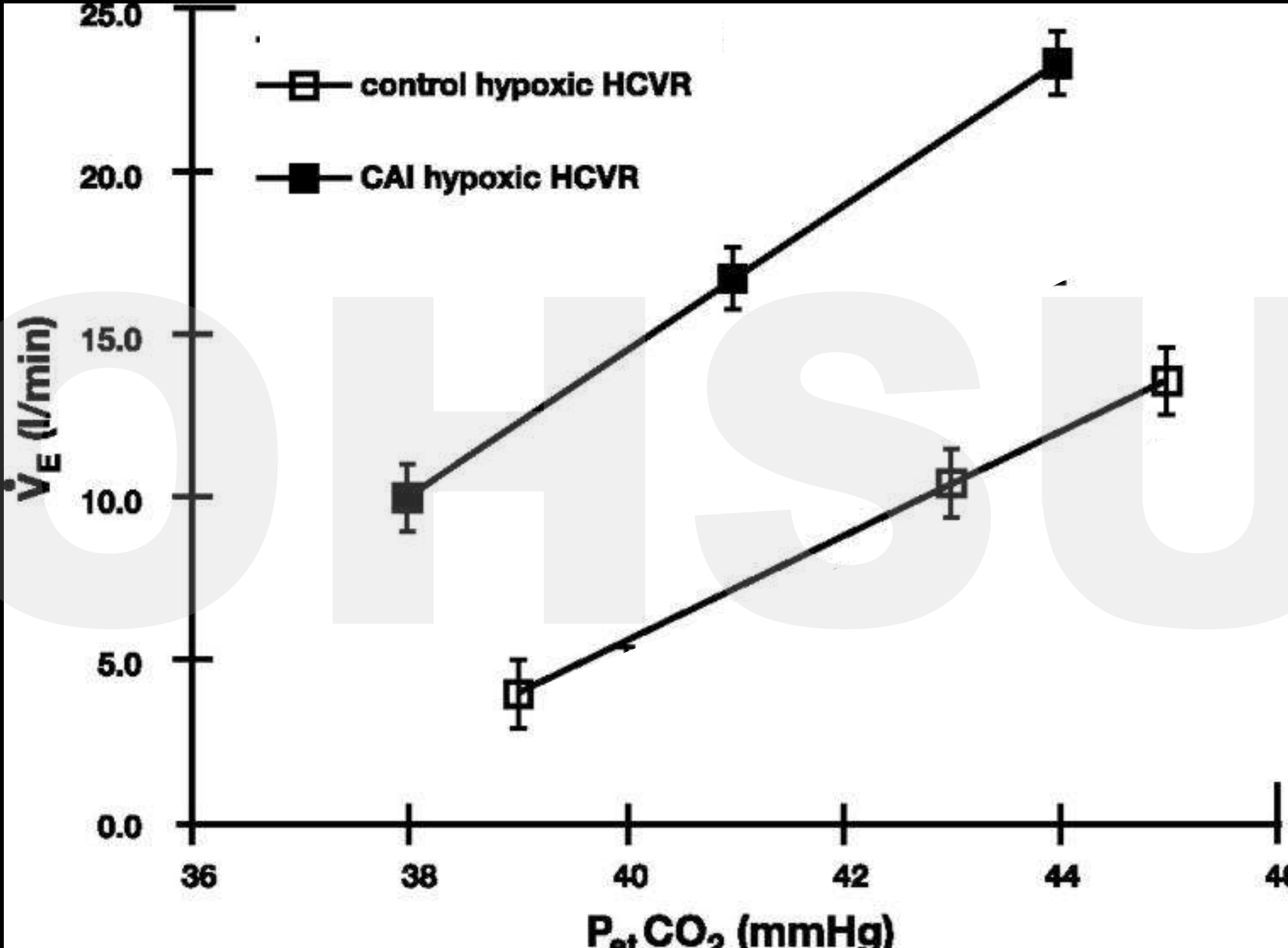
# Therapy

- No further ascent
- Descent or oxygen
- Time
  - Resolves 1-3 days
- Acetazolamide
  - 125 - 250 mg bid
- Dexamethasone
  - Rebound

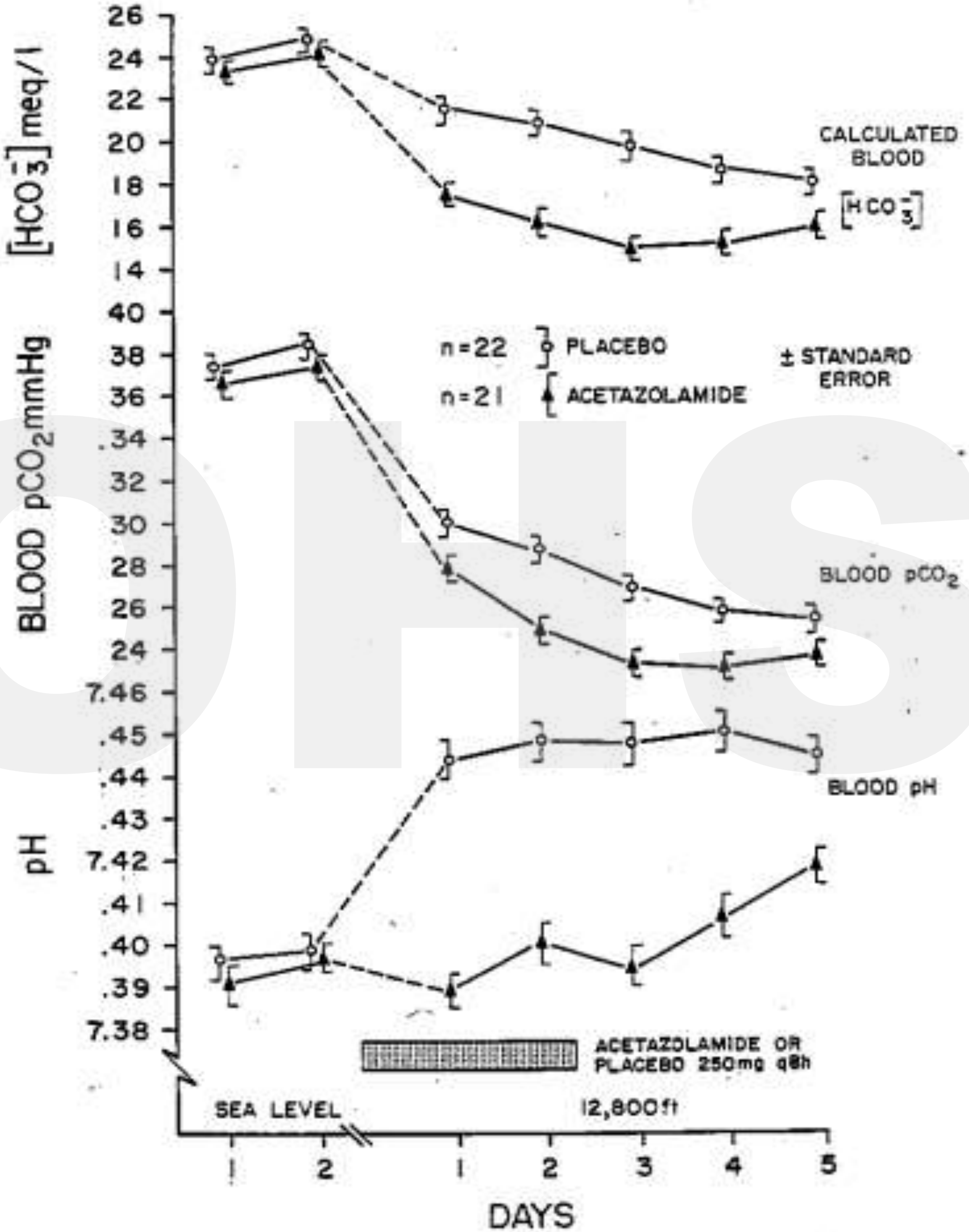
# Acetazolamide



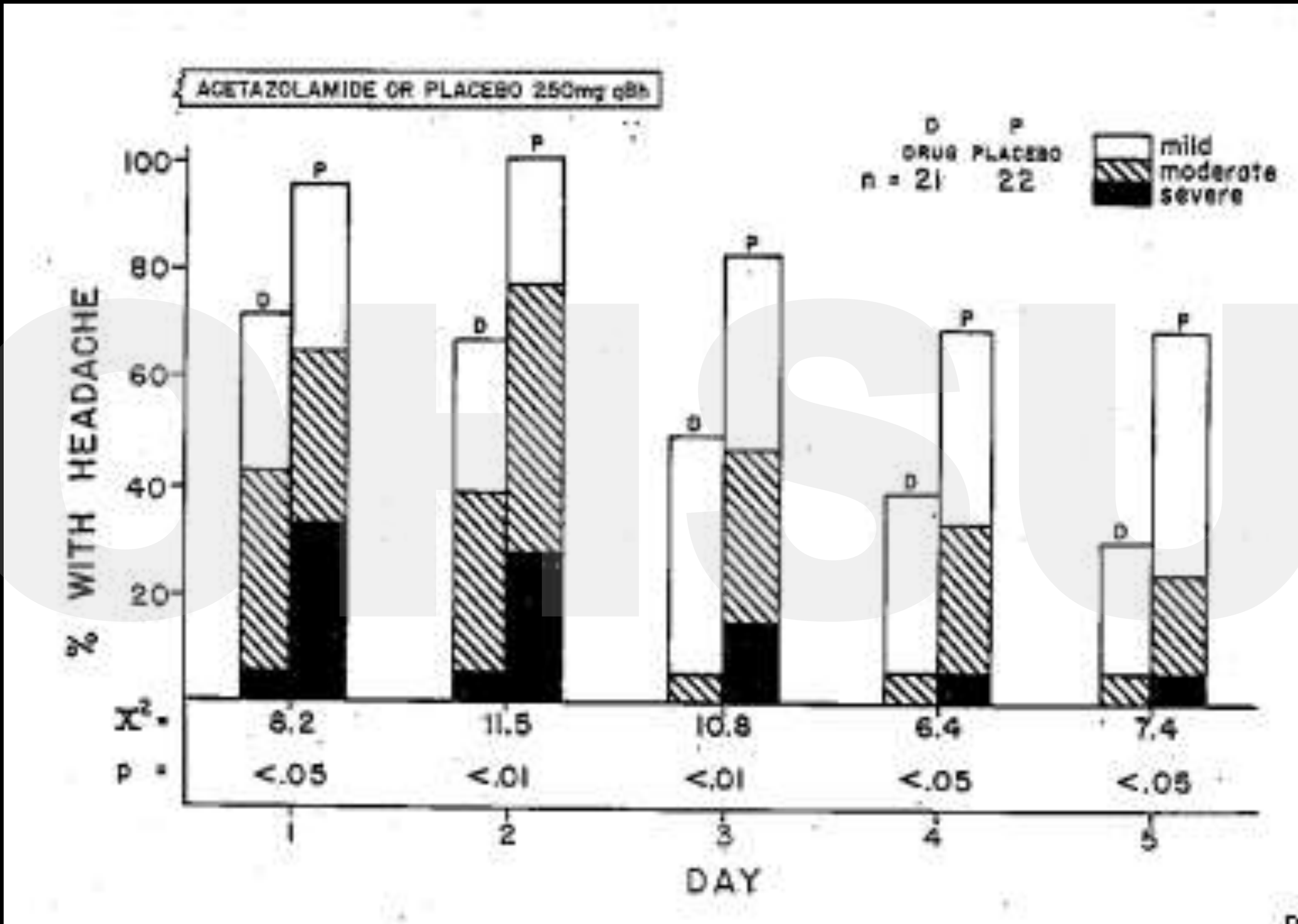

- Carbonic anhydrase inhibitor
  - Increases ventilation
  - Diuresis
- Speeds acclimatization
- Maintains oxygenation
- Treatment/prophylaxis



control hypoxic HCVR
CAI hypoxic HCVR
V̇E (l/min)
25.0
20.0
15.0
10.0
5.0
0.0
36
38
40
42
44
46
PetCO2 (mmHg)
OHSU




**Forwand et al Effect of acetazolamide on acute mountain sickness.**
**N Engl J Med. 1968 Oct 17;279(16):839-45**




N Engl J Med. 1968 Oct 17;279(16):839-45

# AMS: Prevention

- Slow ascents
  - > 3000m no increase sleeping elevation by >500m
  - Rest day every 3-4 days
- Acetazolamide
- Dexamethasone

# Acetazolamide

- Standard pharmacological therapy of AMS
- Two RCT show 125 mg BID effective for preventing AMS by 50-60%
  - Reduced incidence of headache
  - Reduced incidence of severe AMS

# Acetazolamide

- RCT
- 3440-->4300-->4928m

| | Placebo | 125 mg BID | 375 BID |
|---|---|---|---|
| AMS | 51% | 24% | 21% |
| $O_2$Sat | 80.7% | 82% | 82.8% |

High Alt Med Biol. 2006 Spring;7(1):17-27.

# RADICAL Trial

- 125 mg BID vs 62.5 mg BID
- N = 73

| | 62.5 mg BID | 125 mg BID |
|---|---|---|
| AMS (%) | 55.3 | 60.0 |
| Daily incidence | 6.7% | 8.9% |
| LLS | 1.102 | 0.097 |

- WEM 30:12-21, 2019

# Dexamethasone

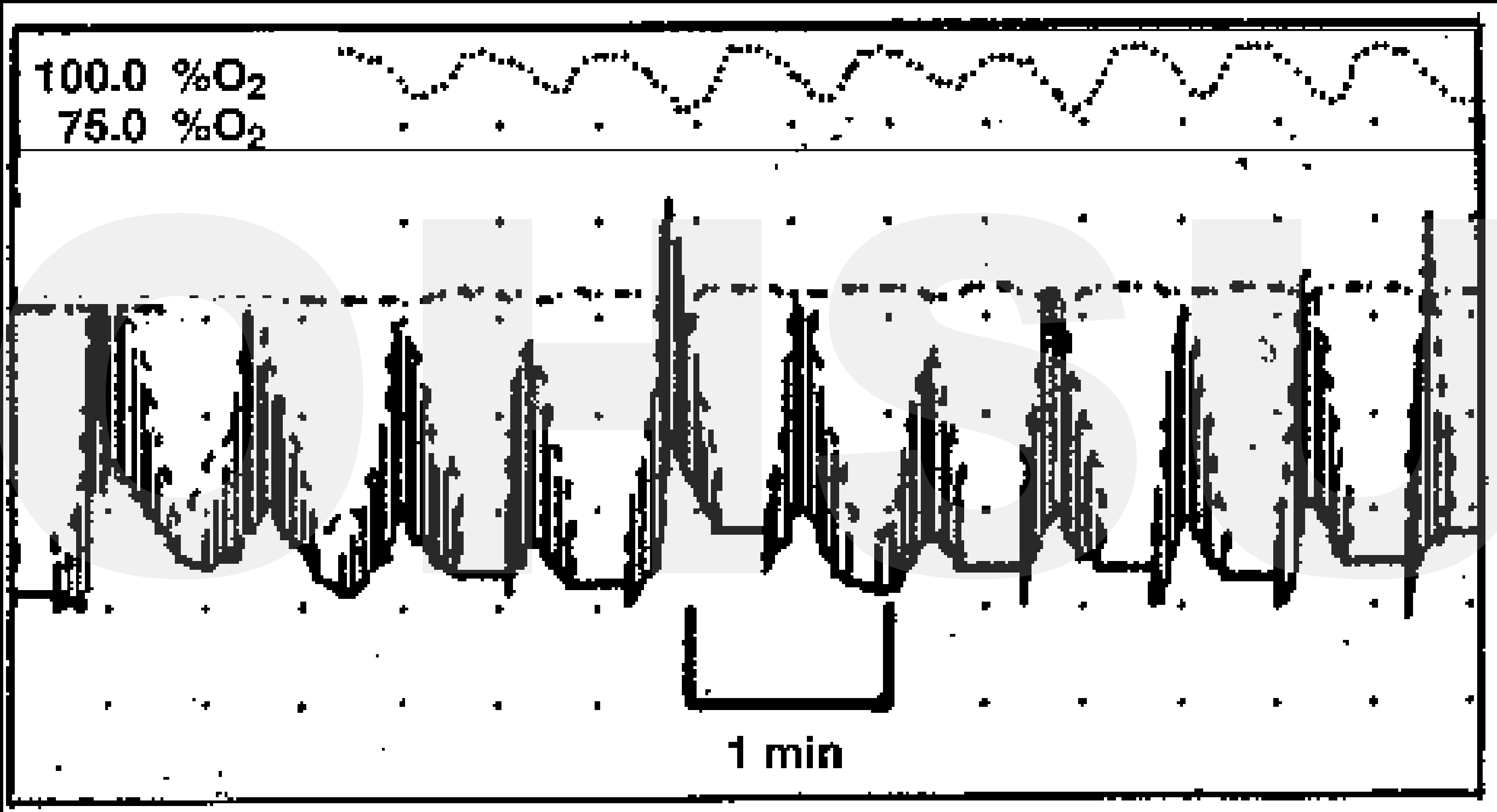
- Effective for treating AMS but does not speed up acclimatization
  - "Rebound"
- May be useful adjunct with acetazolamide for prevention of severe AMS

# AMS: Prediction

- No good tool for predicting who will get AMS except history
- People with good HVR and good sats tend not to get AMS

# Sleep Disturbances

- Poor sleep common
- Disrupted sleep
  - Cheyne-Stokes breathing
- More common with high HVR
- TX: acetazolamide or zolpidem



100.0 %$O_2$
75.0 %$O_2$
1 min

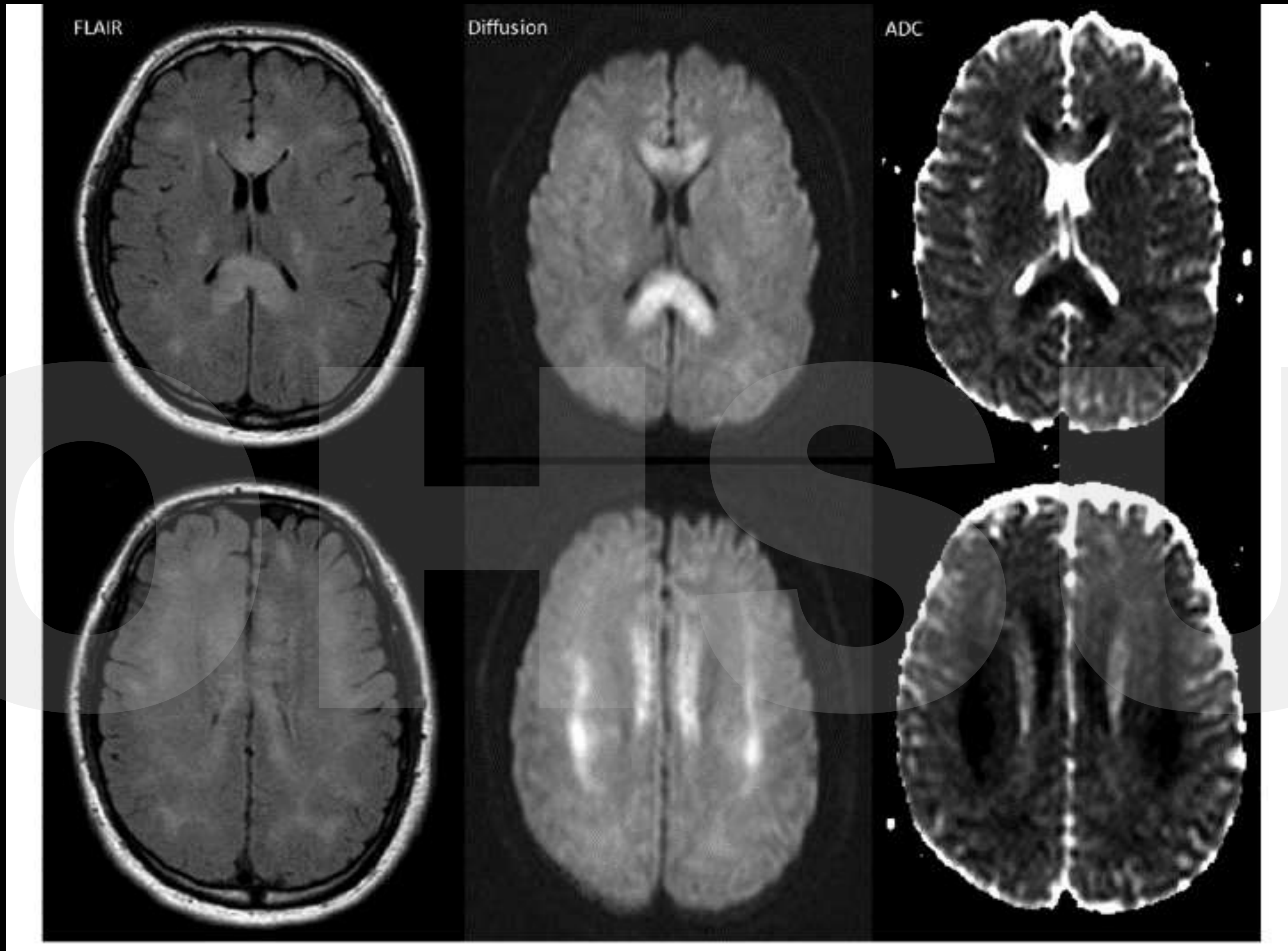
Photo: Deb Robertson

# High Altitude Cerebral Edema

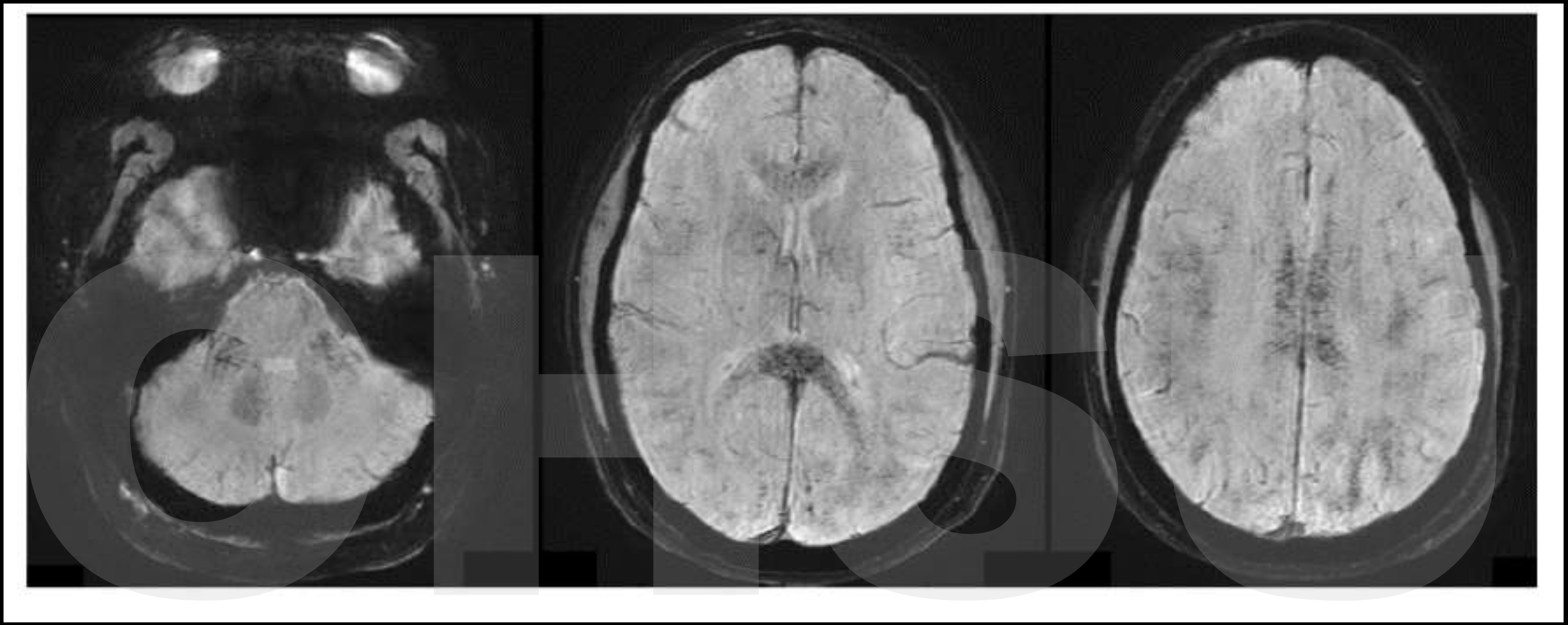
- AMS with
  - Ataxia
  - Altered mental status
  - Seizures
  - Photophobia
- Rate: 1-3%
- Rapidly evolves to coma and death
  - Once coma ensures 60% fatality rate

# HACE:

- Vasogenic cerebral edema
  - microbleeds
- Late stages: thrombosis



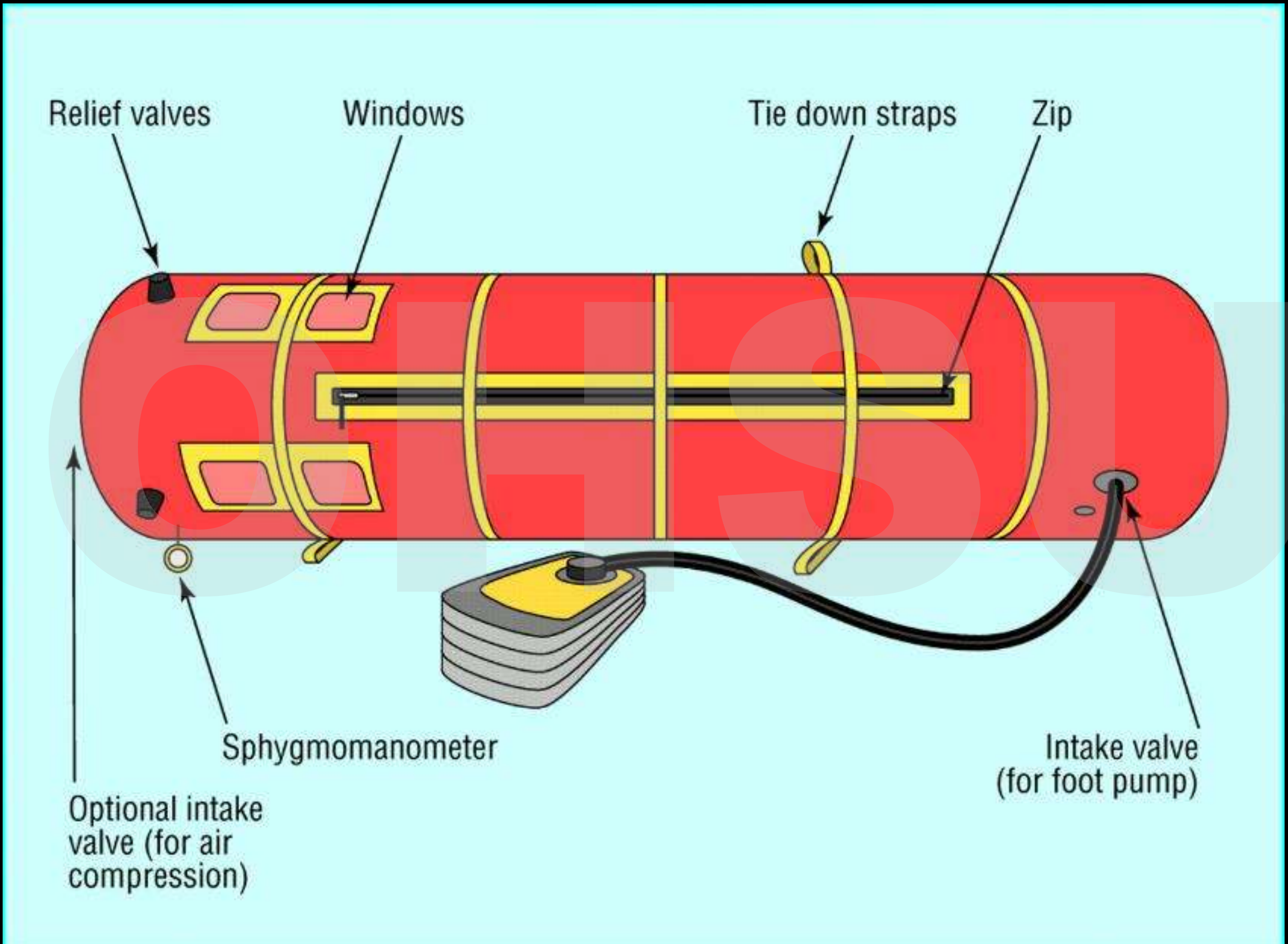

AJNR Am J Neuroradiol 40:464–69 Mar 2019



AJNR Am J Neuroradiol 40:464–69 Mar 2019

# HACE: Therapy

- Descent!!!
- Dexamethasone
- Portable hyperbaric chamber
- Prevention:
  - Same as AMS
  - Early recognition


Relief valves
Windows
Tie down straps
Zip
Sphygmomanometer
Intake valve
(for foot pump)
Optional intake
valve (for air
compression)

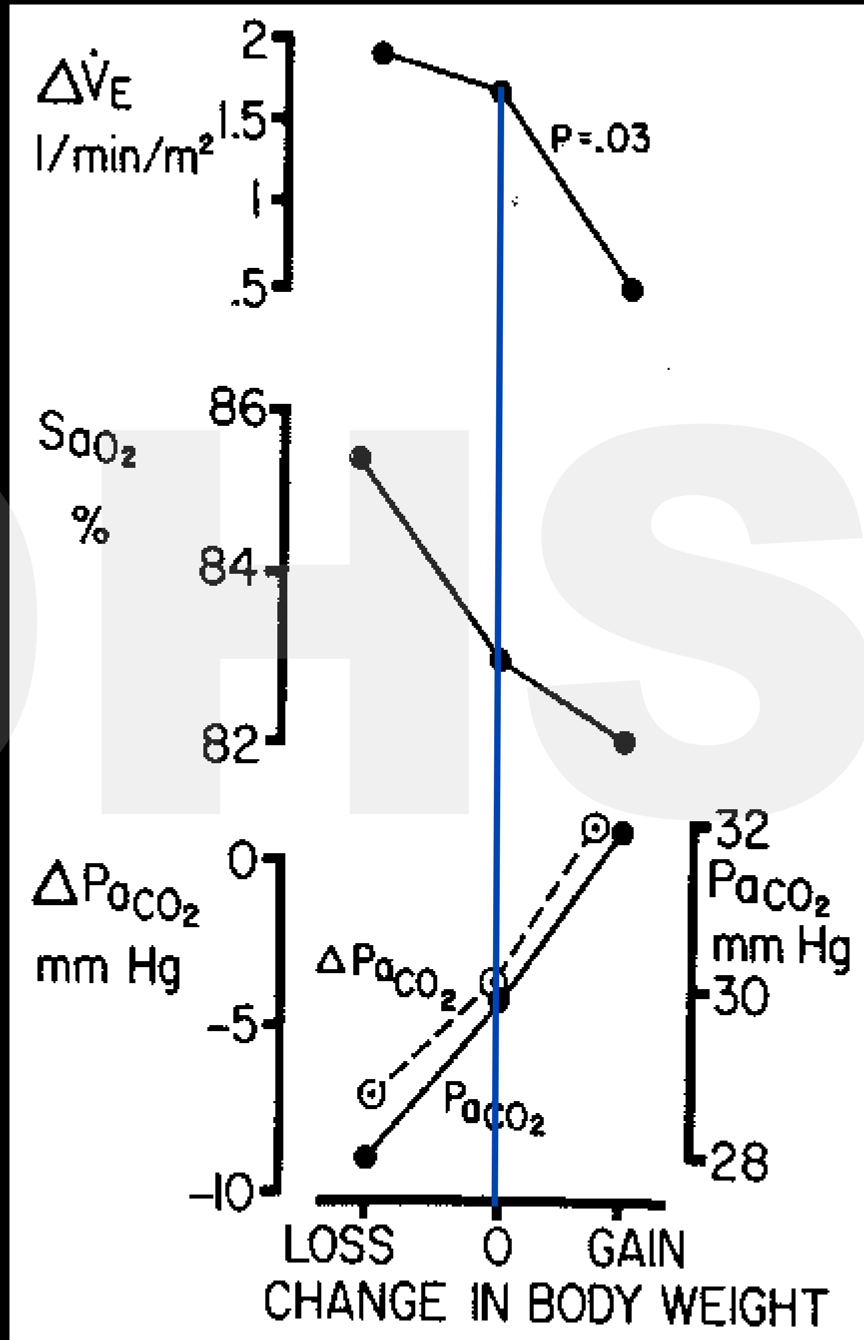

A
B
C

# AMS: Pathogenesis

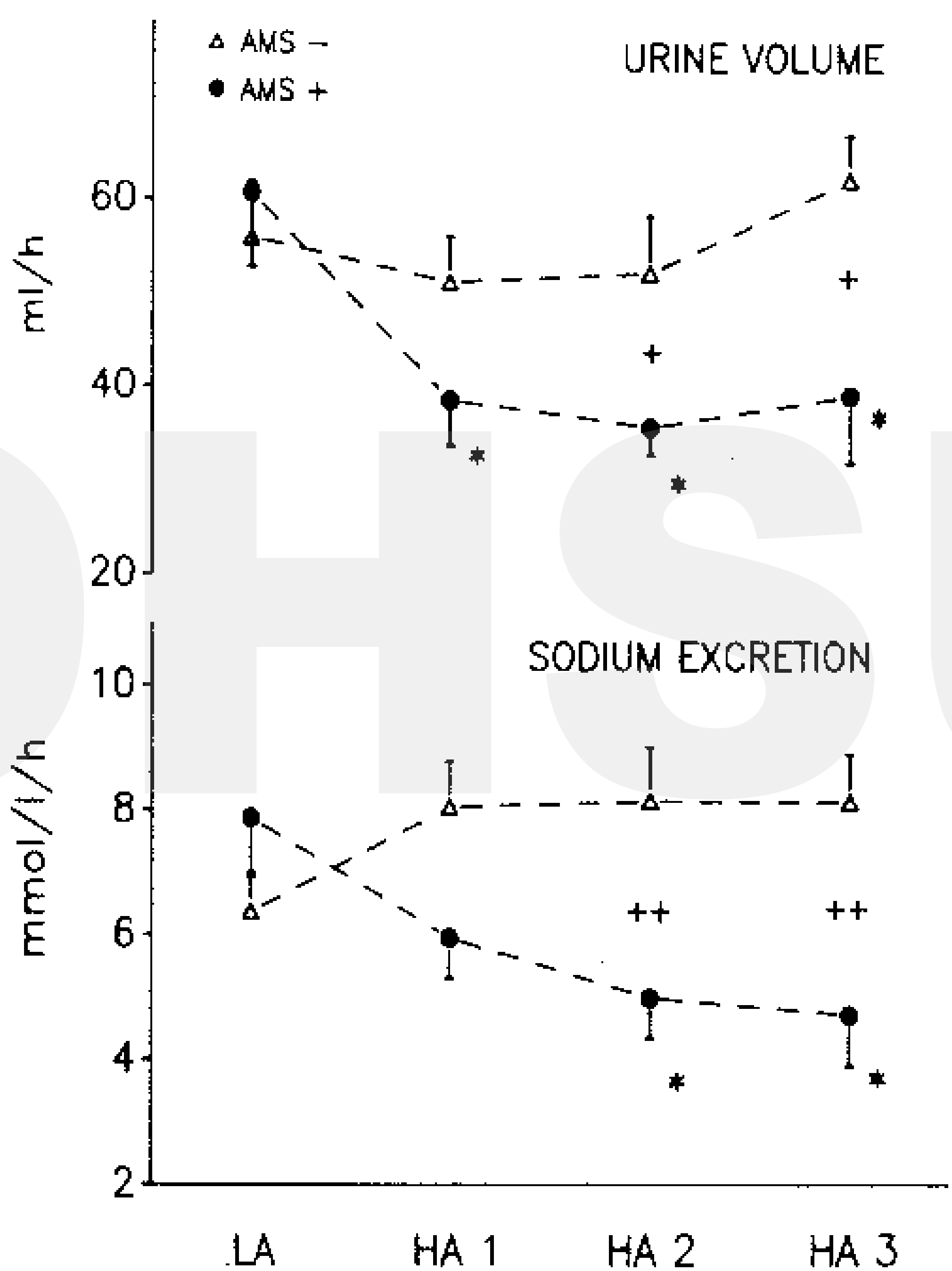
- Hypoxia
  - Poor HVR
- Fluid retention
- Unpredictable
- Individual susceptibility

# Disorder of Fluid Regulation?

- Increased ADH, aldosterone, decrease urine output
- Increase atrial natruretic factor
  - Increase tissue permeability
- General permeability defect?



ΔV̇E
l/min/m²
2
1.5
1
.5
P=.03
SaO₂
%
86
84
82
ΔPaCO₂
mm Hg
0
-5
-10
ΔPaCO₂
PaCO₂
PaCO₂
mm Hg
32
30
28
LOSS
0
GAIN
CHANGE IN BODY WEIGHT



AMS –
AMS +
URINE VOLUME
ml/h
60
40
20
SODIUM EXCRETION
mmol/l/h
10
8
6
4
2
LA
HA 1
HA 2
HA 3

# “Tight Fit” Theory

- Hypoxia and fluid retention led to brain edema
- People with lack of “space” would suffer increase ICP and symptoms
- Evidence:
  - Vasogenic edema common in AMS/HACE
  - Preliminary evidence that brain volume to intracranial volume higher in people susceptible to AMS
  - Things that reduced edema work in AMS
- However…

# “Tight Fit” Theory

- Brain swelling is minimal
  - No difference AMS vs no AMS
- No evidence of ICP
- Evidence of widespread tissue damage
  - High CK's
- Still no consensus on pathogenesis

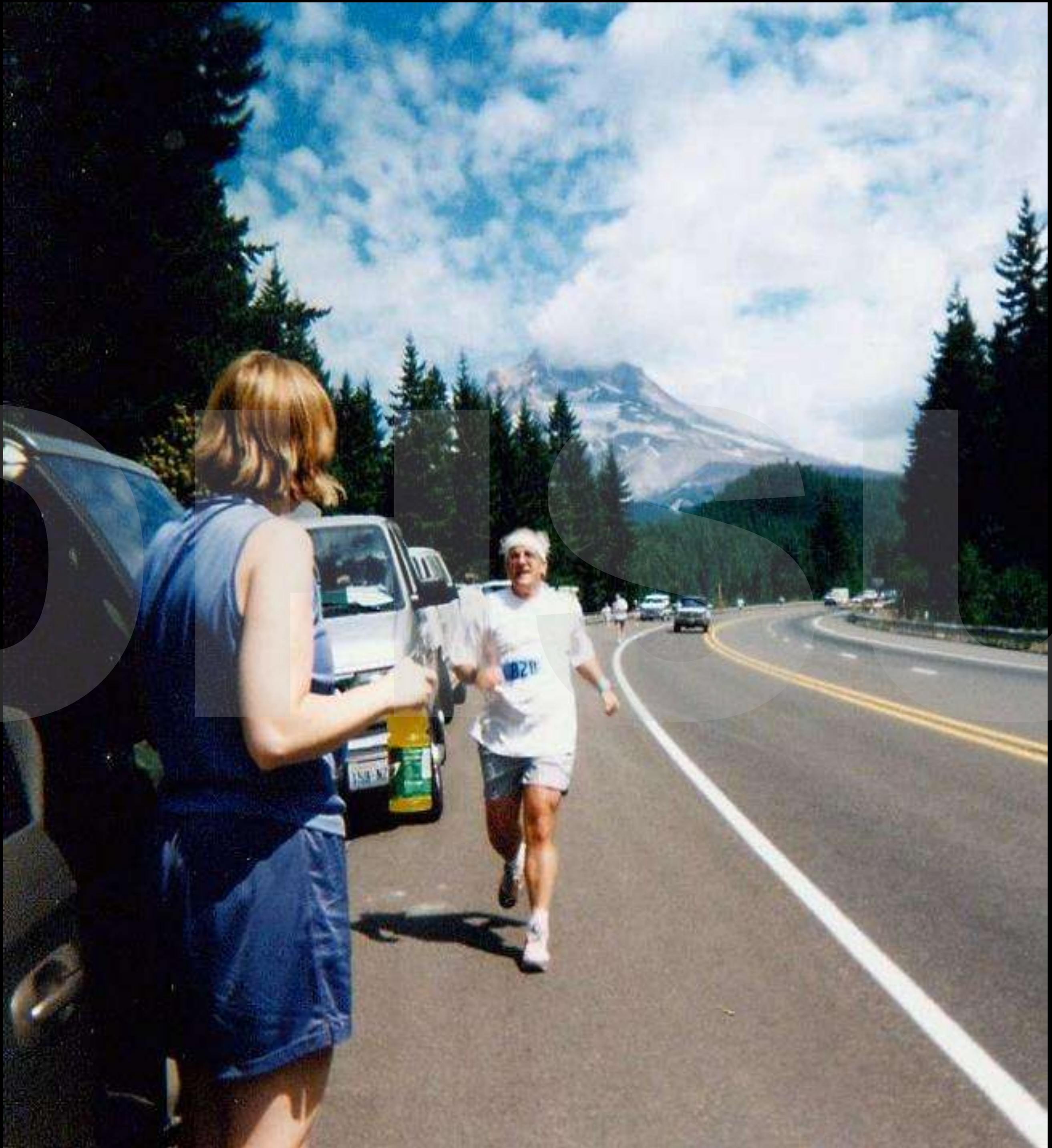
Photo: Lindsey Fell

# High Altitude Pulmonary Edema

- High altitude illness that leads to most deaths
- Occurs in 2-3 days
- Tachycardia/tachypnea
- Orthopnea
- Pink froth
- Severe hypoxia

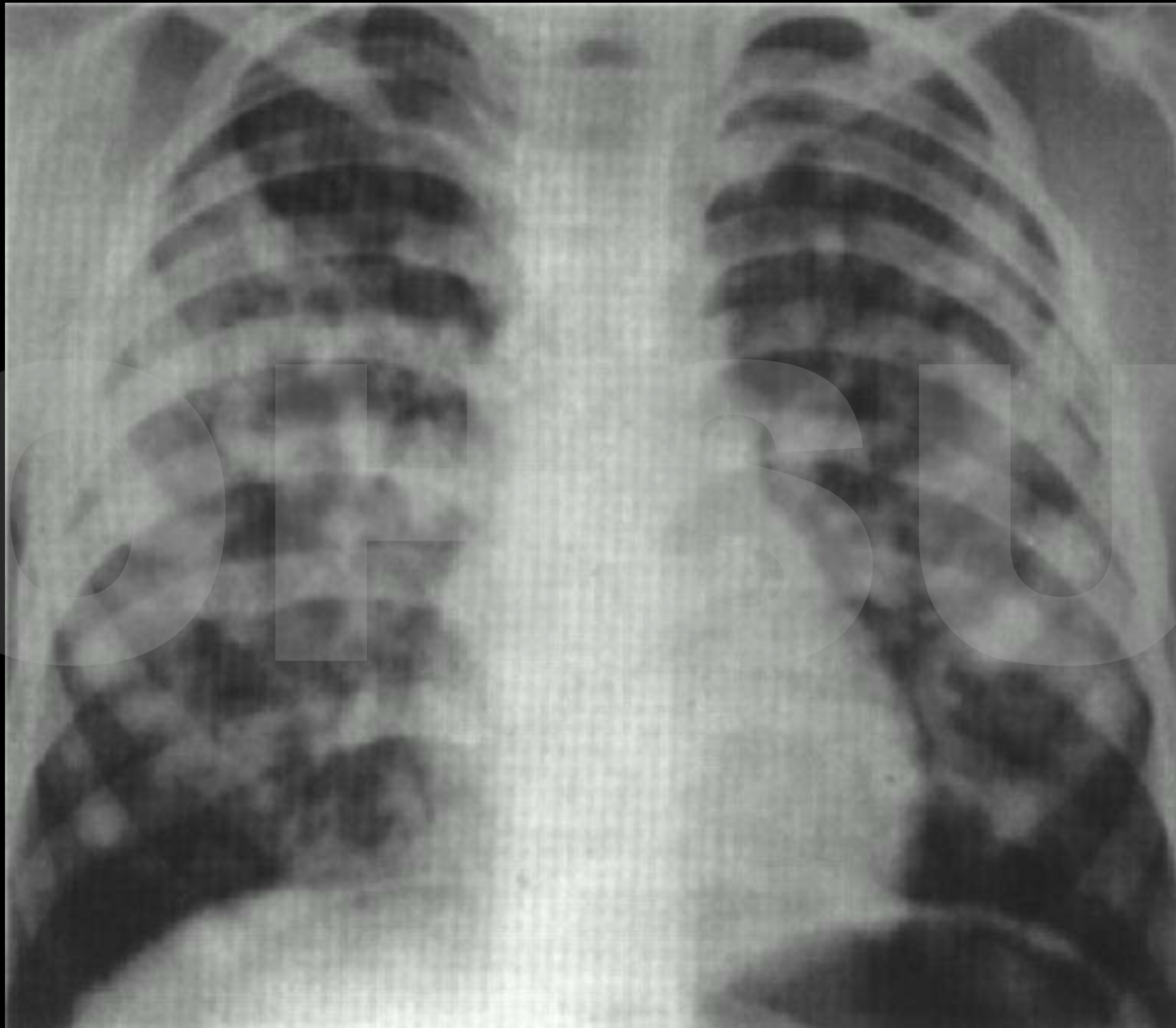
# HAPE: Incidence and Risk Groups

- Severe cases: 1-8%
- Increase lung water seen in up to 75% of climbers
- Risk groups
  - Young men
  - Cold
  - Exercise
- Increasing reports of cases at modest altitudes (1400-2400m)




LOW ALTITUDE
L
A


HIGH ALTITUDE
L
B



# HAPE: Treatment

- Descent
- Oxygen
- Gamow bag
- Nifedipine 10 mg then 30mg SR
- Nitric oxide?
- Phosphodiesterase-5 inhibitors?
- Dexamethasone?

# HAPE: Prophylaxis

- Slow ascents
  - Nifedipine 20-30 mg SR q12
  - Inhaled beta-agonists?
  - Phosphodiesterase-5 inhibitors?
  - Dexamethasone?

# HAPE:
# Phosphodiesterase-5 inhibitors

- Effective for pulmonary HTN
- 4559m study:

| | C | NO | S | NO+S |
|---|---|---|---|---|
| sPaP | 44+10 | 32+6 | 33+6 | 28+5 |

- No change in systemic blood pressure
- Studies showed increase oxygenation
- Appears to be better than Nifedipine

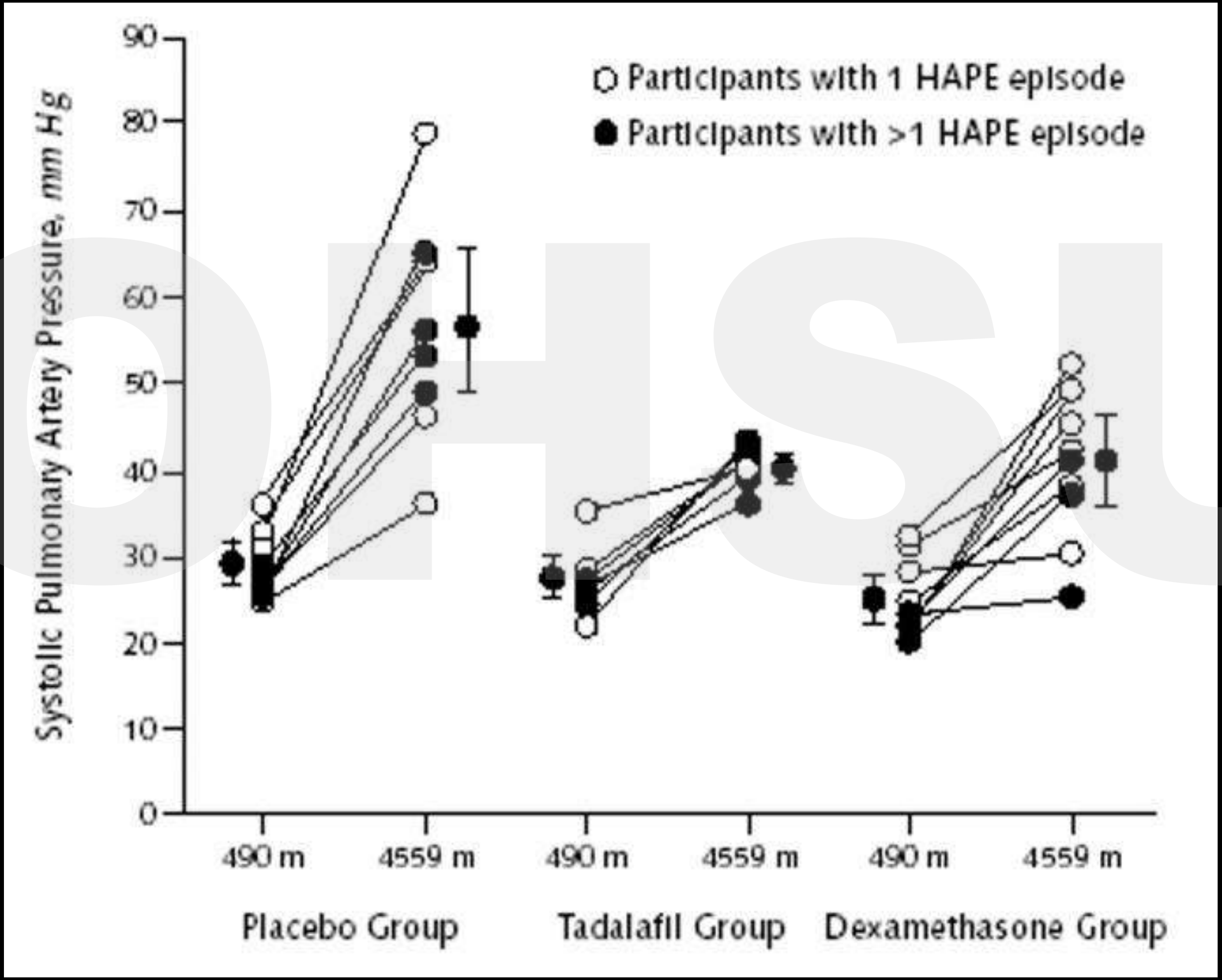
# HAPE: PDE-5 Inhibitor vs Dex

| | Placebo | Tadalafil | Dex |
|---|---|---|---|
| HAPE | 7/9 (78%) | 1/8 (13%) | 0/10 (0) |
| AMS | 8/9 (89%) | 8/10 (80%) | 3/10(30) |
| LLS | 7 | 6.5 | 2.5 |
| Headache | 2 | 2 | 0.5 |

# PDE-5 Inhibitors

- Fading because of cost and concerns about increased AMS incidence

# Dexamethasone

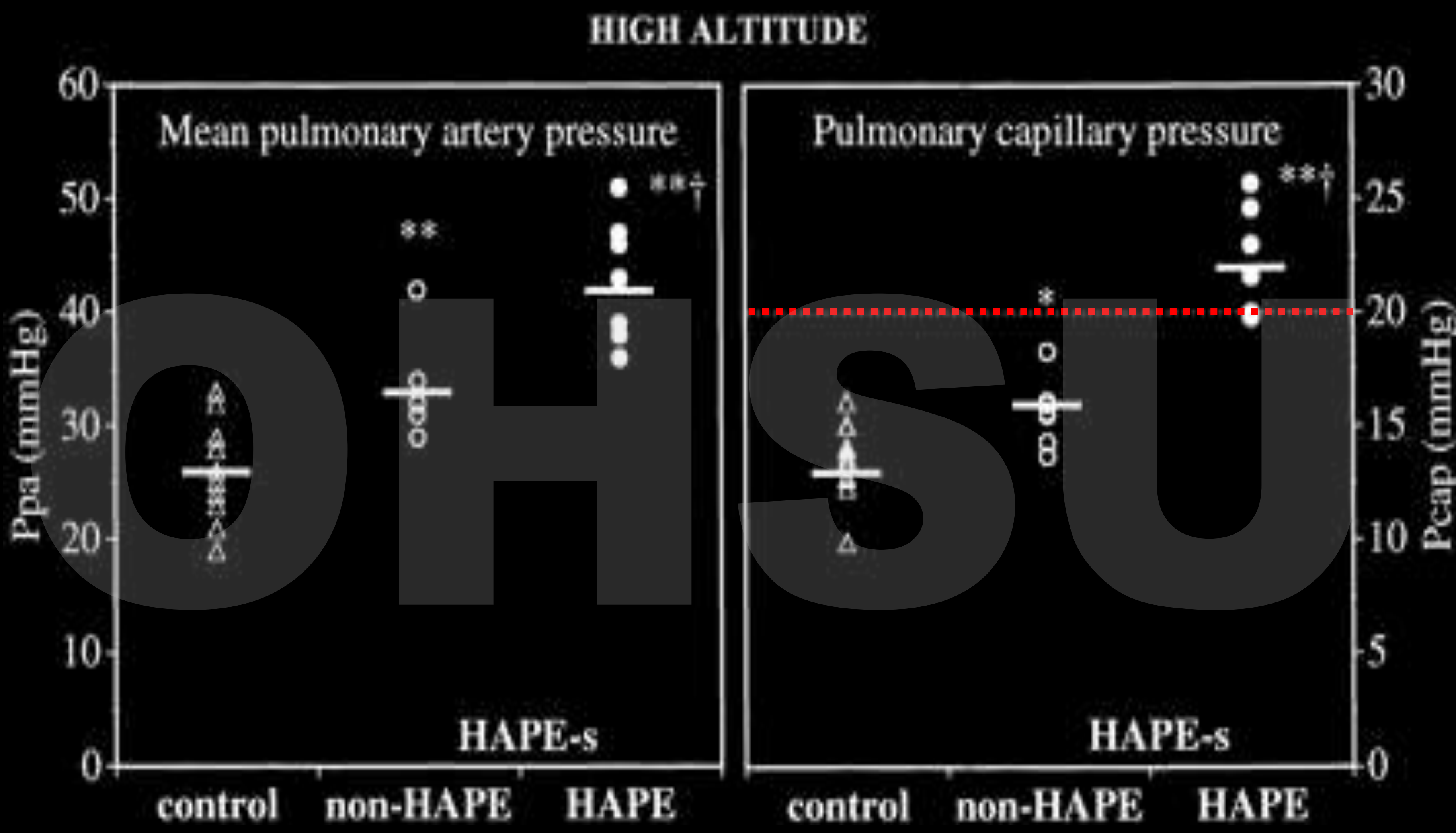


# Dexamethasone

- Lowers pulmonary artery pressures
- Effective for AMS
- Needs more study

# HAPE Pathogenesis

- Increased pulmonary artery pressures
  - Individual susceptibility
  - Hypoxia
- Hydrostatic fluid leak due to stress failure of capillaries
- Then development of inflammation and thrombosis in later stages



HIGH ALTITUDE
Mean pulmonary artery pressure
Pulmonary capillary pressure
Ppa (mmHg)
Pcap (mmHg)
60
50
40
30
20
10
0
30
25
20
15
10
5
0
**
**†
*
**†
HAPE-s
HAPE-s
control
non-HAPE
HAPE
control
non-HAPE
HAPE
OHSU

# High Altitude Retinopathy

- Retinal hemorrhages
- Rarely results in permanent damage
- Incidence
  - Denali: 36% at 14,200
  - Logan: 56% at 17,000
- Etiologies
  - Increased venous pressure
  - No protection from pressure surges

# Altitude and Refractive Eye Surgery

- Radial keratomy:
  - Changes occurs within hours of altitude
  - Usually returns to normal upon descending
- LASIK
  - Seems to be better for extreme altitude
  - No consistent changes with altitude

# Summary

- Adaptation to Altitude
  - Increase ventilation
  - Increase hematocrit
  - Changes in $O_2$ affinity
- Acute mountain sickness (AMS)
- High altitude pulmonary edema (HAPE)
- High altitude cerebral edema (HACE)
- High altitude retinal disease

# Summary

- Adaptation to Altitude
  - Increase ventilation
  - Increase hematocrit
  - Changes in $O_2$ affinity
- Acute mountain sickness (AMS)
- High altitude pulmonary edema (HAPE)
- High altitude cerebral edema (HACE)

Photo: Lindsey Fell