High Altitude

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GENERAL HEMATOLOGY

DISCLOSURE

Relevant Financial Relationship(s)

Speaker Bureau - None

Consultant/Research – none

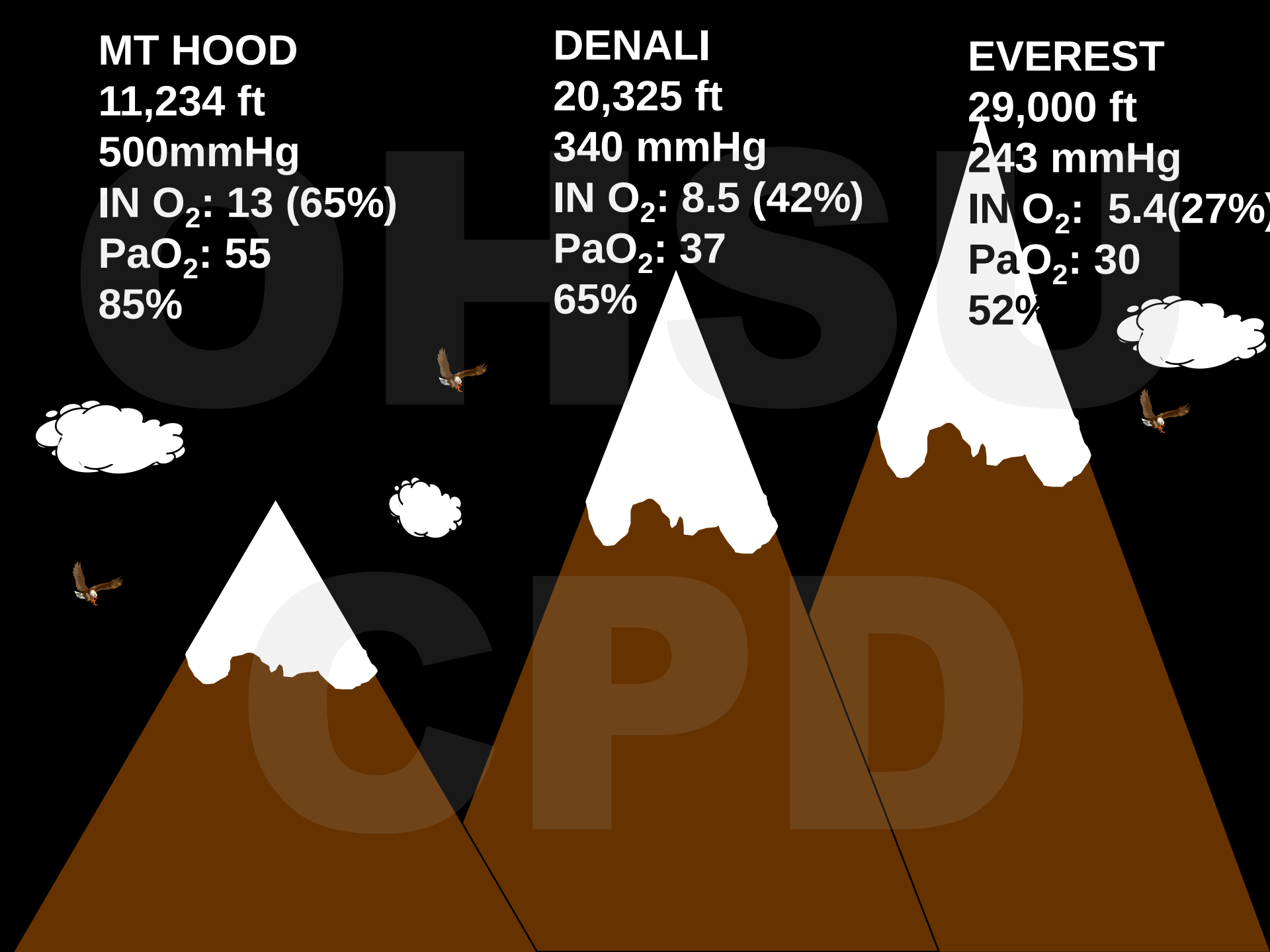
Author – UpToDate (Iron)

Overview

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

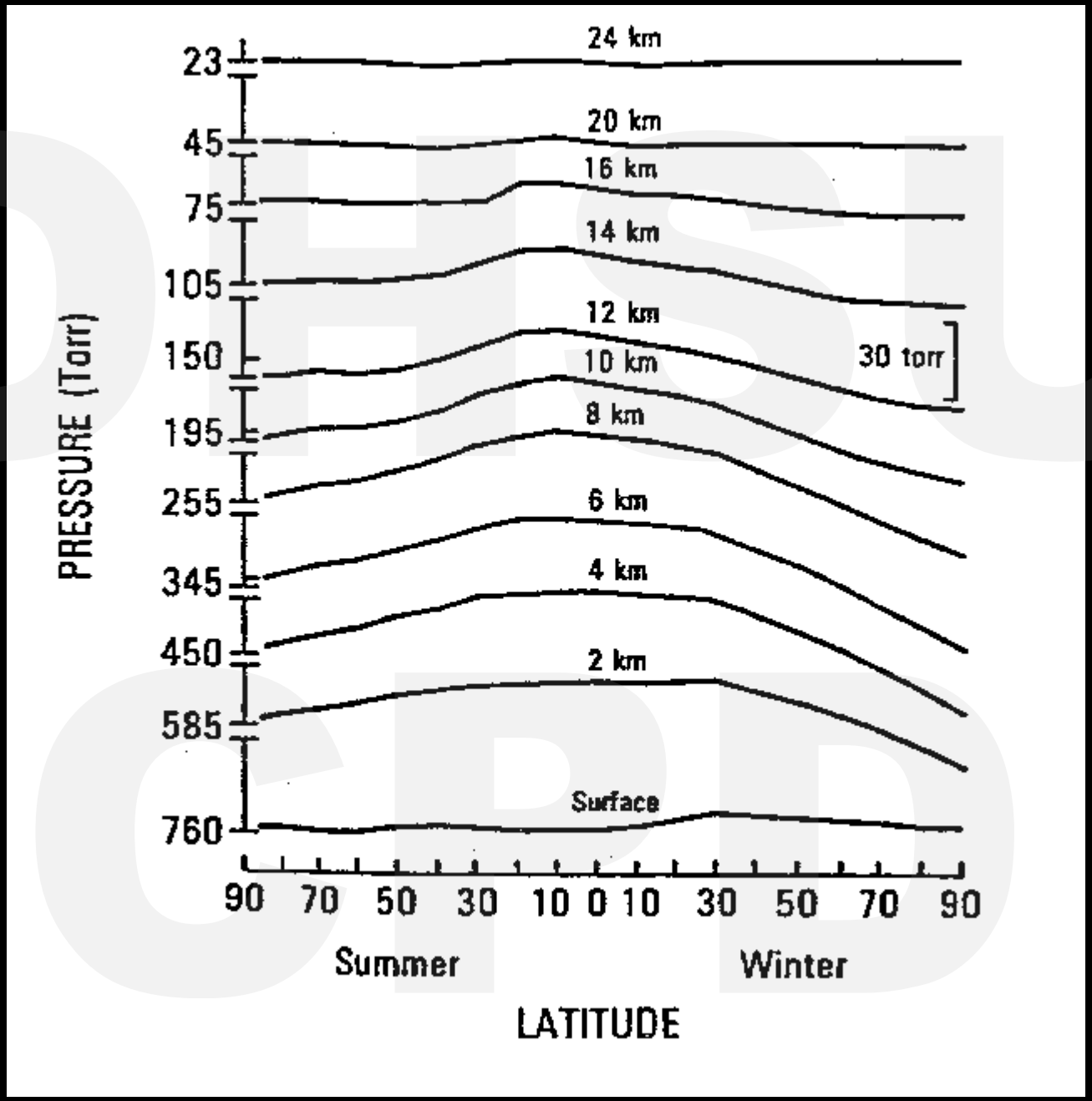
High Altitude Medicine

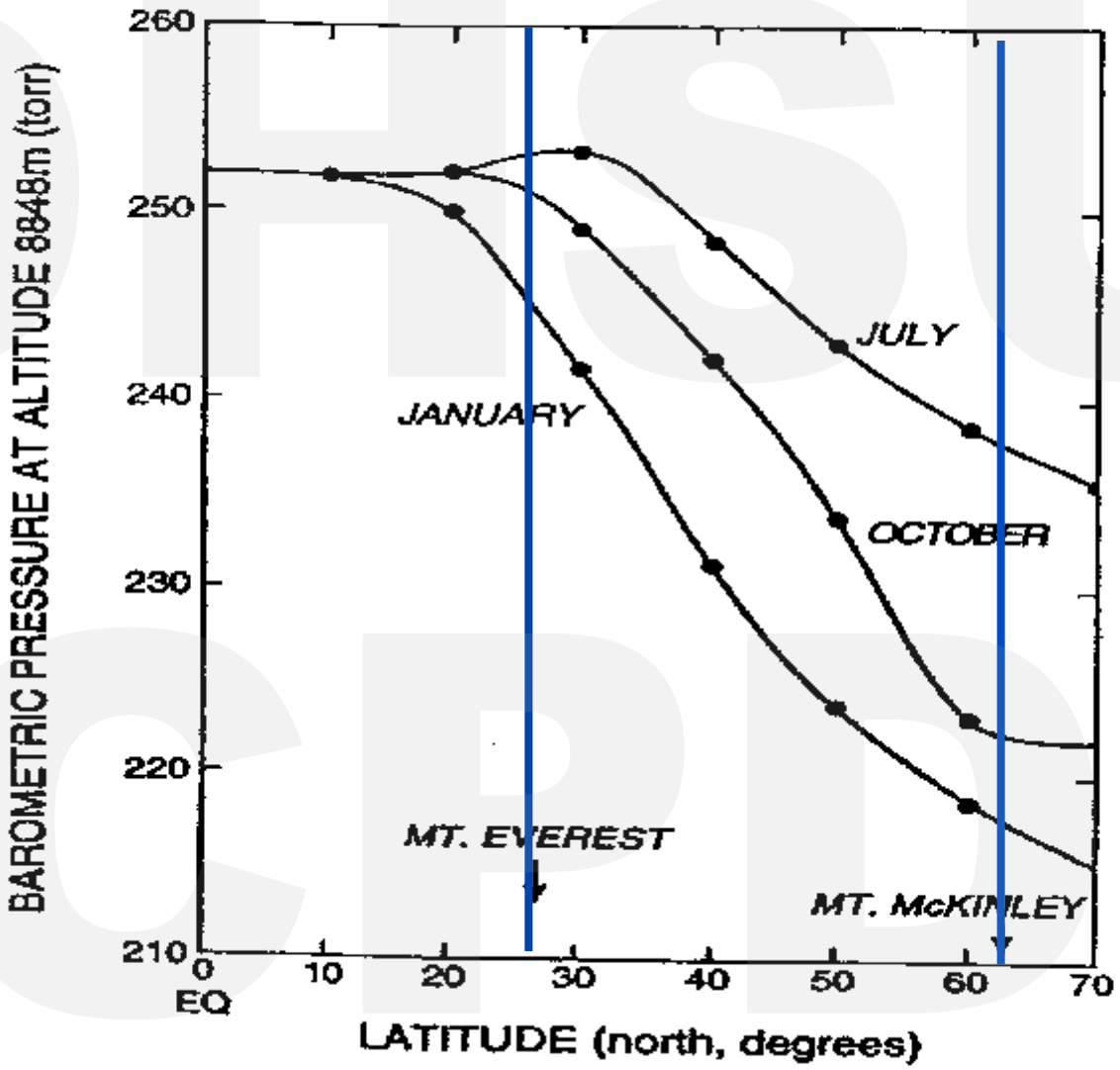
- ~ 80,000,000 people live above 8000 ft
  - 25,000,000 over 10,000 ft
- Unique physiologic changes

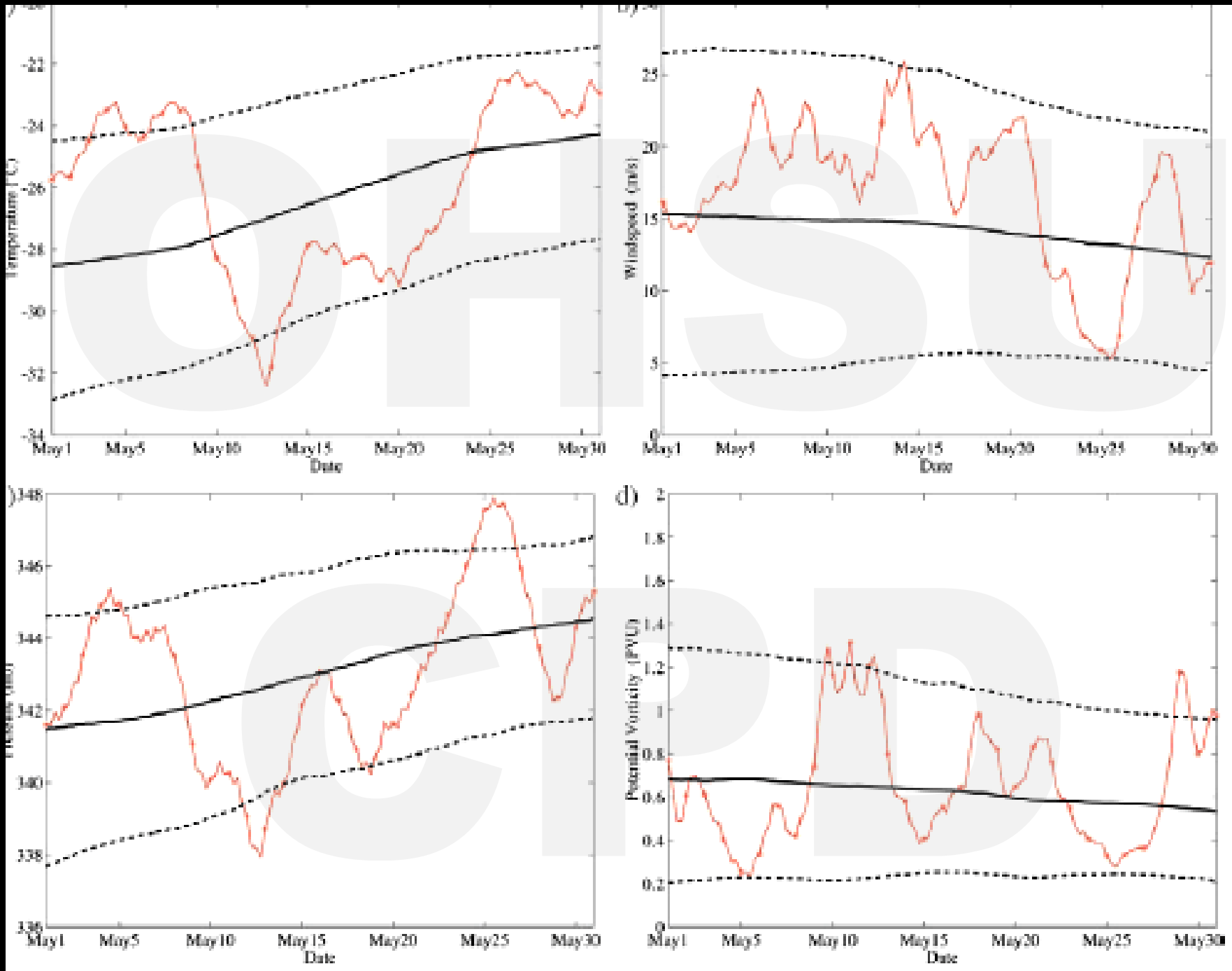

MT HOOD
11,234 ft
500mmHg
IN O_2: 13 (65%)
PaO_2: 55
85%
DENALI
20,325 ft
340 mmHg
IN O_2: 8.5 (42%)
PaO_2: 37
65%
EVEREST
29,000 ft
243 mmHg
IN O_2: 5.4(27%)
PaO_2: 30
52%

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
23
45
75
105
150
195
255
345
450
585
760
PRESSURE (Torr)
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


-22
-24
-26
-28
-30
-32
-34
May1
May5
May10
May15
May20
May25
May30
Date
b)
25
20
15
10
5
0
Windspeed (m/s)
348
346
344
342
340
338
336
d)
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Potential Vorticity (PVU)


CHINA
AIRLINES CARGO

Altitude (Feet)	Time of Useful Consciousness (Minutes)[1,2]	$P_{A_{O_2}}$ (mm Hg)
18,000	20-30	37.8
22,000	10	32.8
25,000	3-5	30.4
28,000	2.5-3	N/A
30,000	1-2	N/A

mm Hg = Millimeters of Mercury

[1] Physical exertion and other factors will reduce this time.

[2] Data taken from the United States Air Force Flight Surgeon's Guide [23]

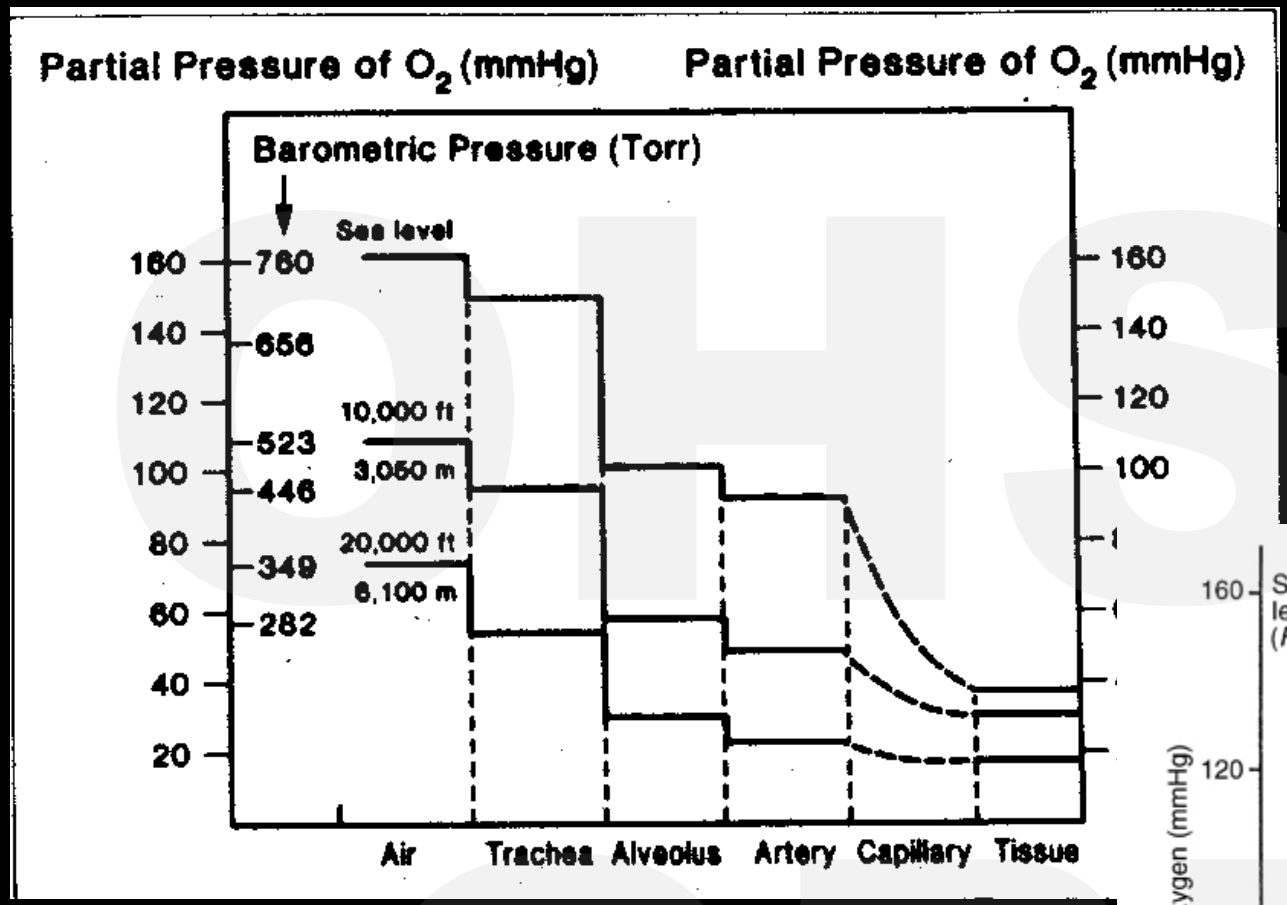
Photo: Lindsey Fell

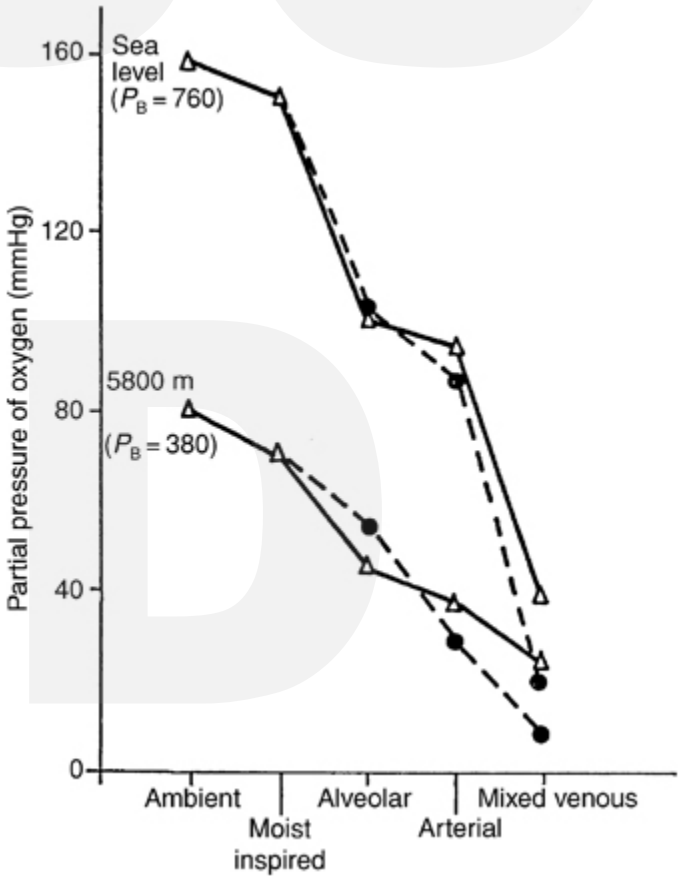
How do we Adapt to Hypoxia???

- Increase oxygen delivery to tissues

Chain of Oxygen

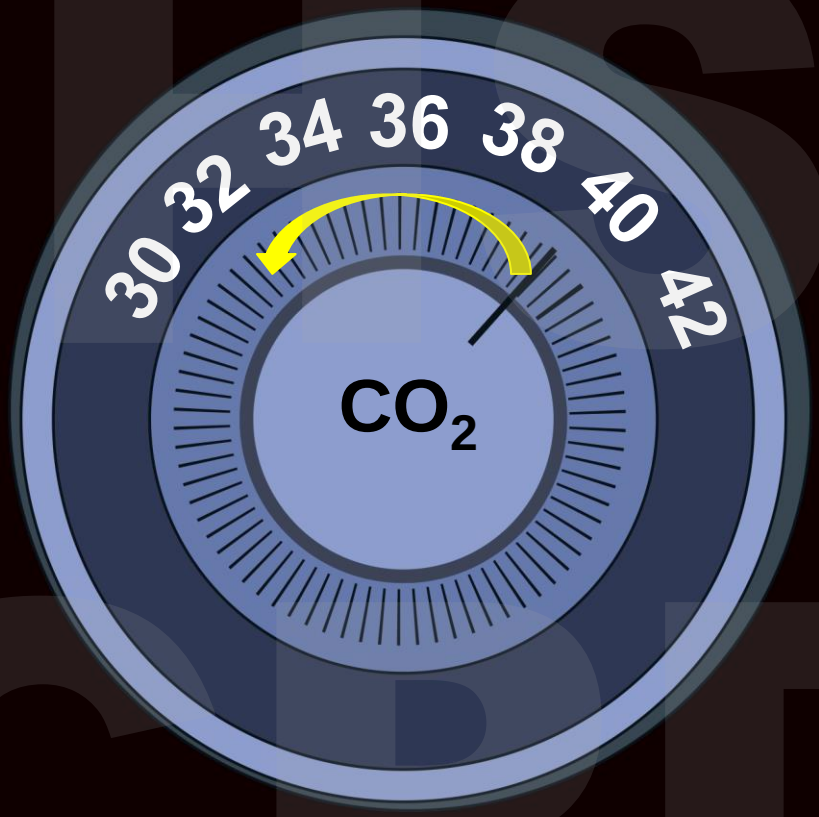
- Lungs
- Blood
- Tissue

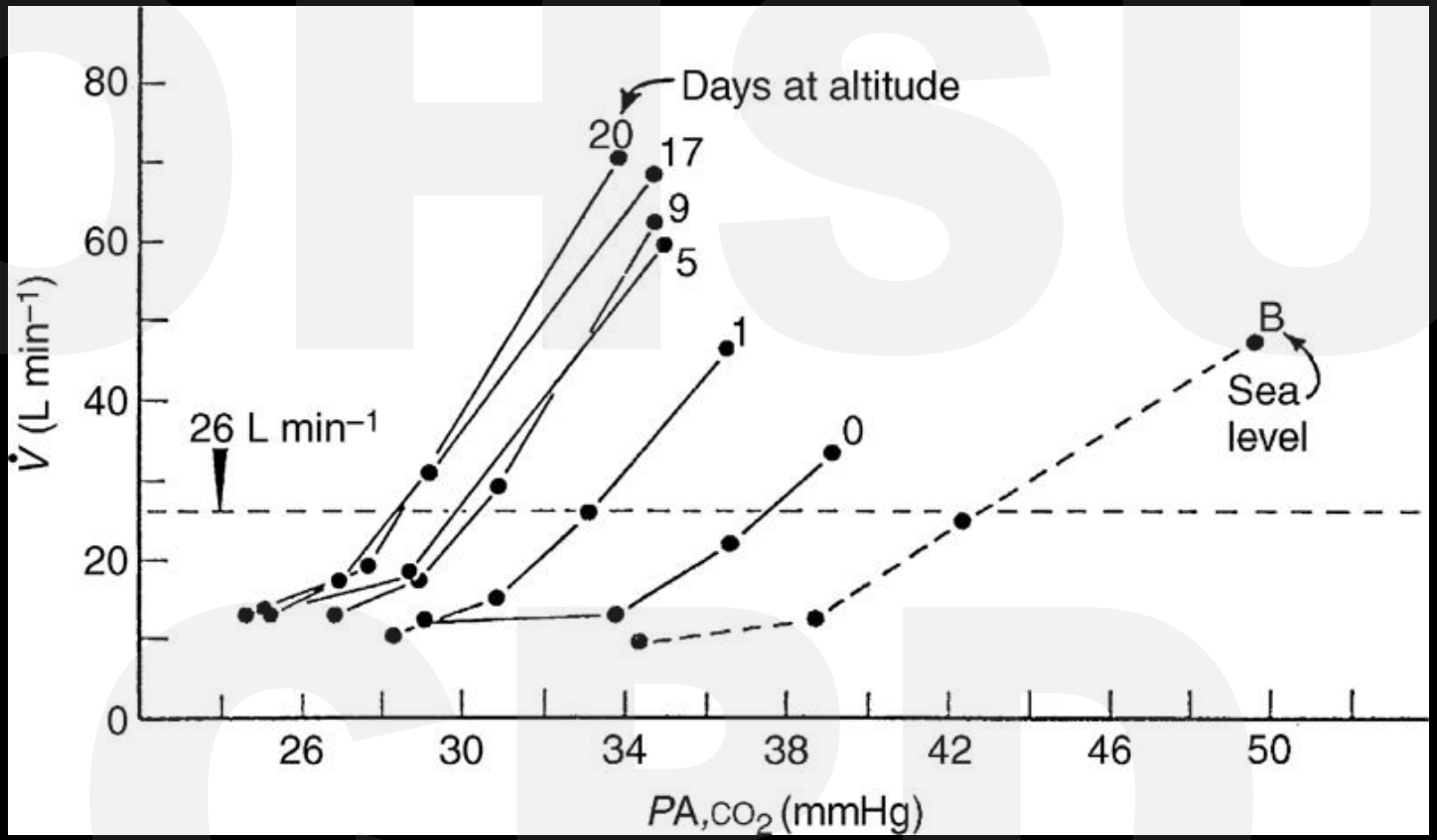

Partial Pressure of O_2 (mmHg)
Partial Pressure of O_2 (mmHg)
Barometric Pressure (Torr)
Sea level
760
656
10,000 ft
3,050 m
523
446
20,000 ft
6,100 m
349
282
160
140
120
100
80
60
40
20
Air
Trachea
Alveolus
Artery
Capillary
Tissue


Partial pressure of oxygen (mmHg)
160
120
80
40
0
Sea level (P_B = 760)
5800 m (P_B = 380)
Ambient
Moist inspired
Alveolar
Arterial
Mixed venous

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

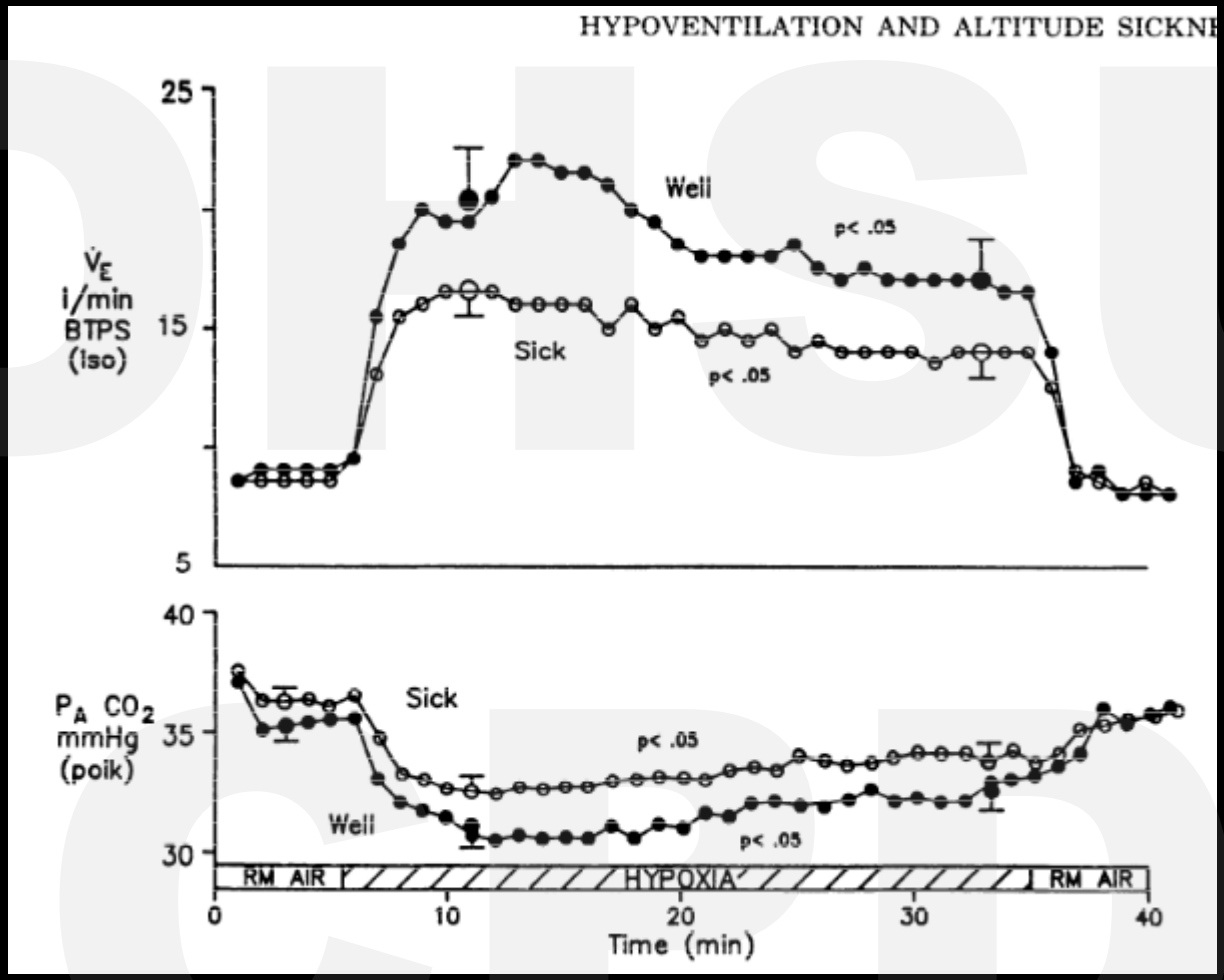

30 32 34 36 38 40 42
CO_2



Semin Respir Crit Care Med. 2023 Oct;44(5):681-695.

Hypoxic Ventilatory Response

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



Journal of Applied Physiology 60:1107-1458, 1986

Exception!

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

Cardiac

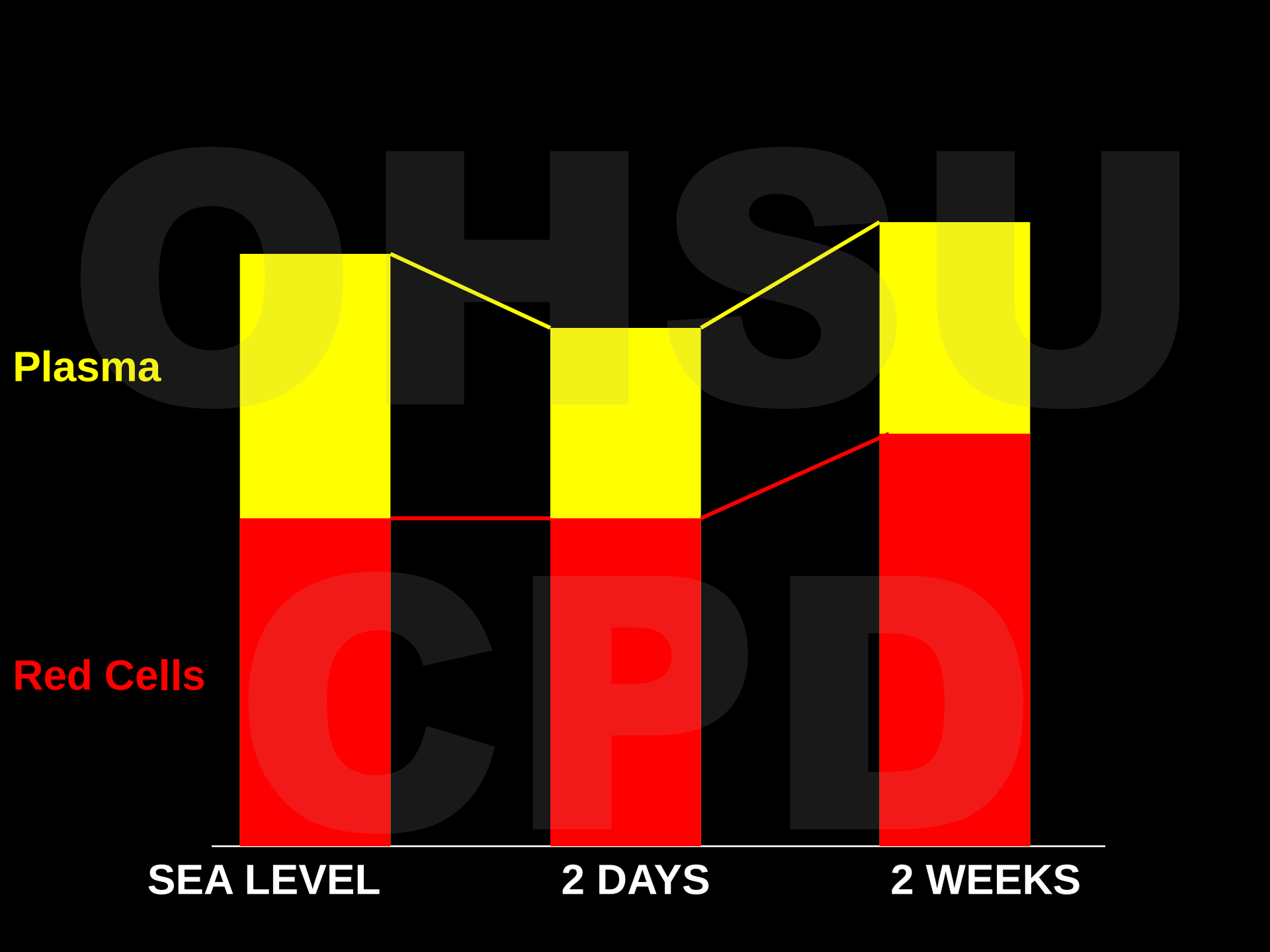
- Decreased cardiac output
  - Decreased stroke volume
    - Decreased plasma volume
    - Decreased heart rate
  - Protects against diffusion limitations?
- No ischemia
- Cardiac output **not** a limiting factor at altitude

Blood

- Changes in hematocrit
- Changes in oxygen disassociation curve

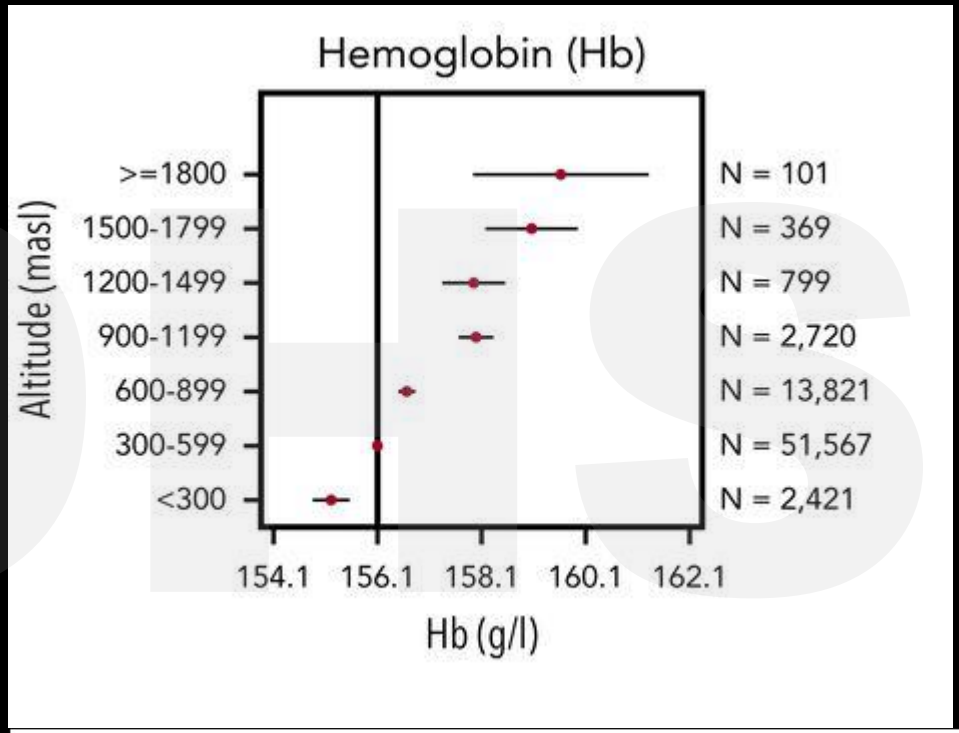
Hematocrit

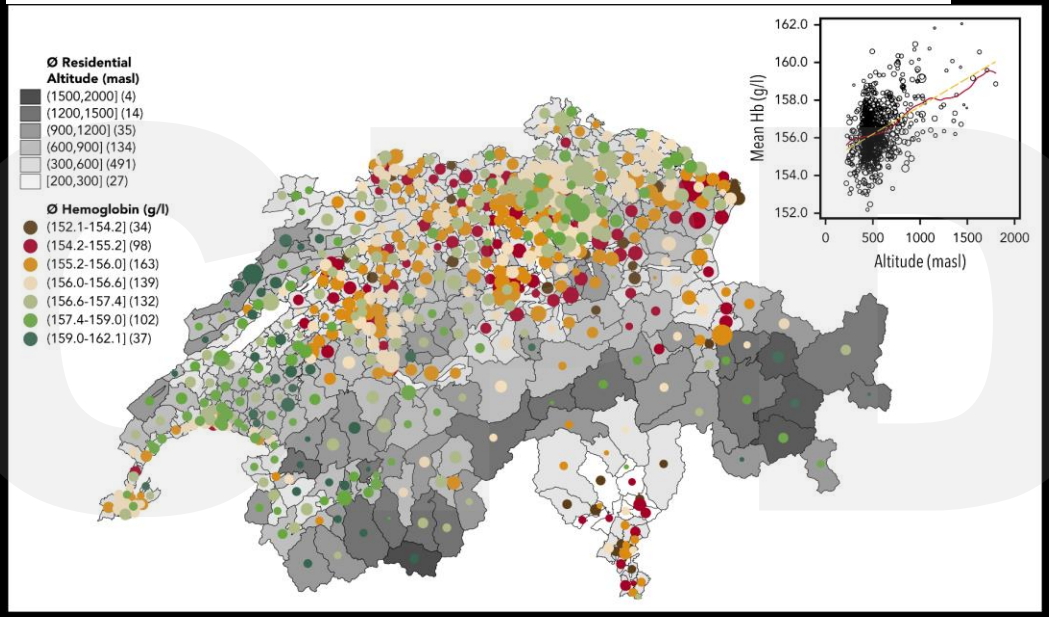
- Rises with exposure to high altitude
- 2 - phases
  - Decreased intravascular volume (hours)
    - Drop in plasma volume of 25% in days
  - Increase red cell mass (days)
- Benefits of increased O_2 delivery by more red cells balance by decreased delivery due to increase viscosity


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%

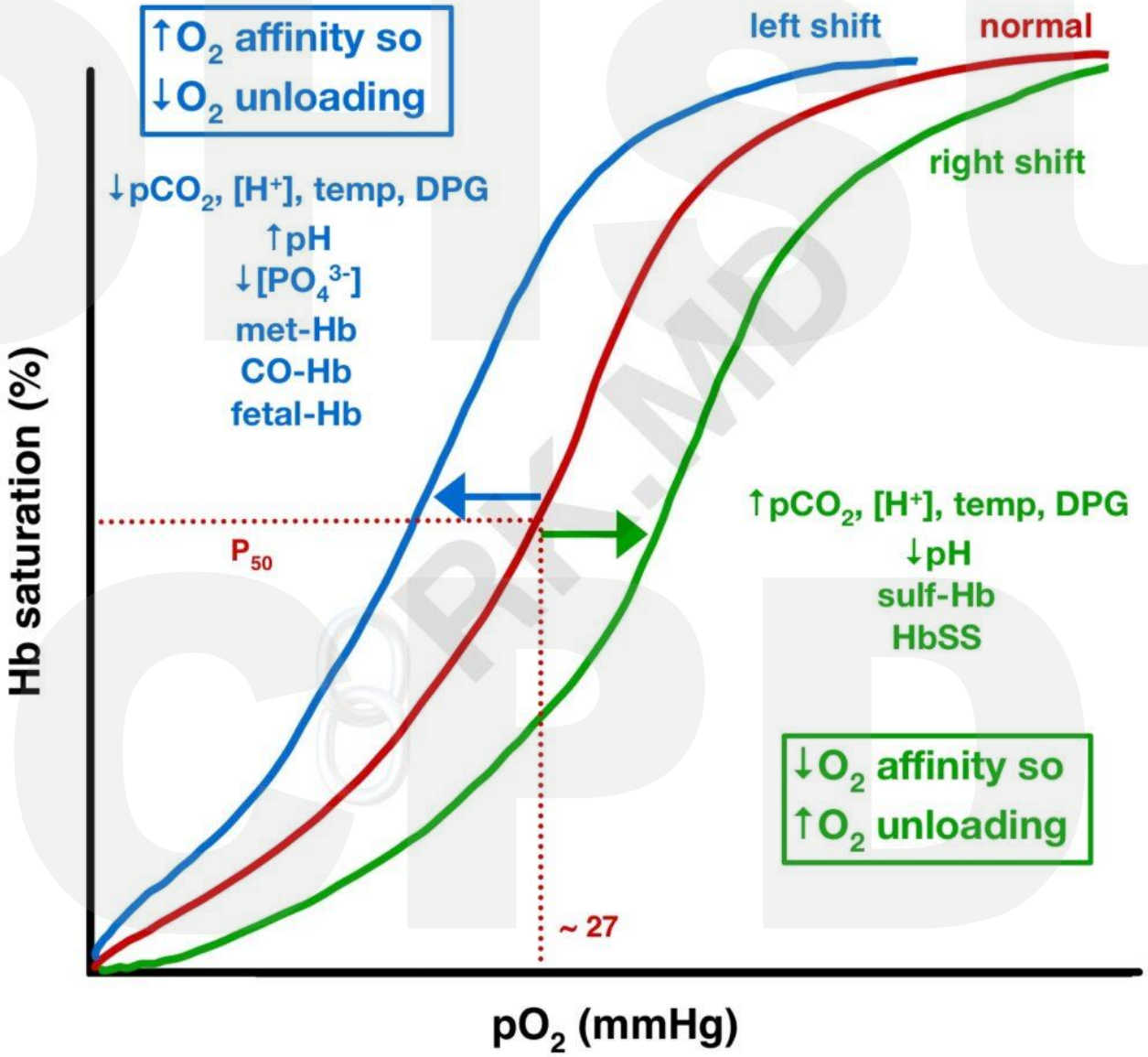


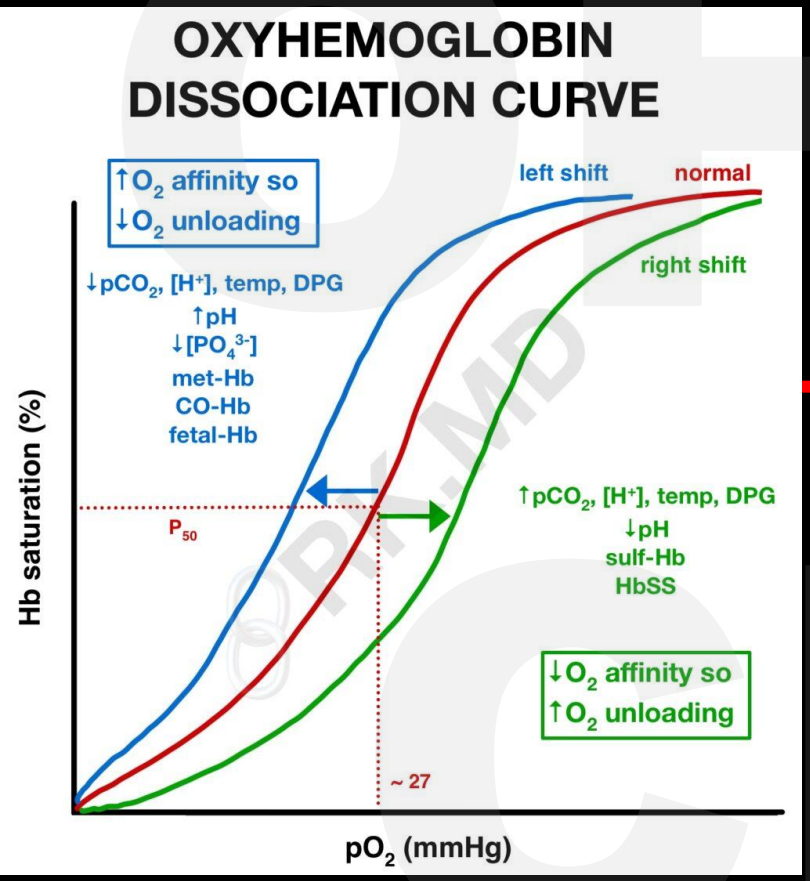


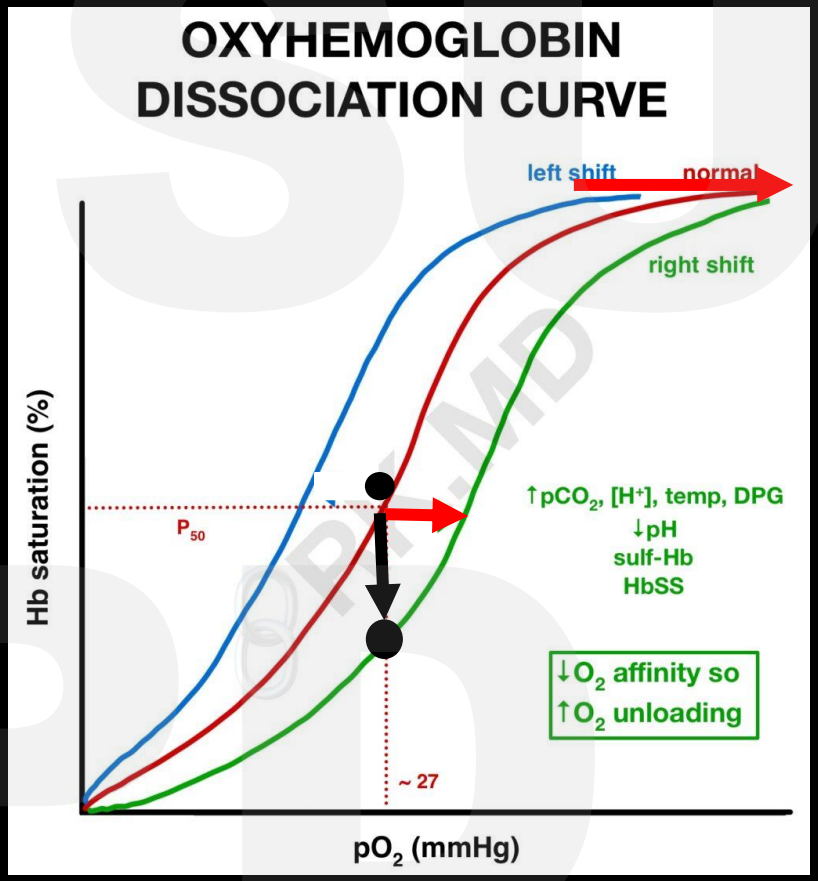
Blood 2020 Mar 26;135(13):1066-1069.

O_2 Disassociation Curve Changes

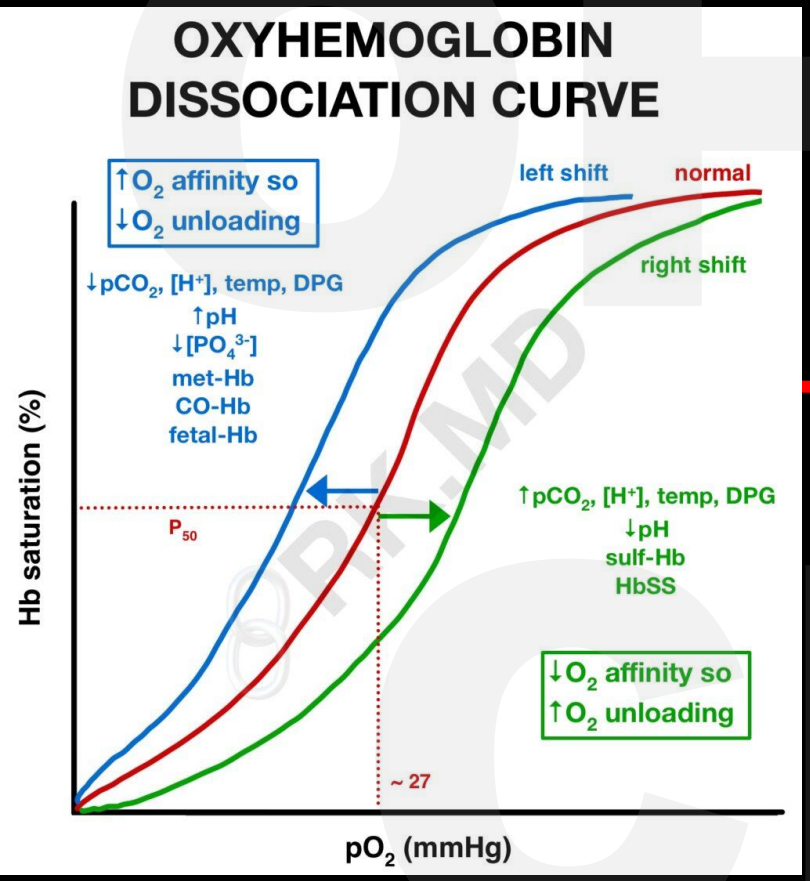
OXYHEMOGLOBIN DISSOCIATION CURVE

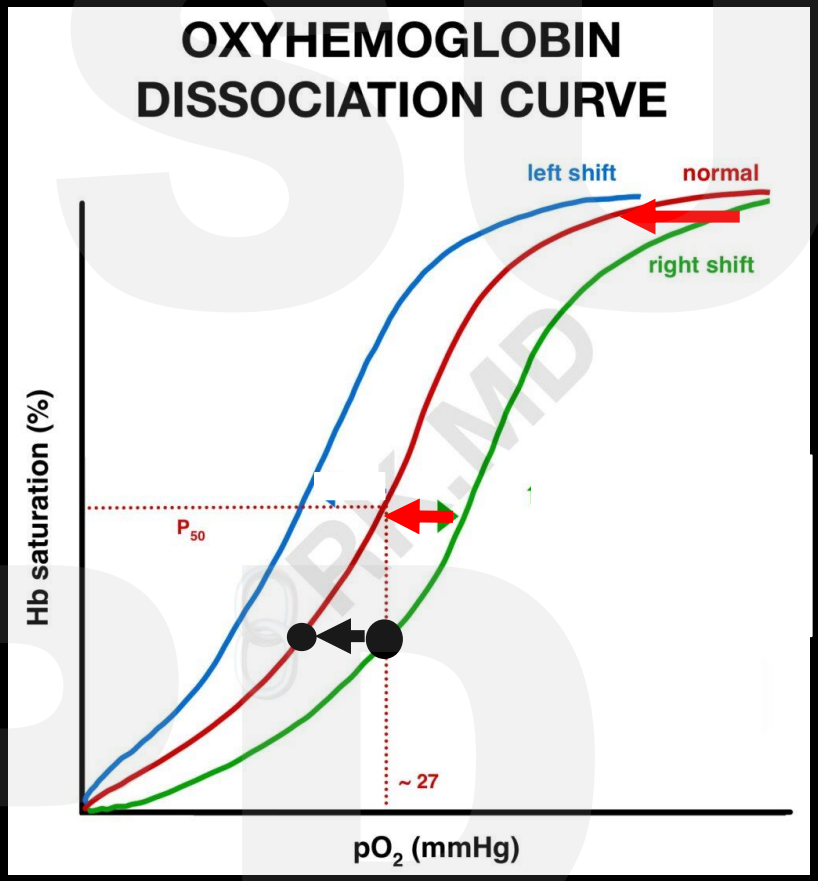






Decreased affinity for Oxygen





Baseline affinity for Oxygen

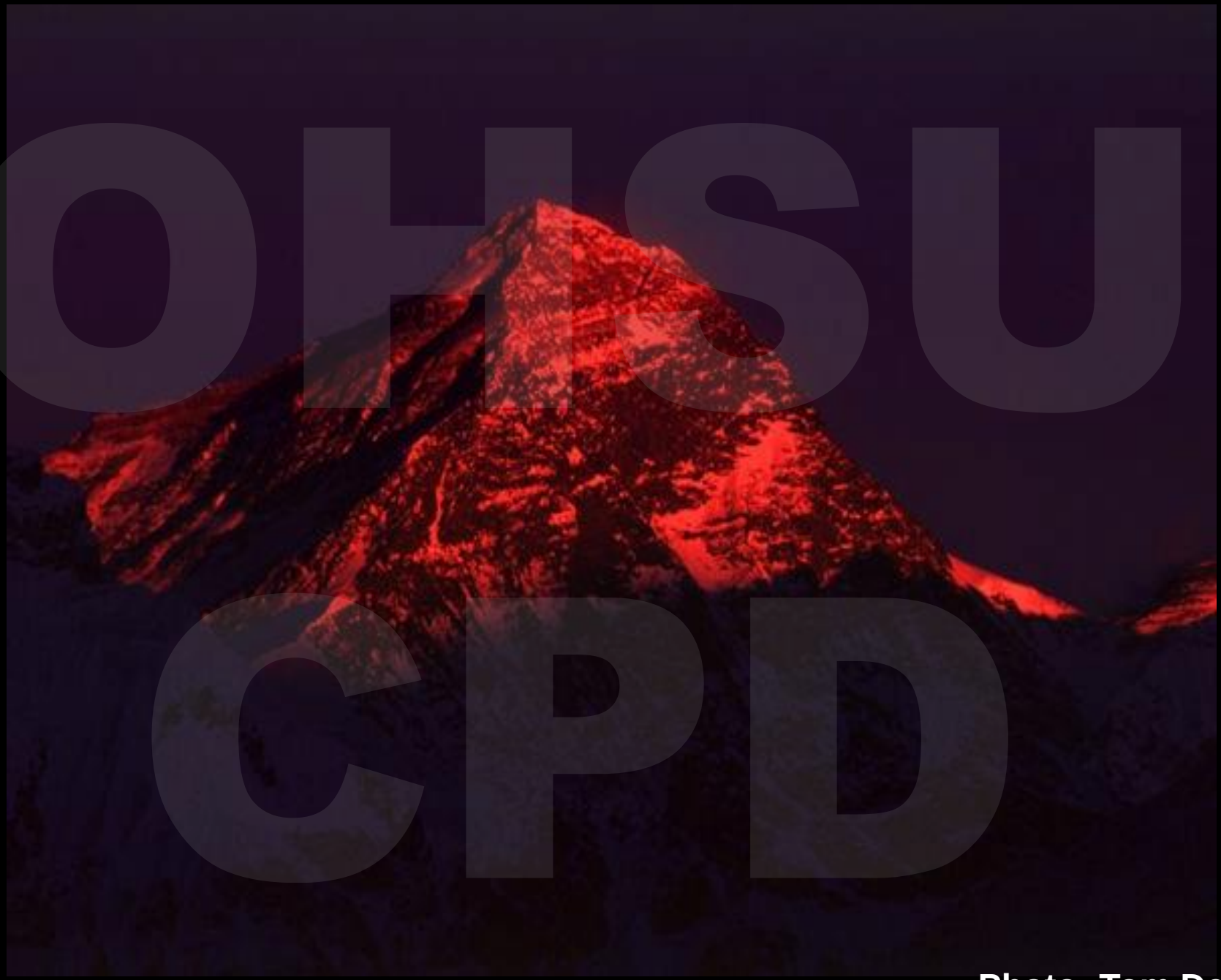
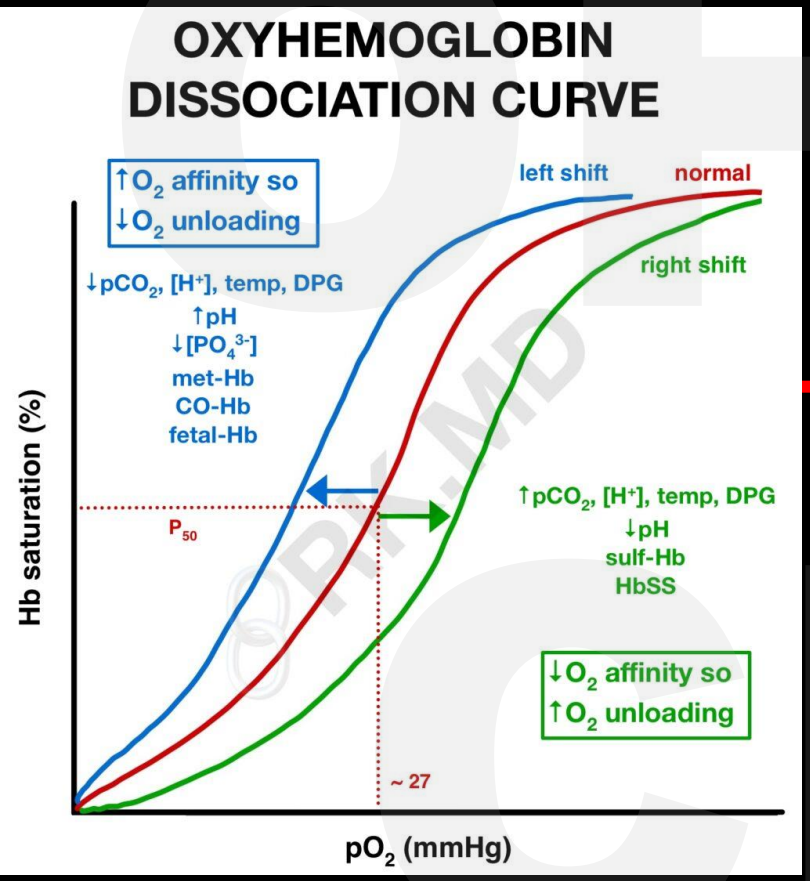
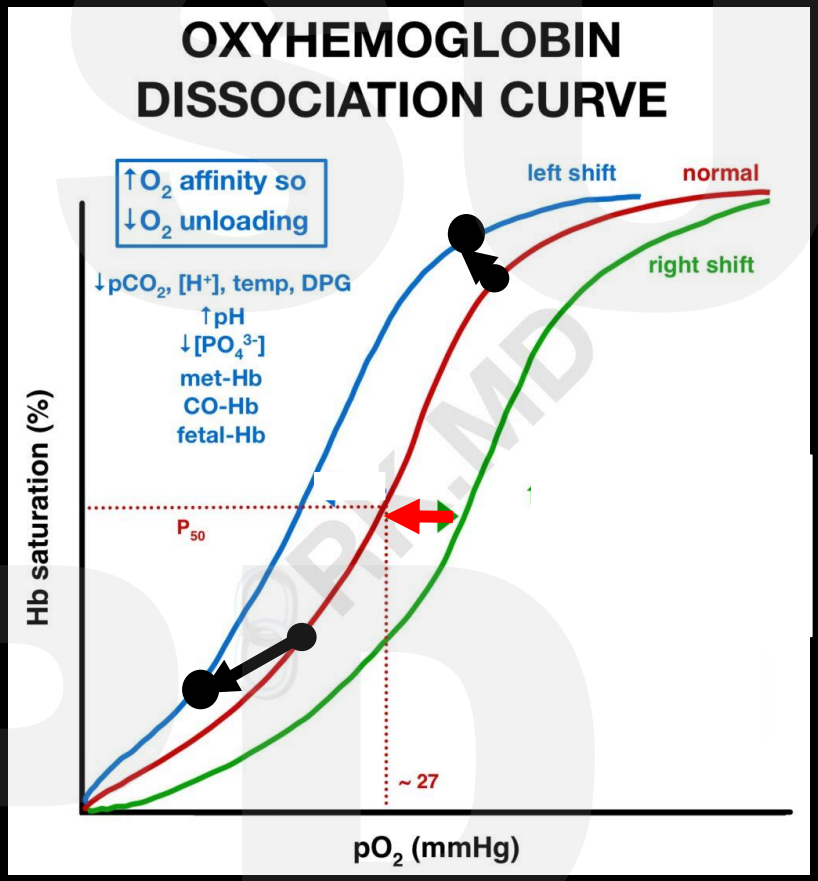


Photo: Tom Deitz





Increased affinity for Oxygen

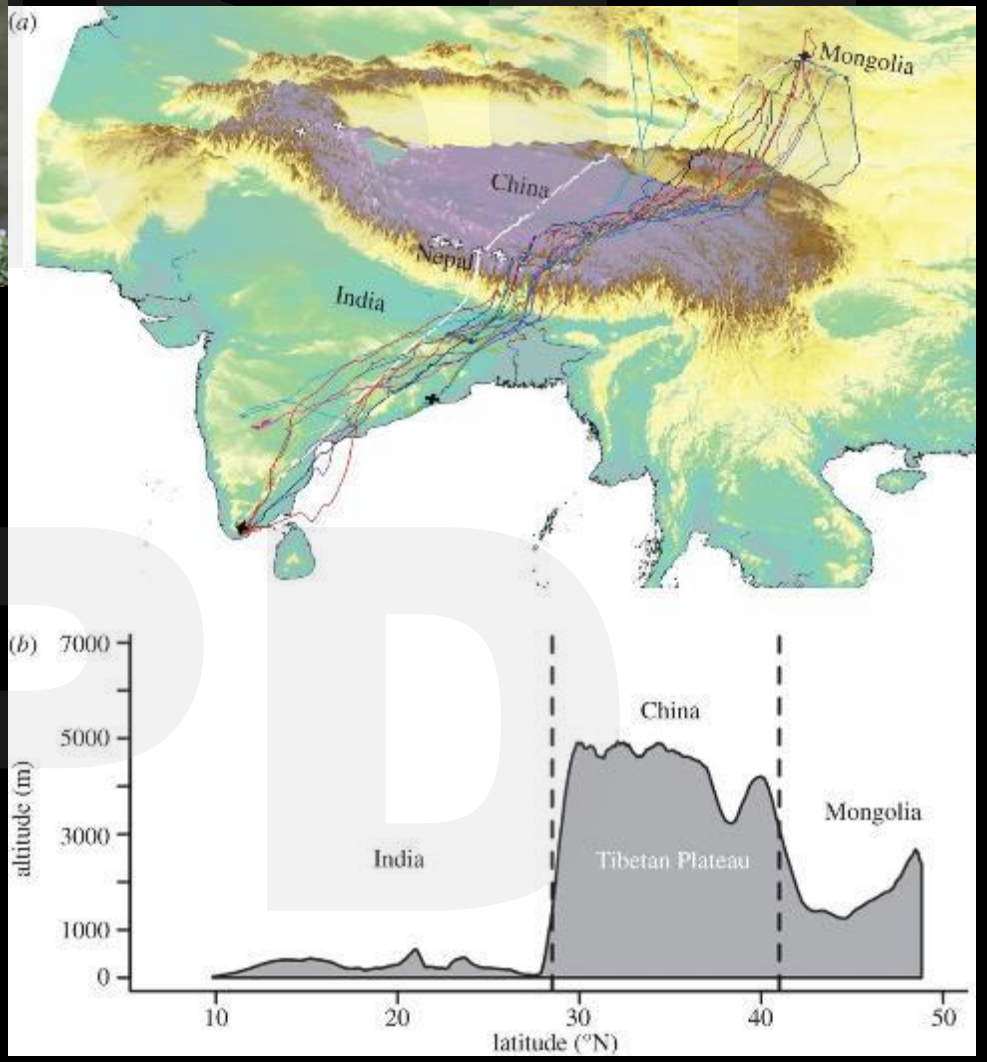
Photo: Deb Robertson

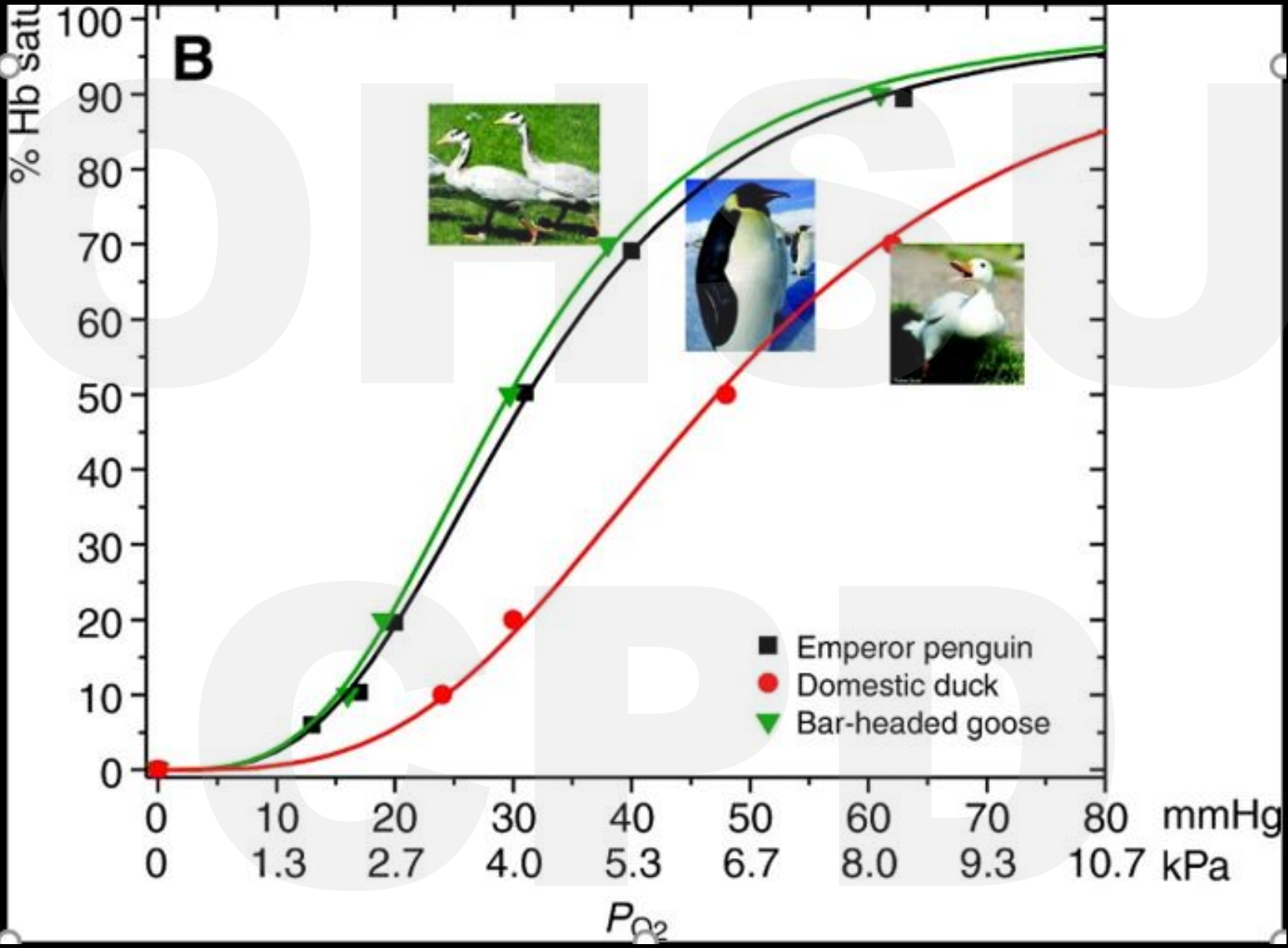
Evidence Increase O_2 Affinity is Beneficial

- 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
- Mayo study – better exercise ability with hypoxia
- J Clin Invest. 1978 Sep; 62(3): 593–600
- J Physiol. 2020 Apr; 598(8): 1475–1490


(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)

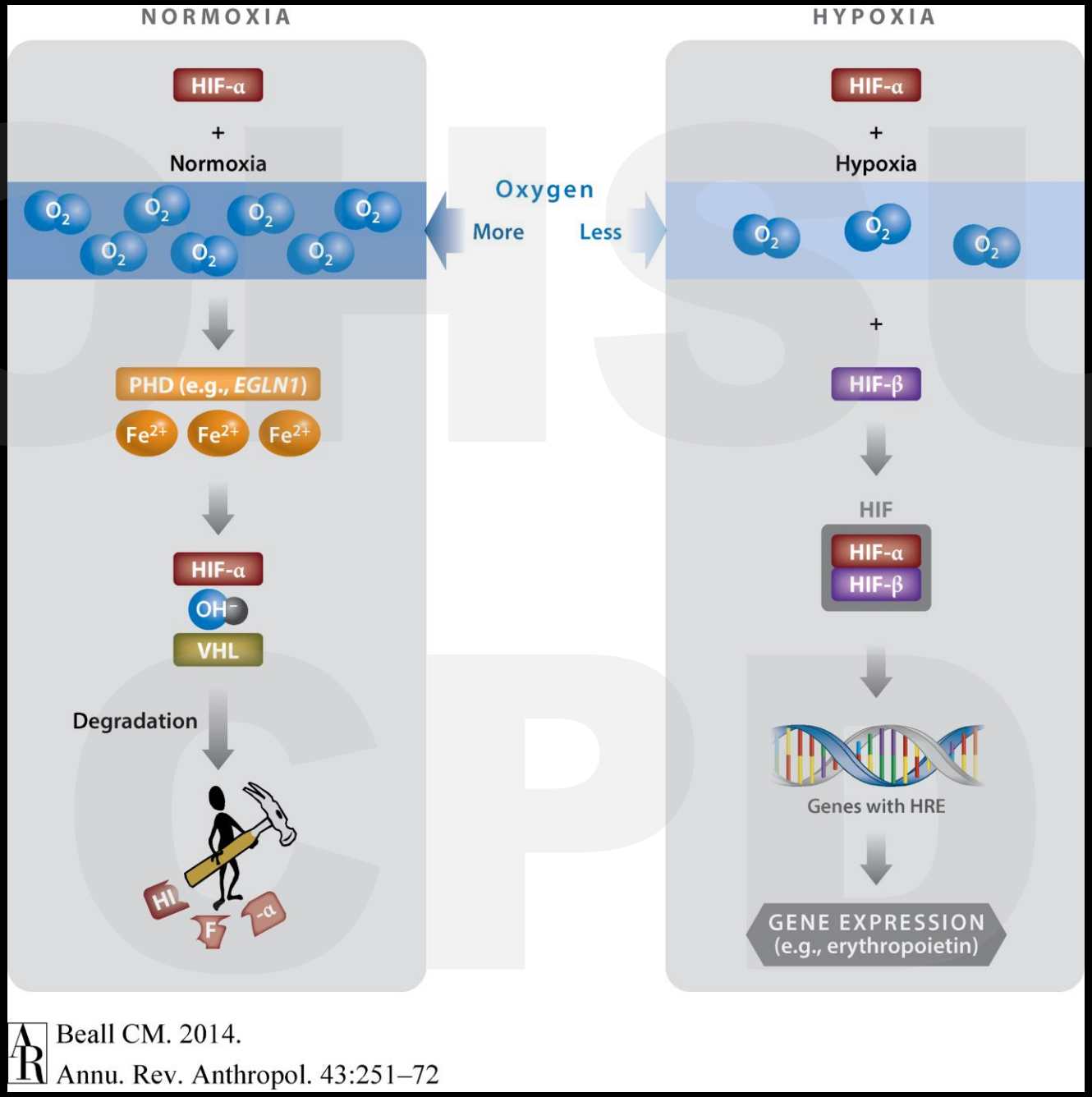

B
% Hb satu
100
90
80
70
60
50
40
30
20
10
0
0 10 20 30 40 50 60 70 80 mmHg
0 1.3 2.7 4.0 5.3 6.7 8.0 9.3 10.7 kPa
P_{O_2}
Emperor penguin
Domestic duck
Bar-headed goose

Tibetans

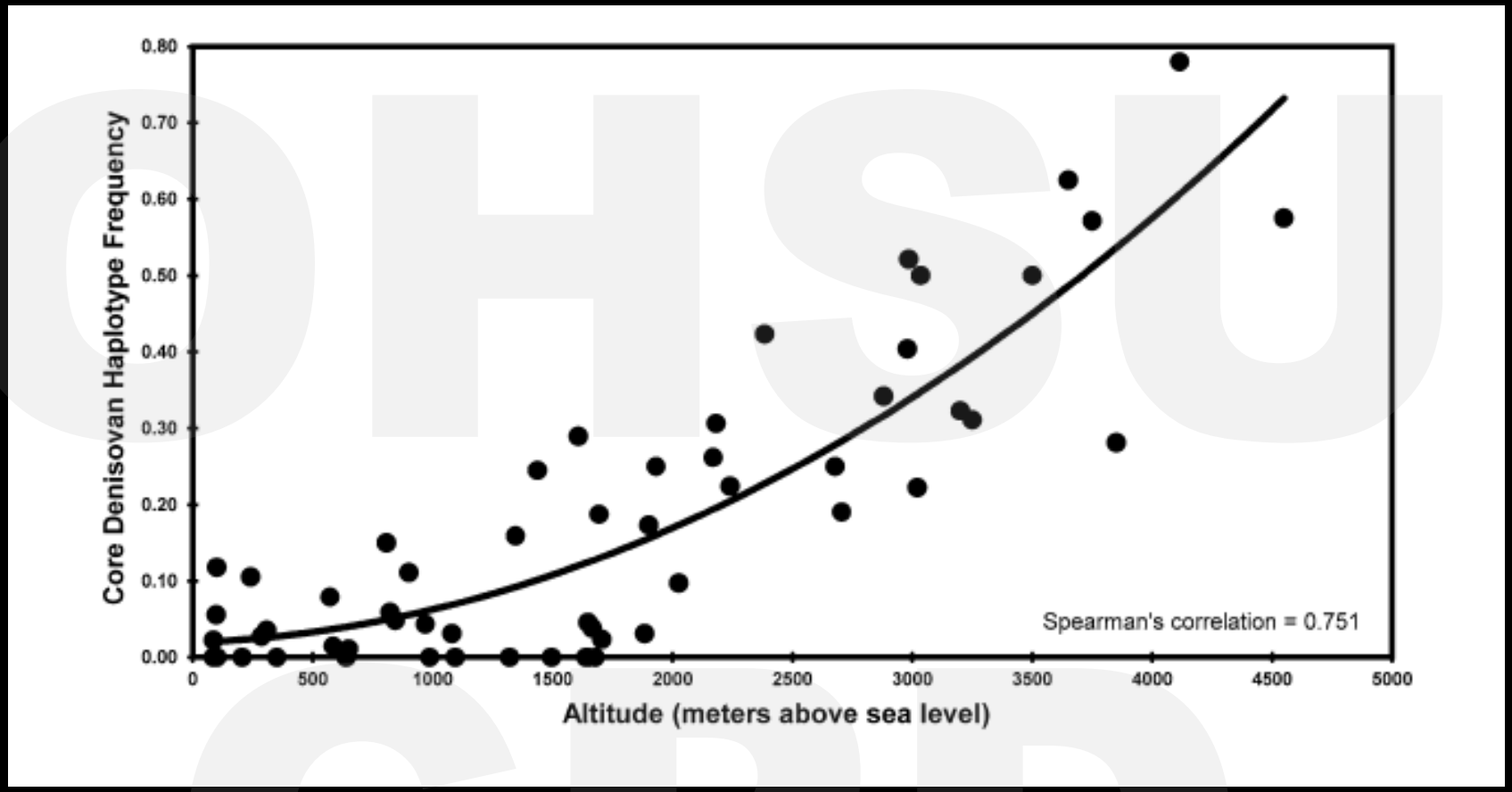
- Evolved in high altitudes
- Tibetans
  - Less erythrocytosis
  - Lower P50
  - Altitude adaptation legendary

EPAS1 (HIF-2α)

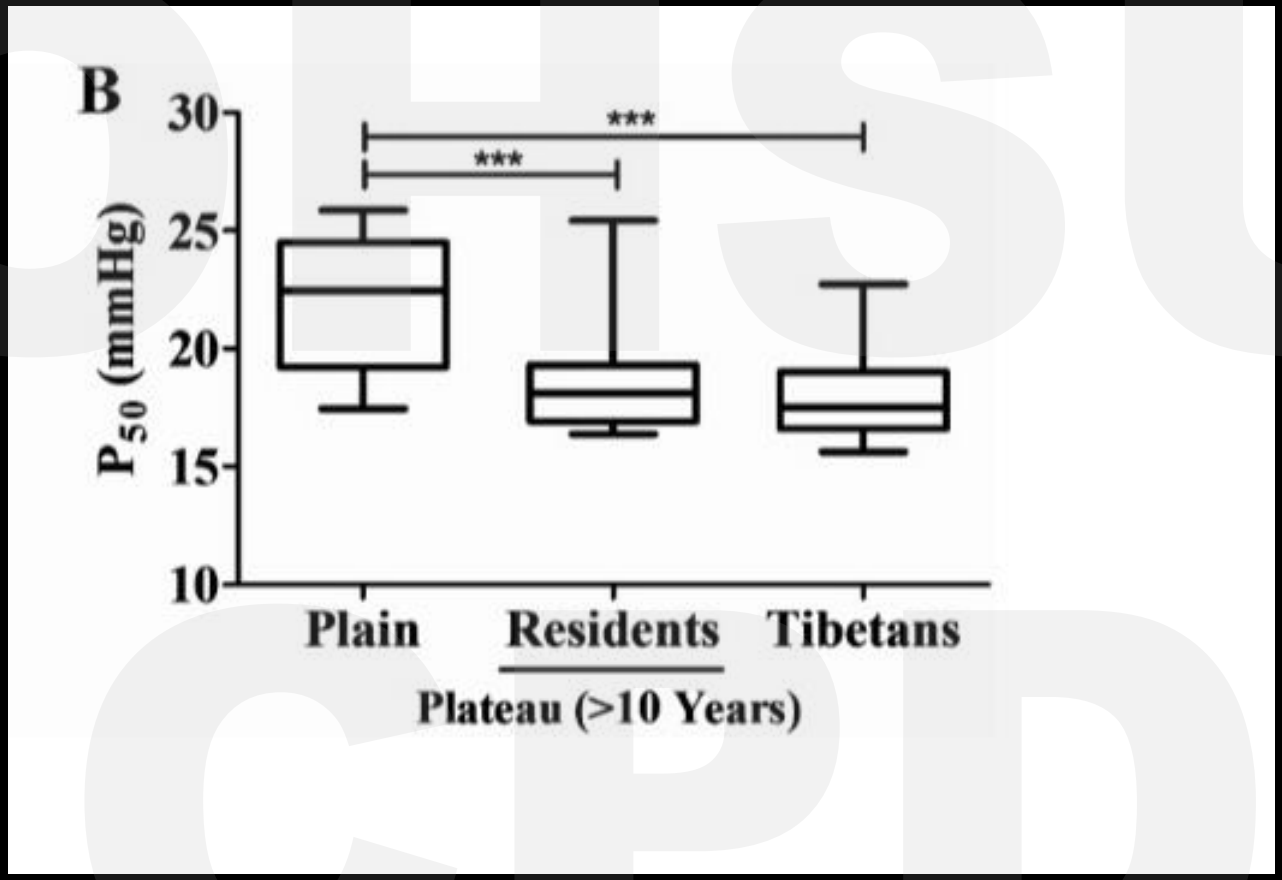
- Found in Tibetan populations
- Decreased HIF pathway sensitivity to hypoxia
- Acquired from Denisovans
- Prevalence increased with altitude



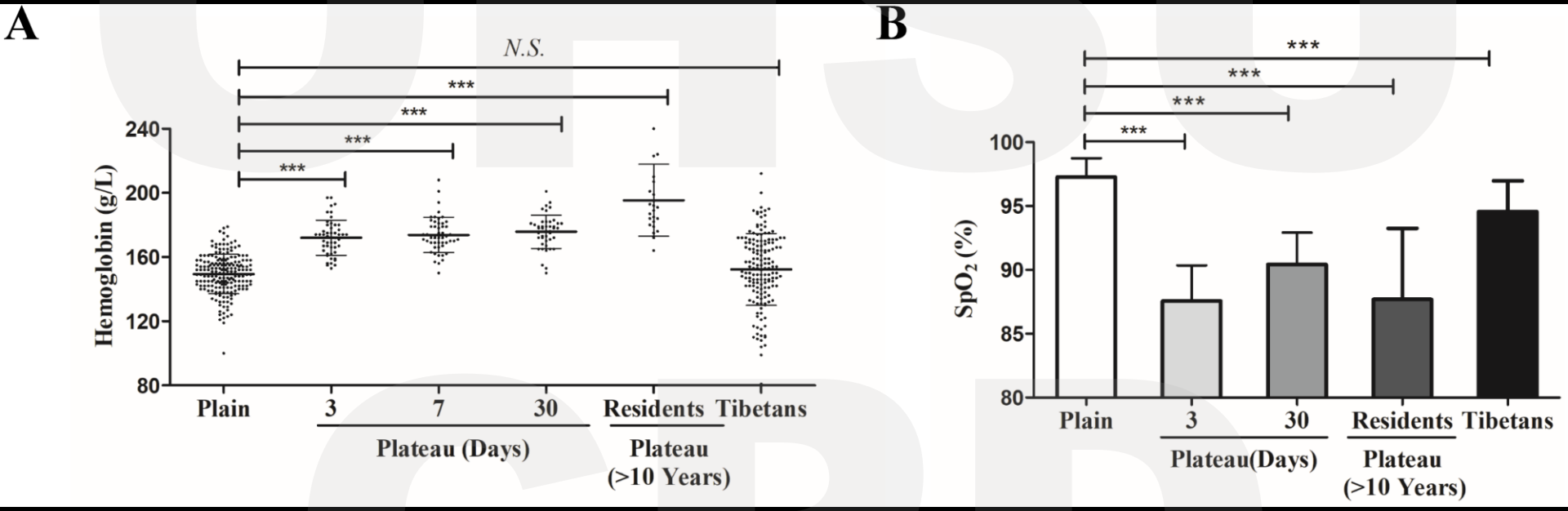
Beall CM. 2014.
Annu. Rev. Anthropol. 43:251–72



Hum Genet (2016) 135:393–402



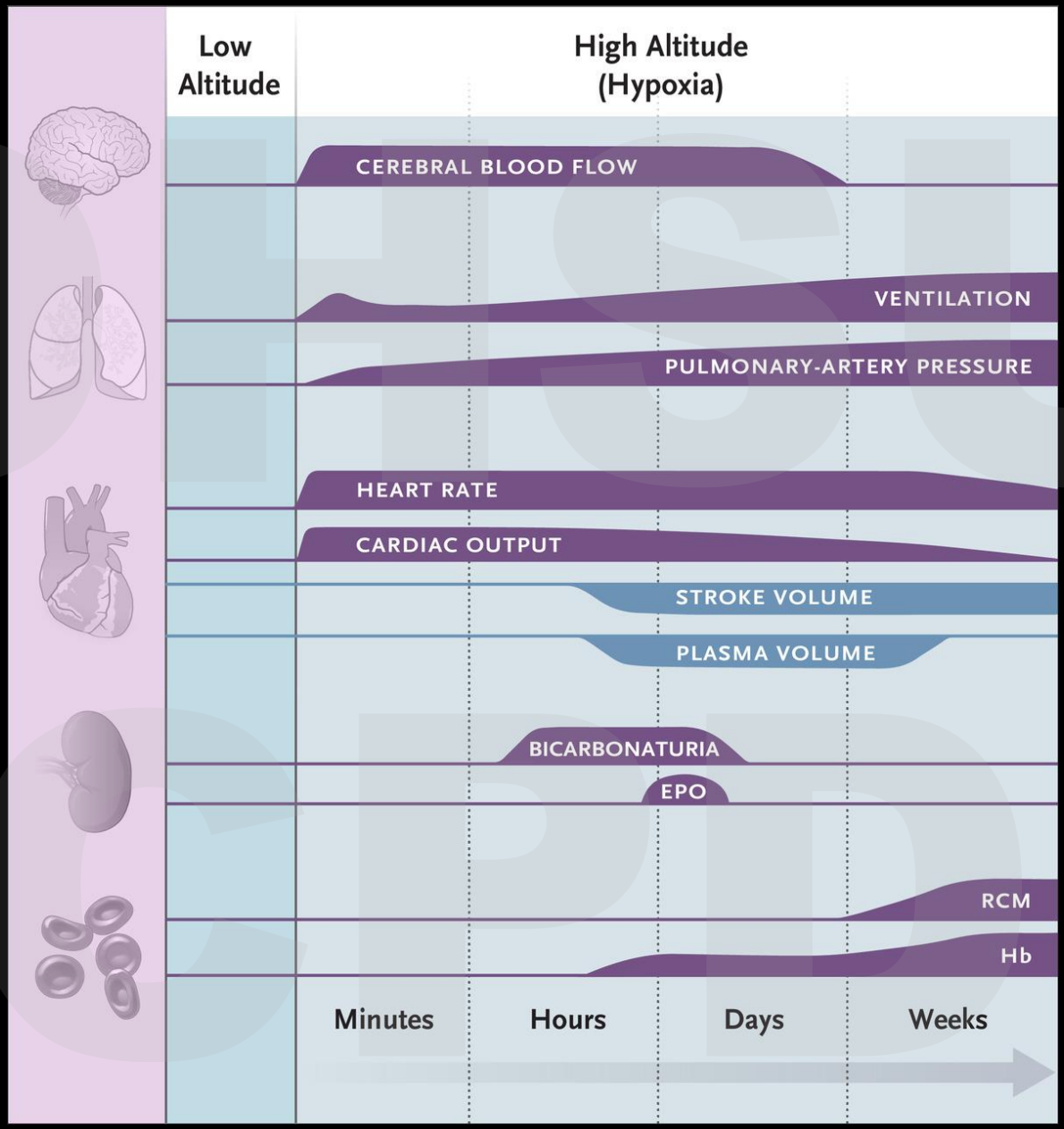
HEMATOLOGY, 2018
VOL. 23, NO. 5, 309–313



PeerJ. 2019 Oct 28;7:e7943

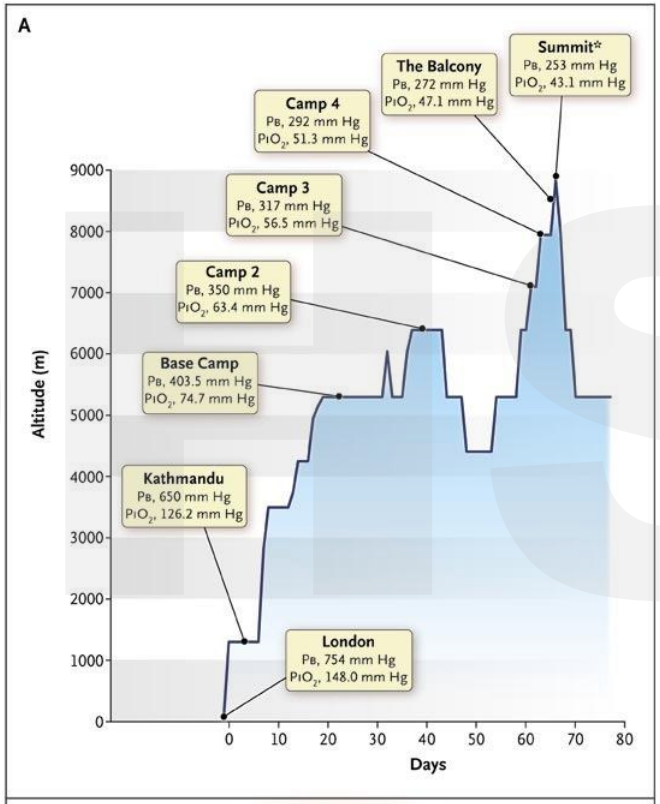
Tissues

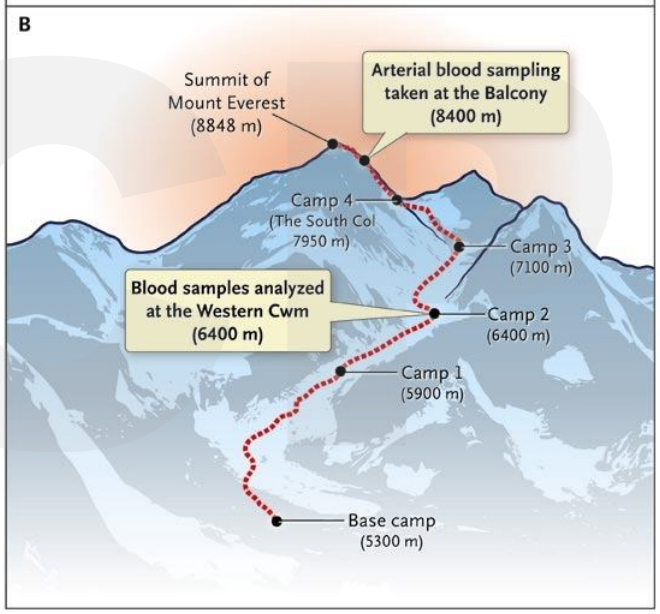
- Increase capillary density
- Decrease muscle mass



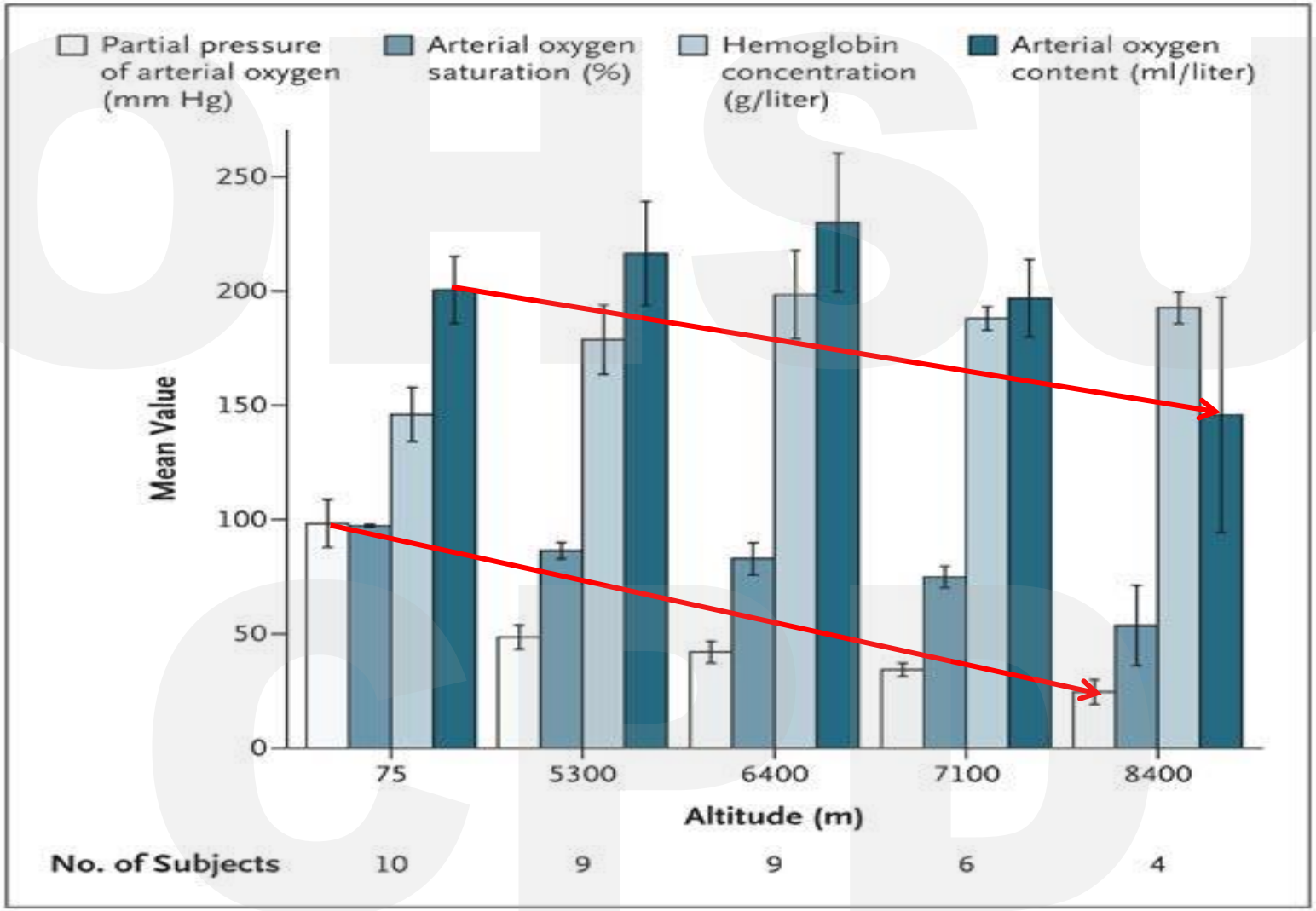
AM Luks, PH Hackett. N Engl J Med 2022;386:364-373.

Photo: Lindsey Fell





N Engl J Med 2009;
360:140-149



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
PAO_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, PAO_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, $PaCO_2$, PAO_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.

** PAO_2 was calculated with the use of the full alveolar gas equation.

Photo: Lindsey Fell

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	50	50%	2-3	1:625
Rainier	10,000	14,409	67	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)

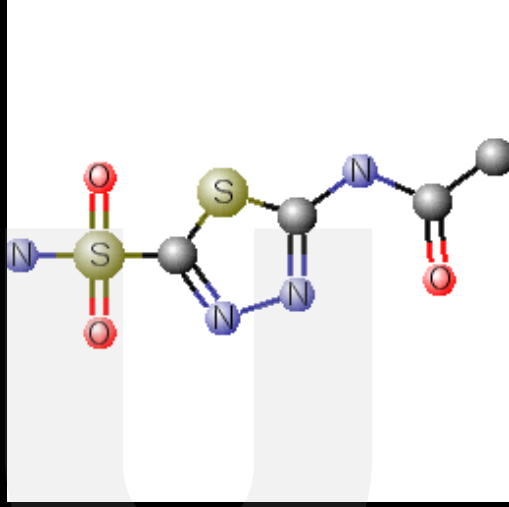
AMS:
Headache plus:
Self-reported ≥ 4
Total > 5

2018 revision
Sleep dropped
AMS ≥ 3

Therapy

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

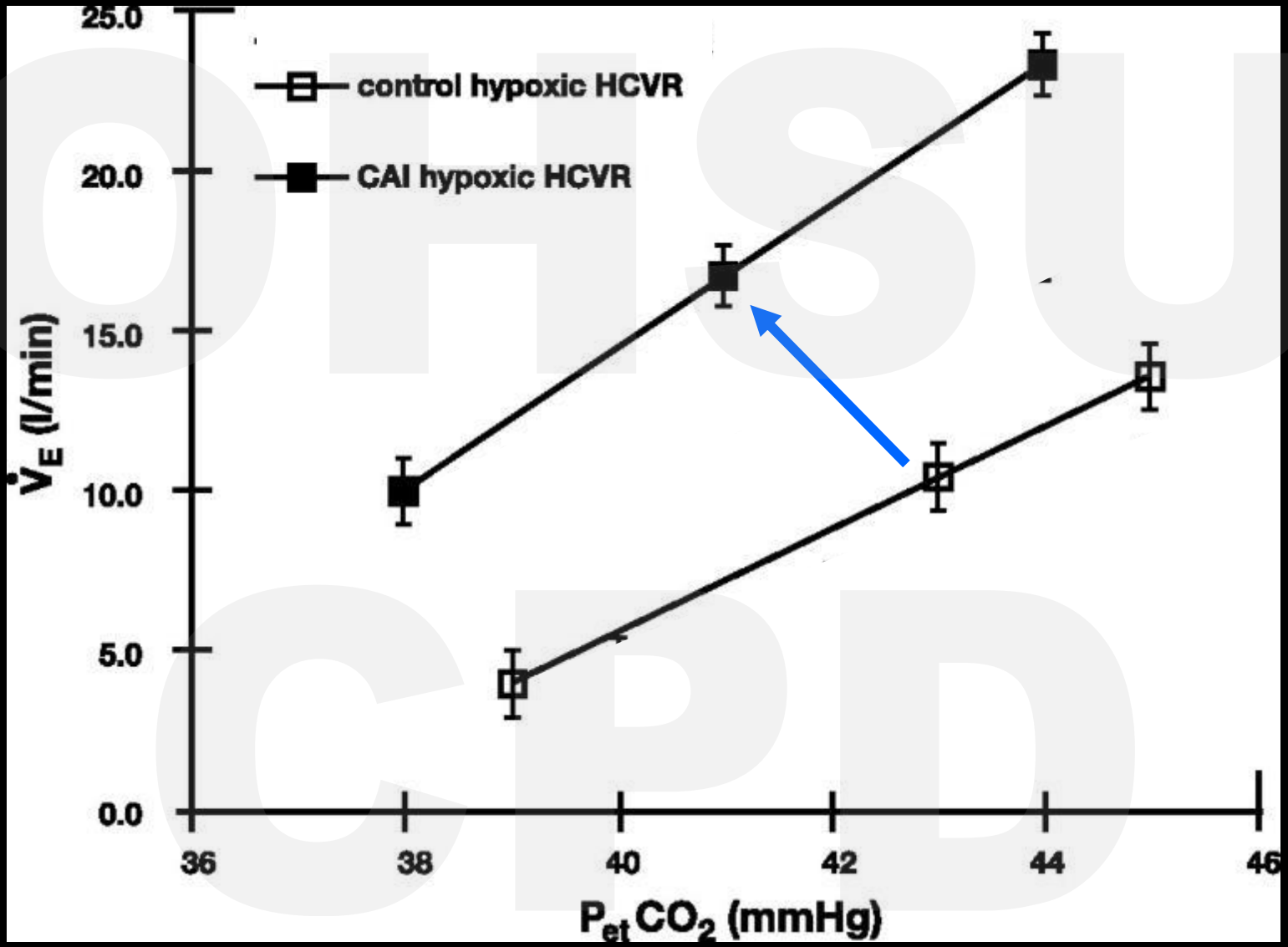
Acetazolamide

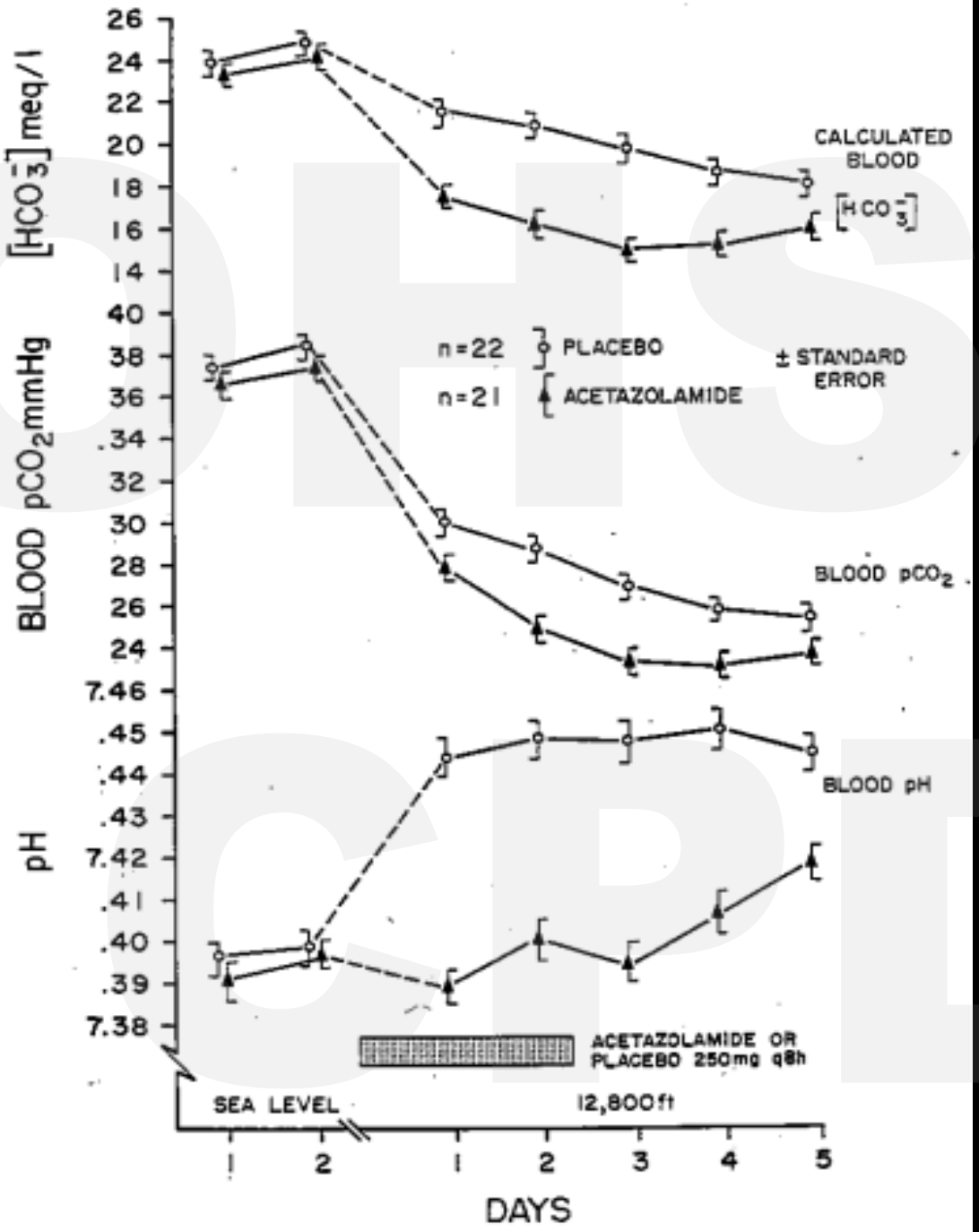


- Carbonic anhydrase inhibitor
  - Increases ventilation
  - Diuresis
- Speeds acclimatization
- Maintains oxygenation
- Treatment/prophylaxis

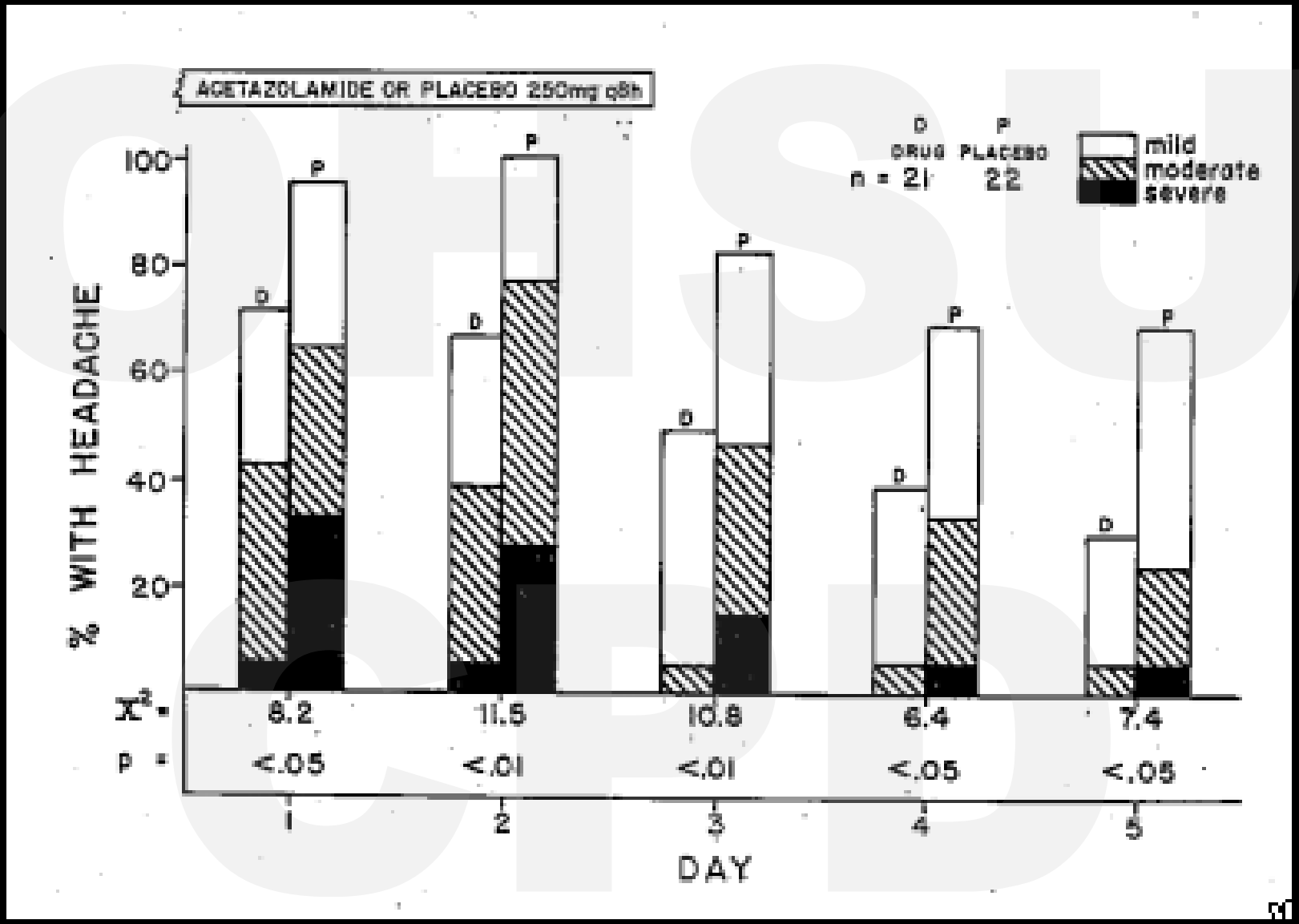
Acetazolamide

- Increase urine loss of HCO_3
  - Counteract respiratory alkalosis
- Decrease blood pH
  - Increases respiration
- Decreases tissue pH
  - Increases respiration


control hypoxic HCVR
CAI hypoxic HCVR
25.0
20.0
15.0
10.0
5.0
0.0
$\dot{V}_E$ (l/min)
36
38
40
42
44
46
$P_{et}CO_2$ (mmHg)



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

Acute Mountain Sickness: Prevention

- Slow ascents
  - Above 10,000 ft ascend no more than 1000ft/night
  - Above 8,000 ft ascend no more than 2-4,000/day with a day of rest after each ascent
- Acetazolamide
- Dexamethasone
  - History of severe AMS

WMS Risk Stratification

- **Low Risk**
  - No history and < 2800m
  - Gradual ascents (>2 days to 2500-3000m)
- **Moderate Risk**
  - History of AMS and 2500-2800 in 1 day
  - No history AMS and > 2800m in 1 day
  - All climbing > 500m/day above 3000m
    - Consider acetazolamide

WMS Risk Stratification

- High Risk
  - History of AMS ascending >2800m in 1 day
  - All with history of HAPE or HACE
  - All ascending > 3500m in 1 day
  - All ascending > 500m/day above 3500m
  - Very rapid ascents (> 3500m)
    - Acetazolamide and consider dexamethasone

- Wilderness Environ Med. 2024 Mar;35(1_suppl):2S-19S

	Risk Category		
Variable	**Low**	**Moderate**	**High**
History of acute altitude illness	None or mild AMS ☐	Moderate-Severe AMS ☐	HAPE or HACE ☐
Sleeping elevation on Day 1 (meters)	< 2800 ☐	2800-3500 ☐	> 3500 ☐
Ascent rate (meters/day)	≤ 500 m/d above 3000 m with extra days for acclimatization every 1000 m ☐	≥ 500 m/d above 3000 m with extra days for acclimatization every 1000 m ☐	≥ 500 m/d above 3000 m without extra days for acclimatization every 1000 m ☐

- **Wilderness Environ Med. 2024 Mar;35(1_suppl):2S-19S**

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_2Sat	80.7%	82%	82.8%

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

Lower Dose?

- 125 mg BID vs 62.5 mg BID
- N = 106

	62.5 mg BID	125 mg BID
AMS (%)	55	45
Headache	15%	8%
LLS	1.6	1.4

- 62.5 inferior to 125mg
- Heavier people did worse with 62.5 mg
- AJM 133:e706, 2020

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
- Research underway for better predictors

Sleep Disturbances

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

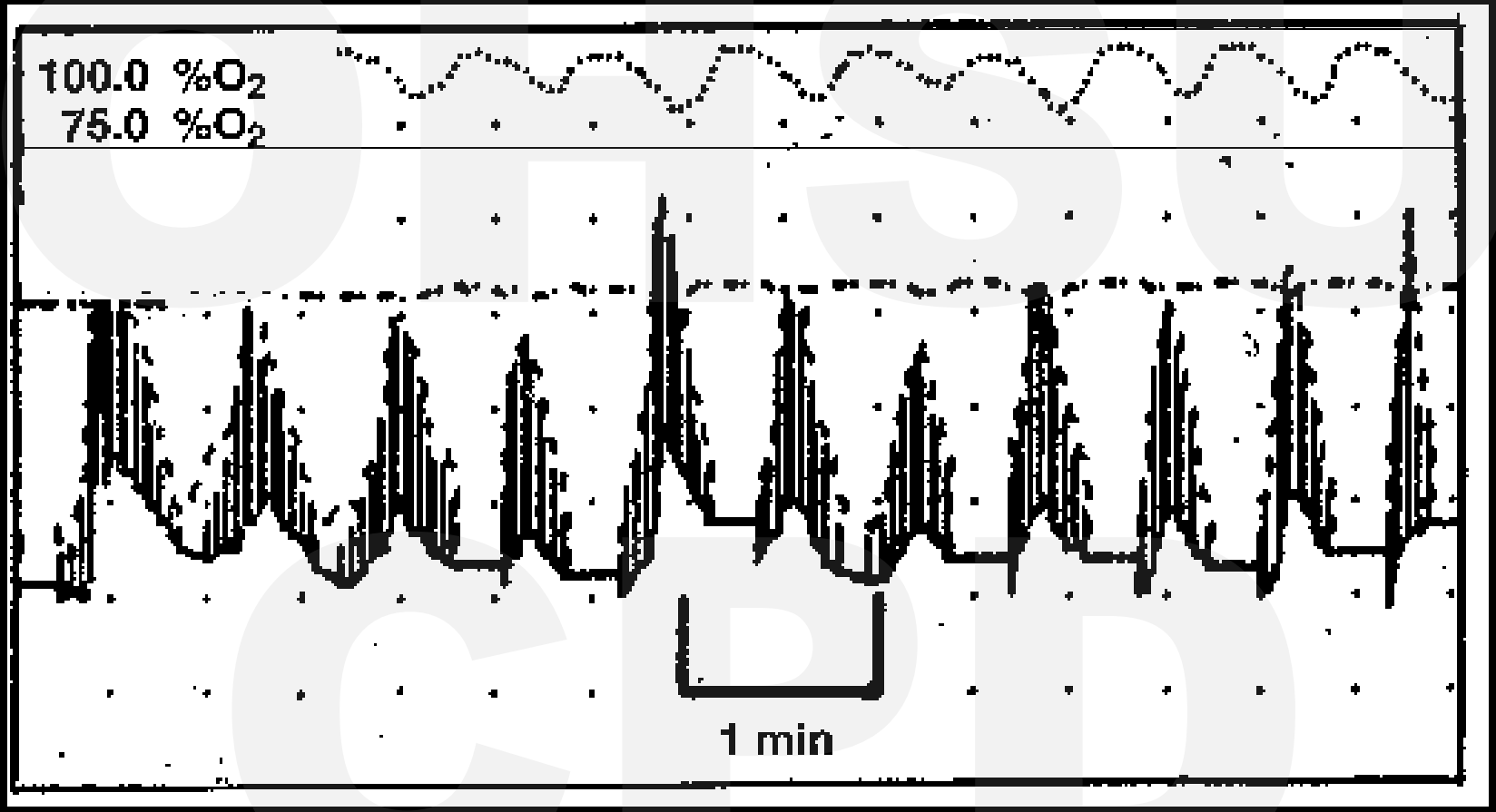

100.0 %O2
75.0 %O2
1 min

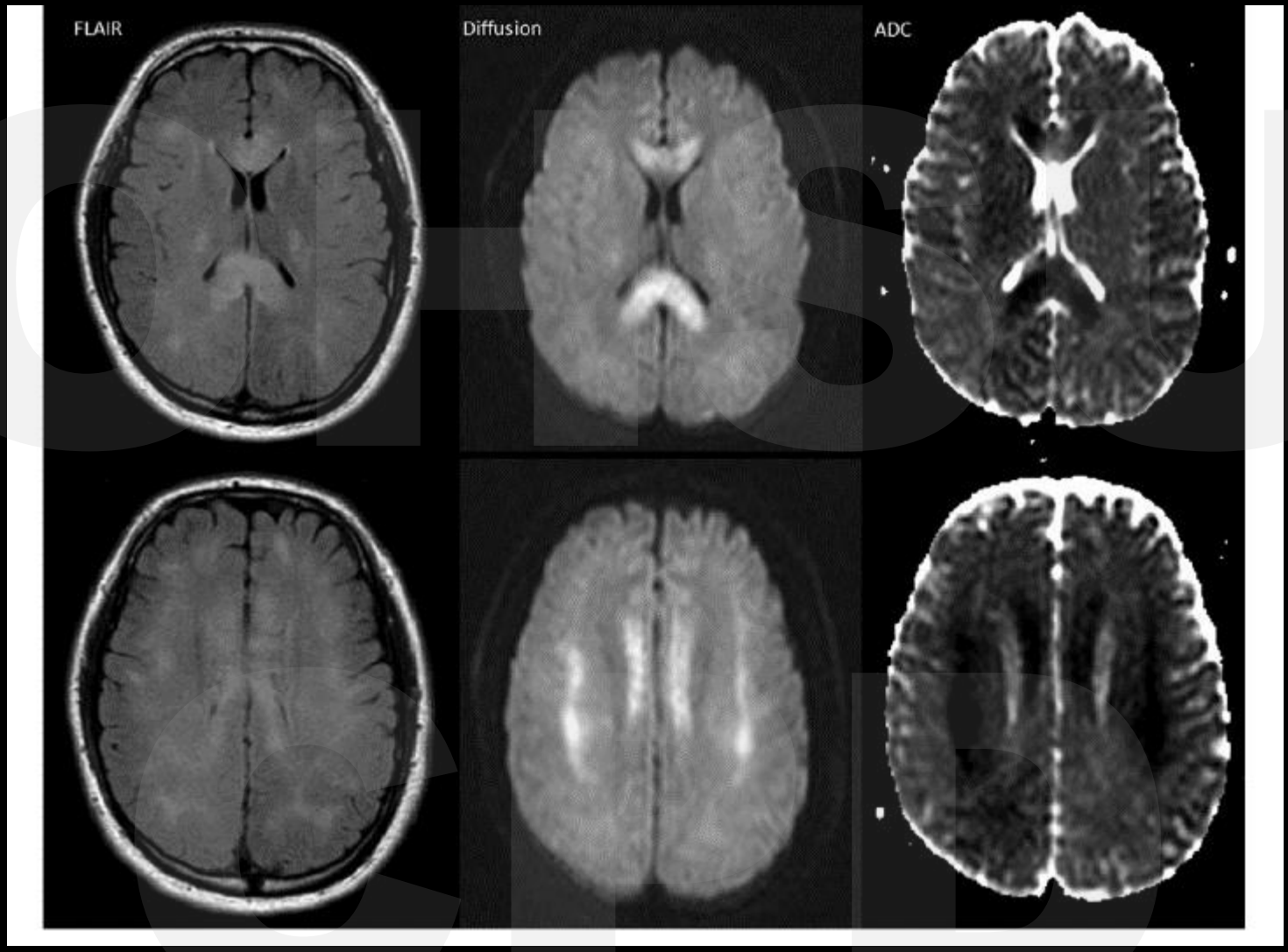
Photo: Deb Robertson

High Altitude Cerebral Edema

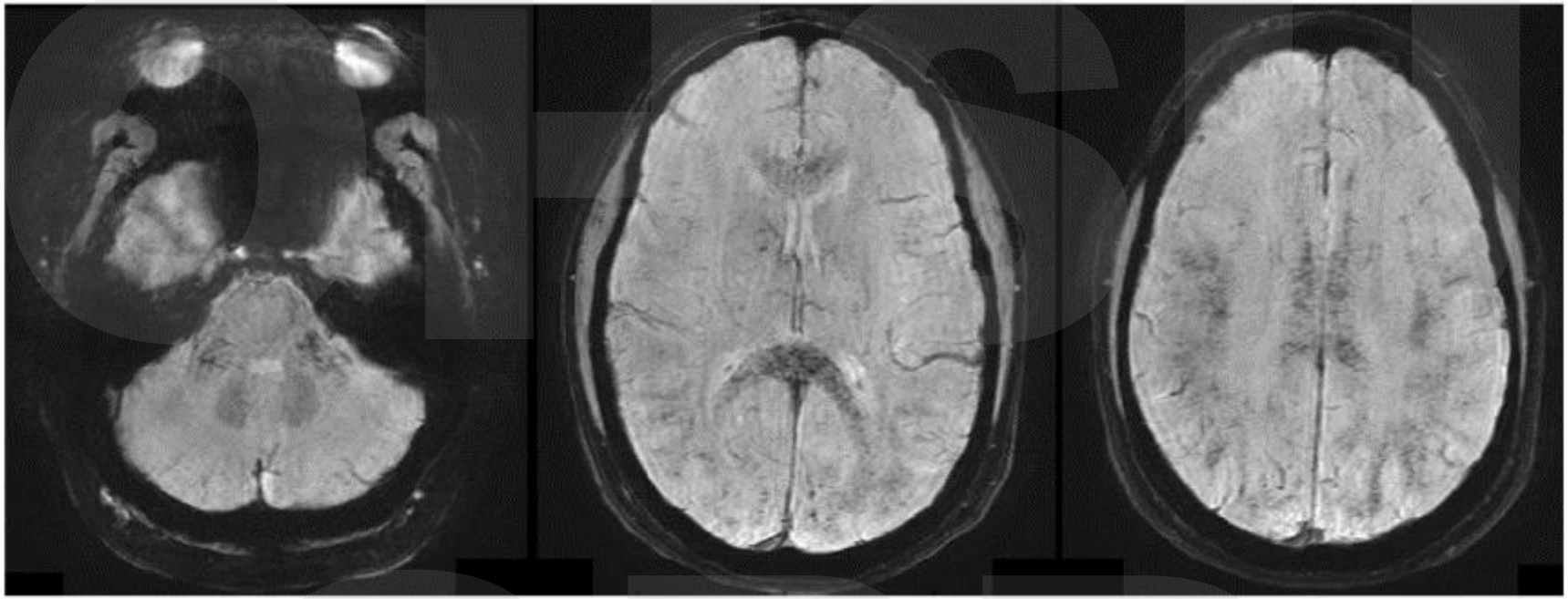
- AMS with
  - Ataxia
  - Altered mental status
  - Seizures
  - Photophobia
- Rate: 1-3%
- Rapidly evolves to coma and death
  - Once coma ensures 60% fatality rate

HACE:

- Vasogenic cerebral edema
  - microbleeds
- Late stages: thrombosis



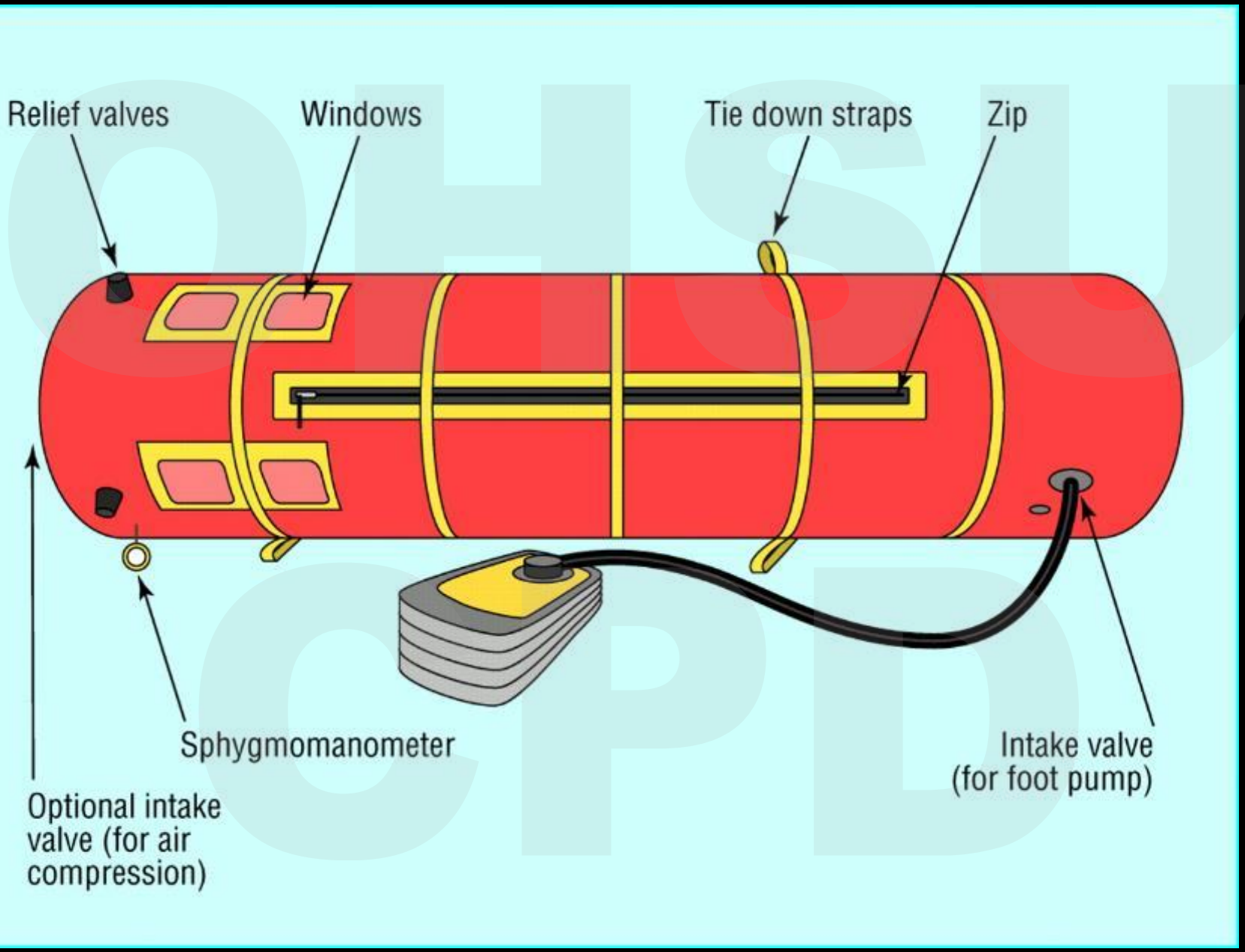
AJNR Am J Neuroradiol 40:464–69 Mar 2019



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

Not all Headaches are HACE

- 11 patients initially dx with HACE but had hyponatremia
- HACE slower onset and higher altitude
- HypoNa fast onset and seizures
- Wilderness Environ Med. 2025 Jun;36(2):182-189

Photo: Lindsey Fell

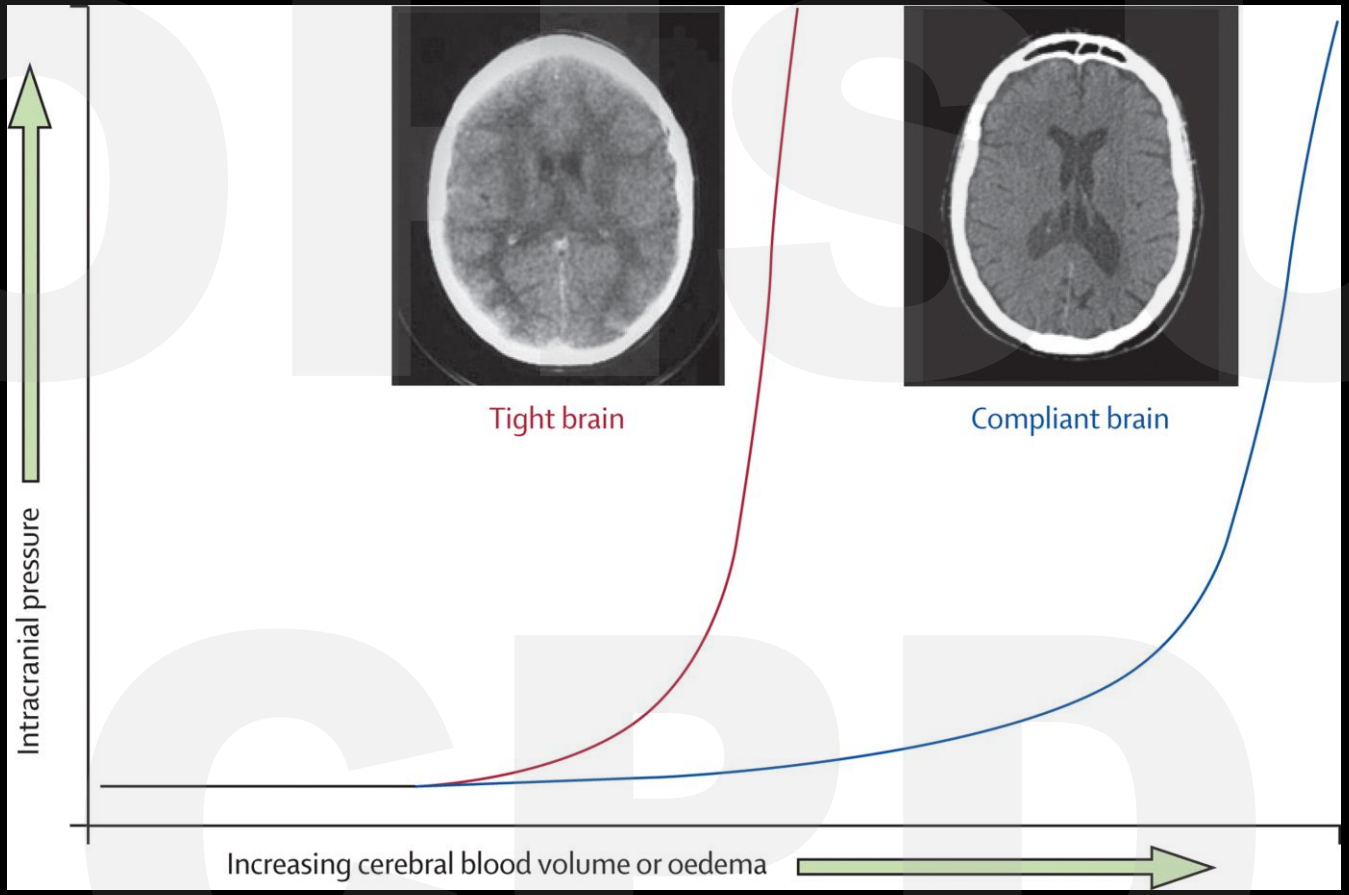
AMS: Pathogenesis

- Hypoxia
  - Poor HVR
- Unpredictable
- Individual susceptibility

“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

Figure 3



The Lancet Neurology 2009 8175-191DOI: (10.1016/S1474-4422(09)70014-6)

“Tight Fit” Theory

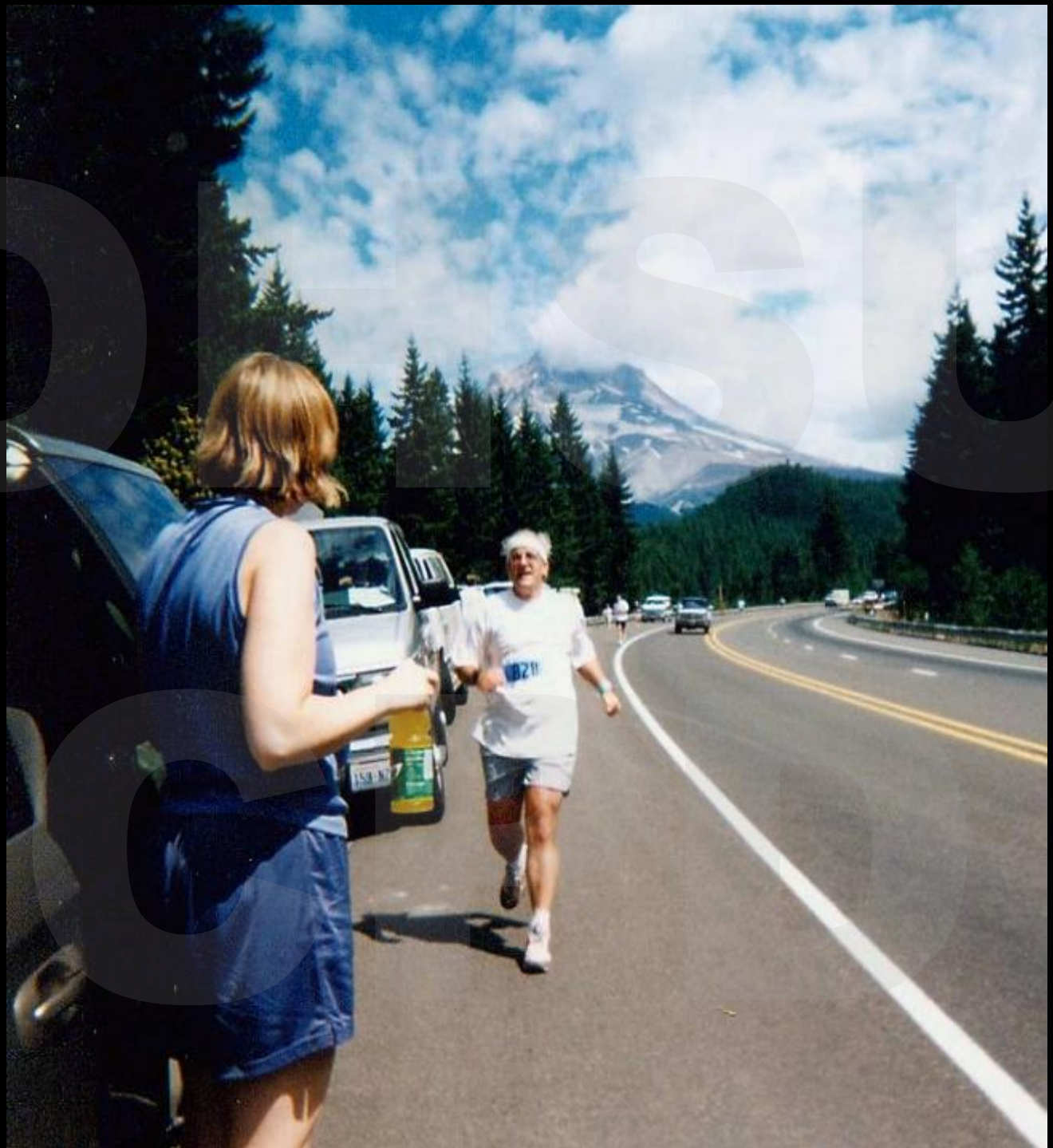
- May not explain everything
  - ICP increases in all people
- Evidence of fluid retention
- Inflammatory markers increased
- More research needed!

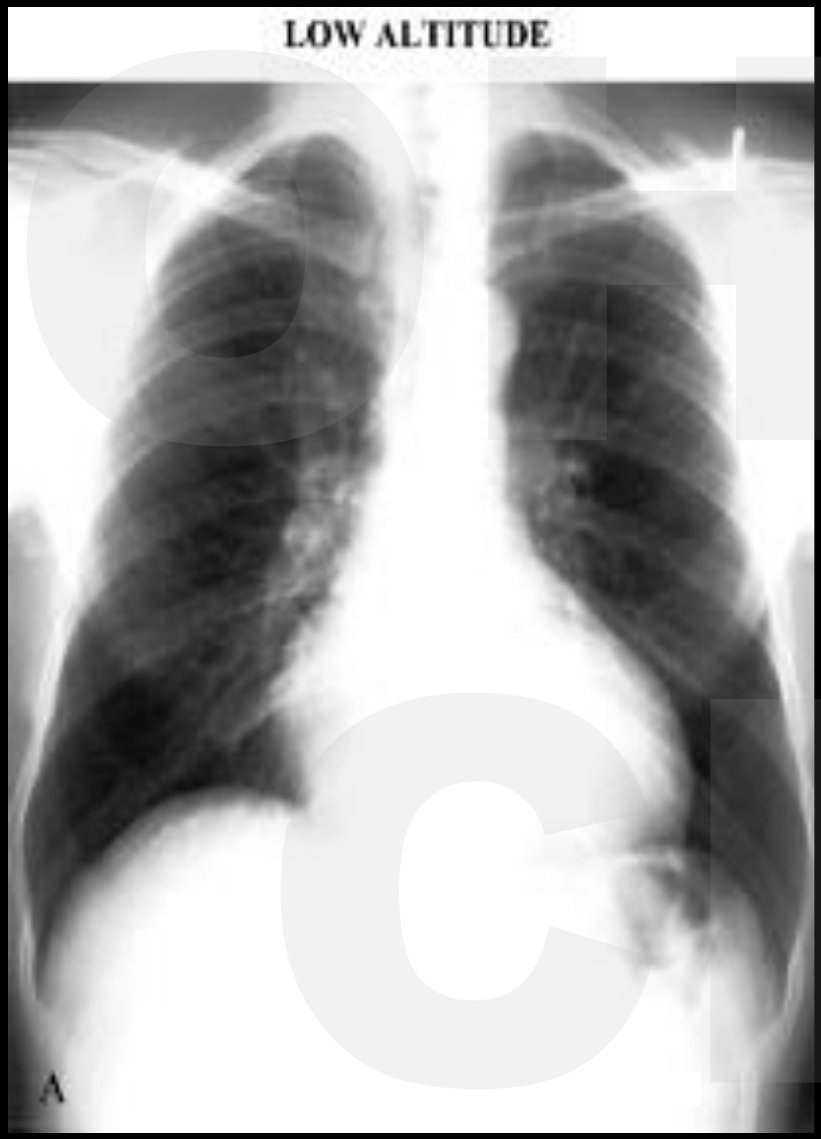
High Altitude Pulmonary Edema

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

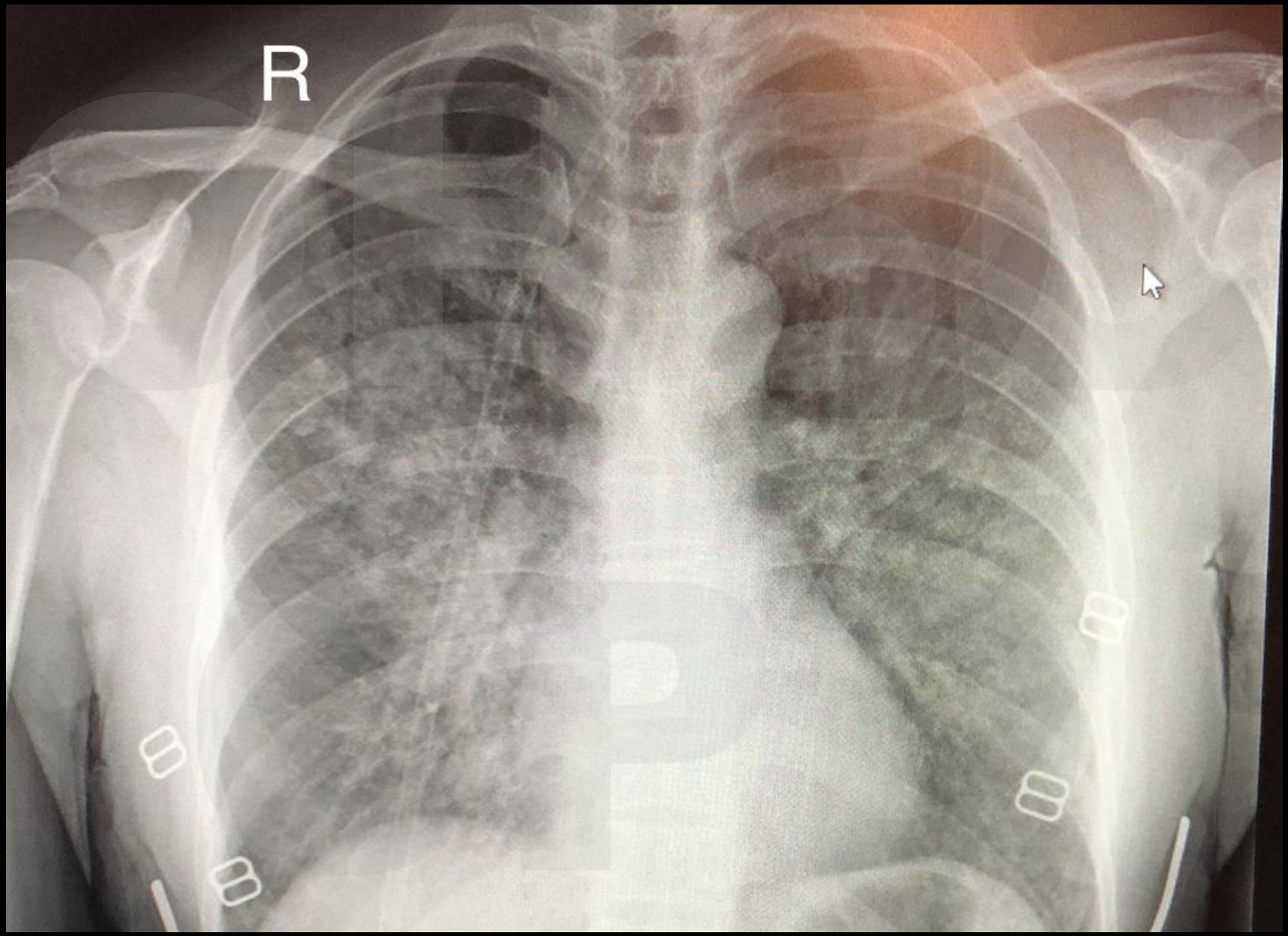
HAPE: Incidence and Risk Groups

- 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
A


HIGH ALTITUDE
L
B


R

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

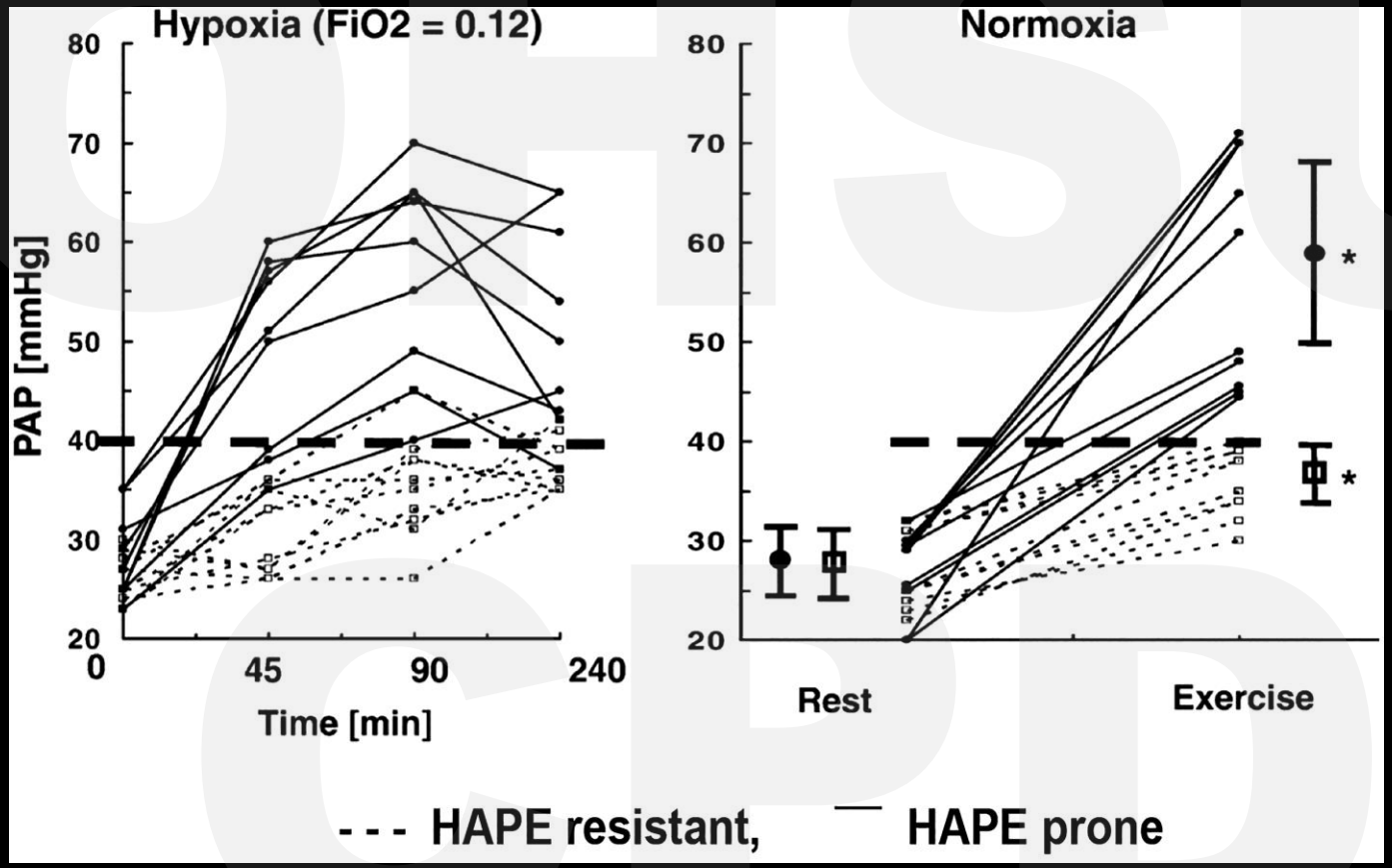
	Placebo	Tadalafil	Dex
HAPE	7/9 (78%)	1/8 (13%)	0/10 (0)
AMS	8/9 (89%)	8/10 (80%)	3/10(30)
LLS	7	6.5	2.5
Headache	2	2	0.5

PDE-5 Inhibitors

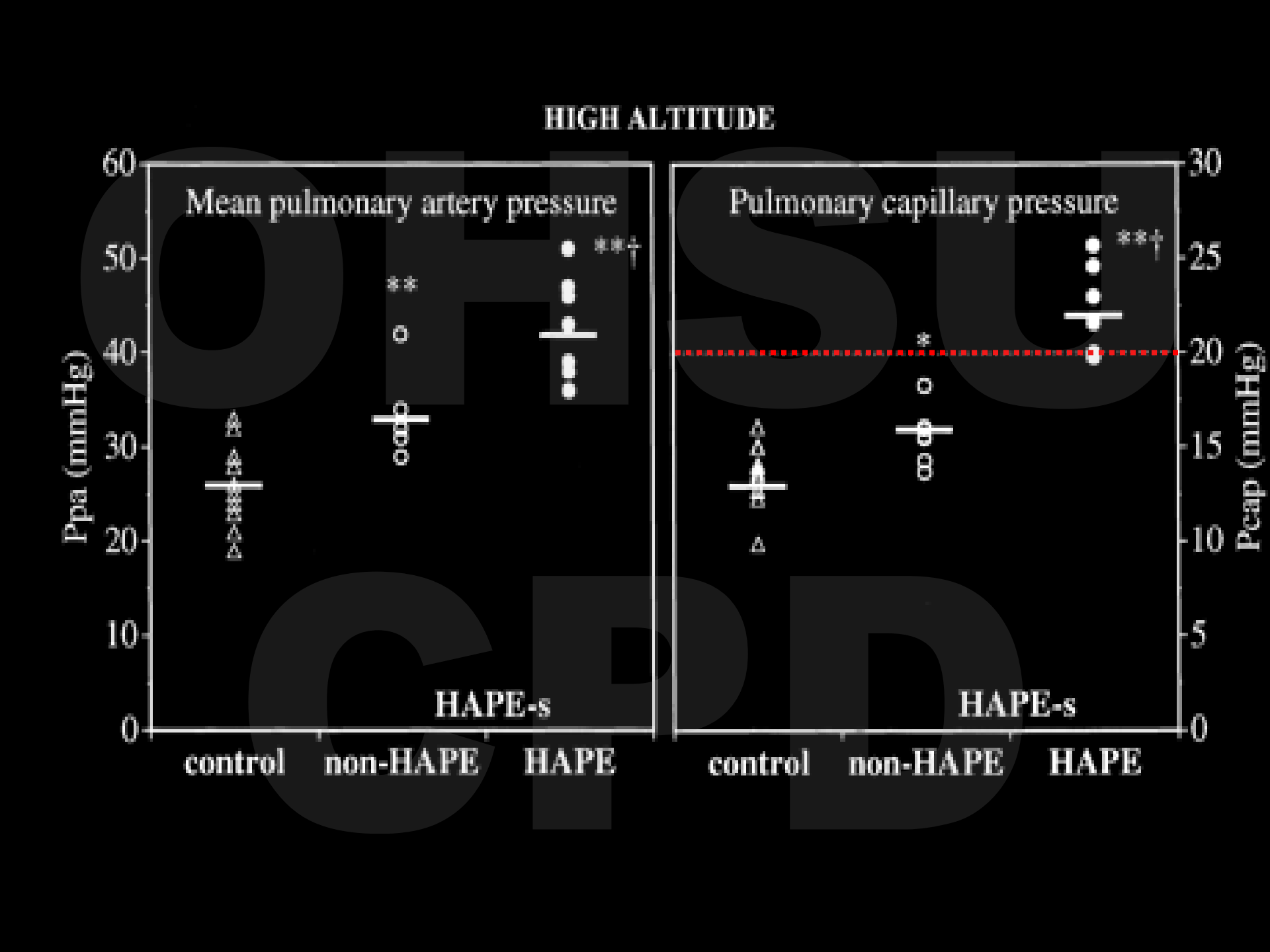
- Fading because of cost and concerns about increased AMS incidence

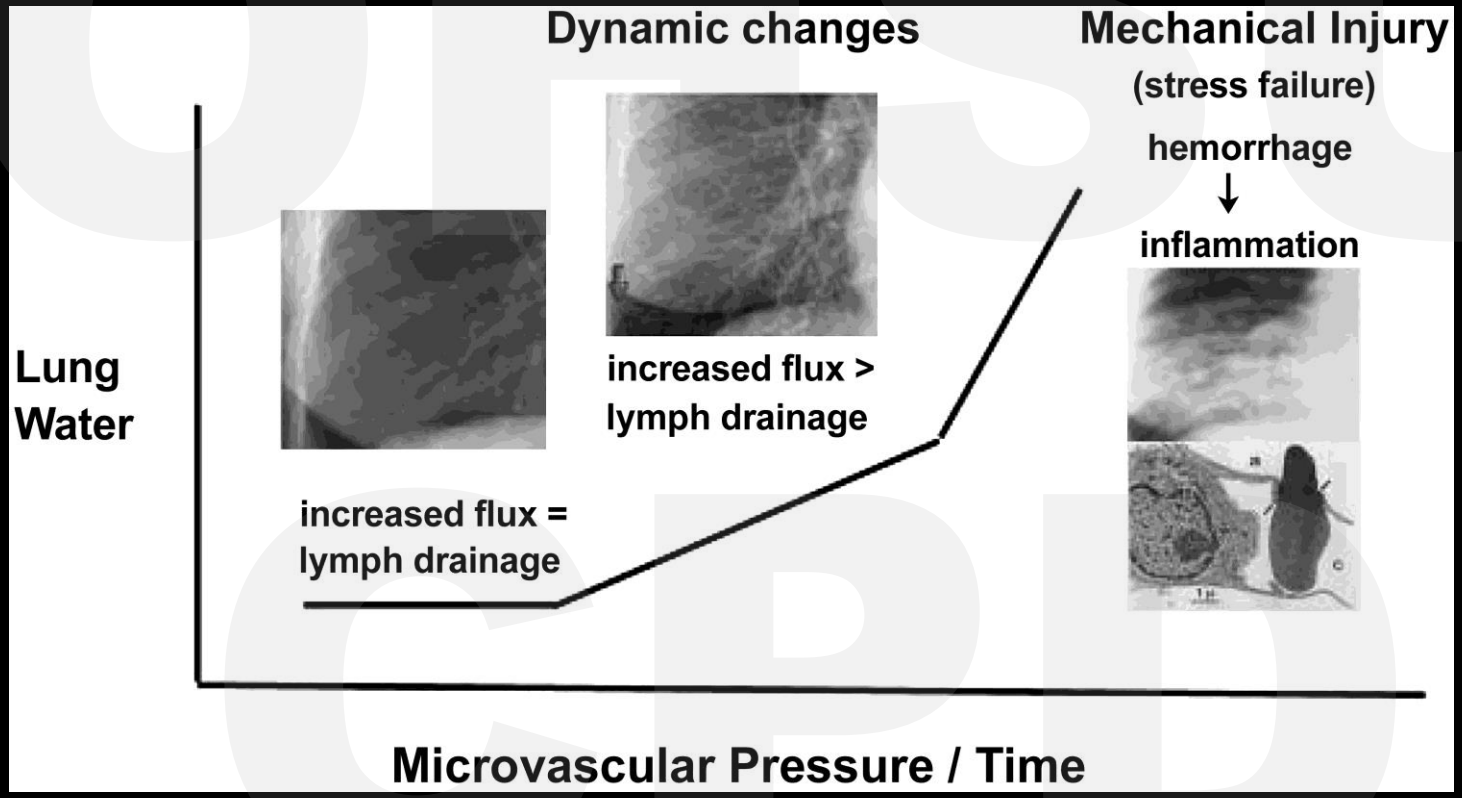
HAPE Pathogenesis

- 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



DOI: (10.1152/japplphysiol.00824.2019)


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



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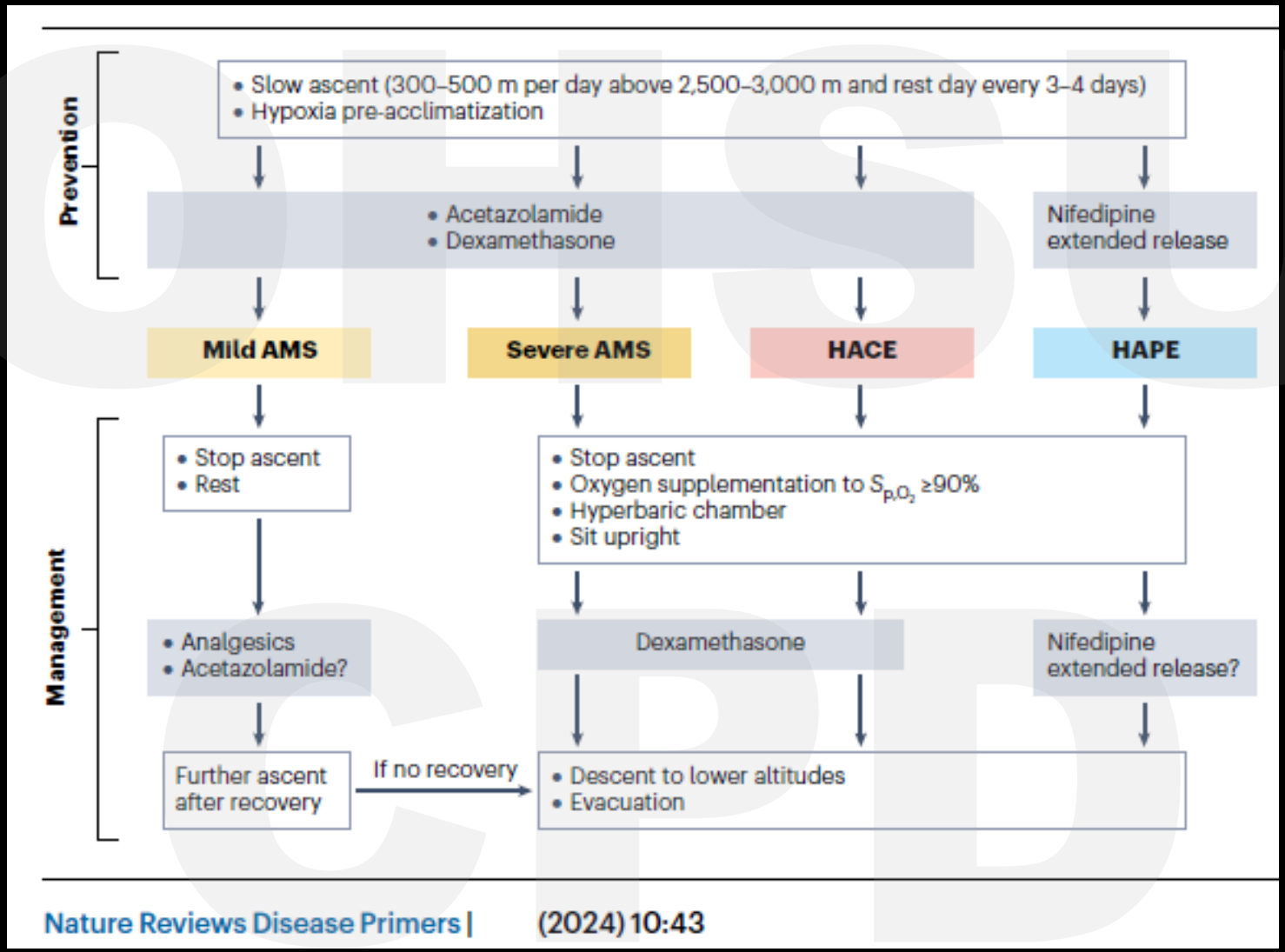
Prevention
• Slow ascent (300–500 m per day above 2,500–3,000 m and rest day every 3–4 days)
• Hypoxia pre-acclimatization
• Acetazolamide
• Dexamethasone
Nifedipine extended release
Mild AMS
Severe AMS
HACE
HAPE
Management
• Stop ascent
• Rest
• Stop ascent
• Oxygen supplementation to S_{p,O_2} ≥90%
• Hyperbaric chamber
• Sit upright
• Analgesics
• Acetazolamide?
Dexamethasone
Nifedipine extended release?
Further ascent after recovery
If no recovery
• Descent to lower altitudes
• Evacuation

Photo: Lindsey Fell

Altitude and Refractive Eye Surgery

- Radial kerectomy:
  - Changes occurs within hours of altitude
  - Usually returns to normal upon descending
- LASIK
  - May better for extreme altitude than RK
  - Some vision changes with altitude
- Photorefractive keratectomy
  - Best from altitude standpoint
  - No vison changes

Blood Clots!

- Air travels ~ 2x risk of blood clots
- Starts after 4 hours
  - 26% increase risk every 2 hrs of travel
- Immobility >>> hypoxia
- Stocking best thrombosis prevention
- Wilderness Environ Med. 2022

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