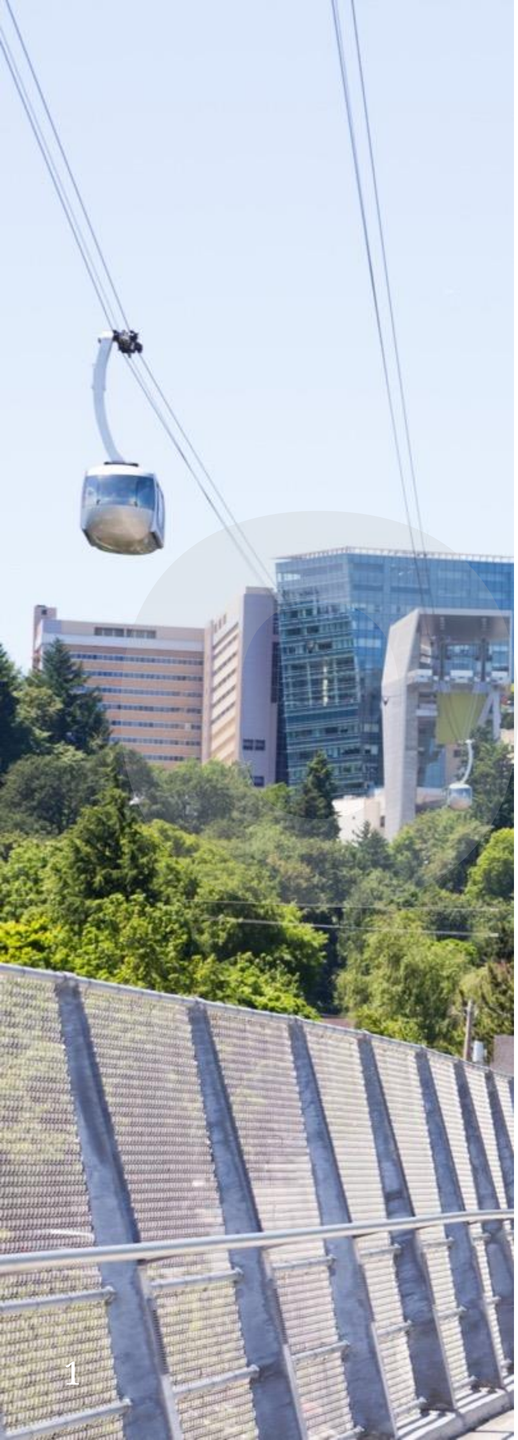

Travel-Free CME

Thin Air Thick Blood: High Altitude Medicine

Thomas DeLoughery, MD

Disclosure

The planners and presenter have nothing to disclose

Upcoming webinars

June 24: Building Your Wellness Toolkit: Promoting Connection to Joy and Purpose
James Clements, MD

July 1: No Session

July 8: COVID Clotting Catastrophes
Thomas DeLoughery, MD

July 15: Update on the Diabetic Foot
Dave Griffin, DPM

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High Altitude

Tom DeLoughery, MD MACP FAWM @bloodman

Oregon Health &Sciences University

OHSU GENERAL HEMATOLOGY

DISCLOSURE

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

Speaker Bureau - None

Consultant/Research – none

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Overview

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

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High Altitude Medicine

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

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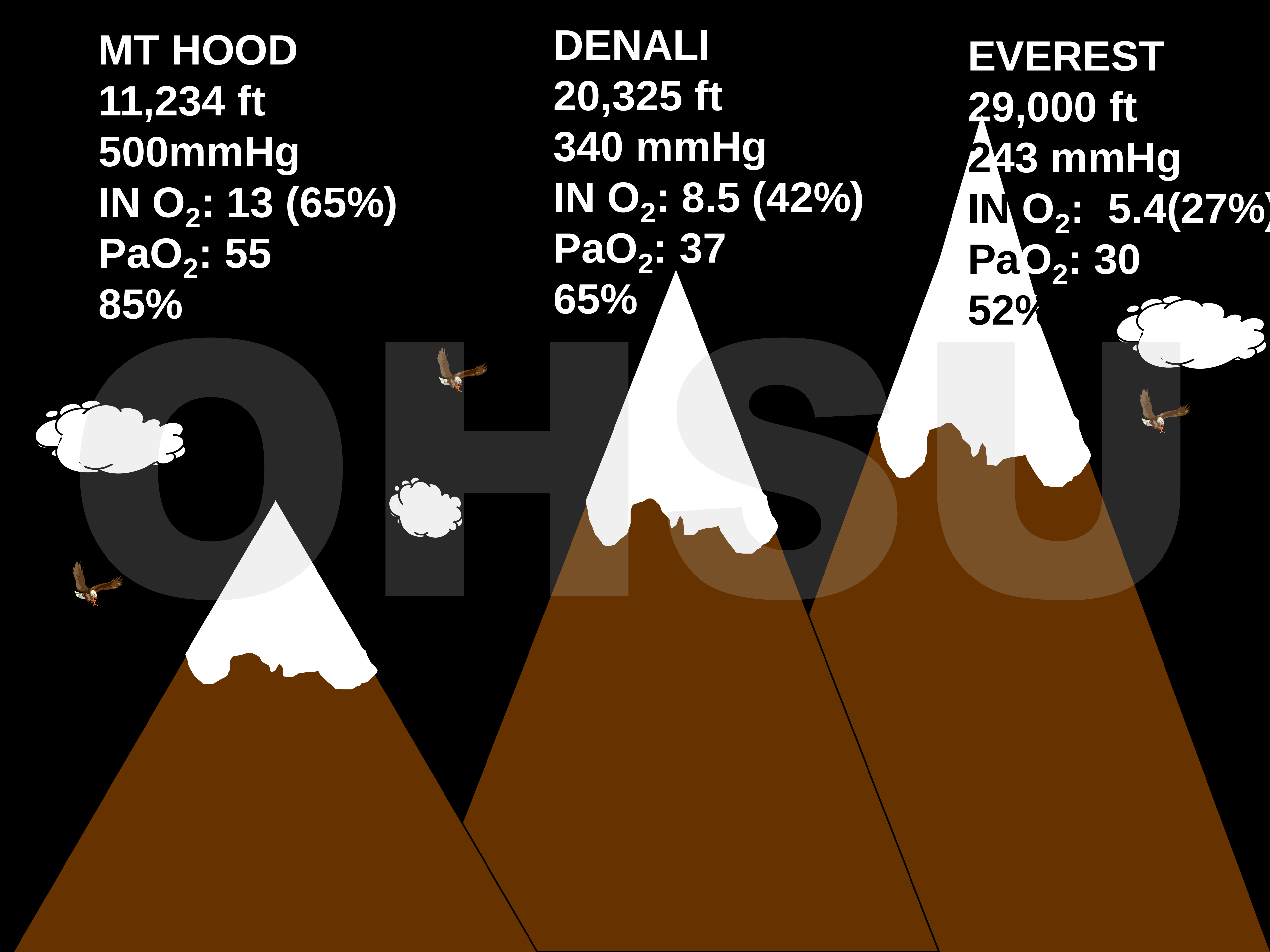
MT HOOD
11,234 ft
500mmHg
IN O_2: 13 (65%)
PaO_2: 55
85%
DENALI
20,325 ft
340 mmHg
IN O_2: 8.5 (42%)
PaO_2: 37
65%
EVEREST
29,000 ft
243 mmHg
IN O_2: 5.4(27%)
PaO_2: 30
52%
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High Altitude

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

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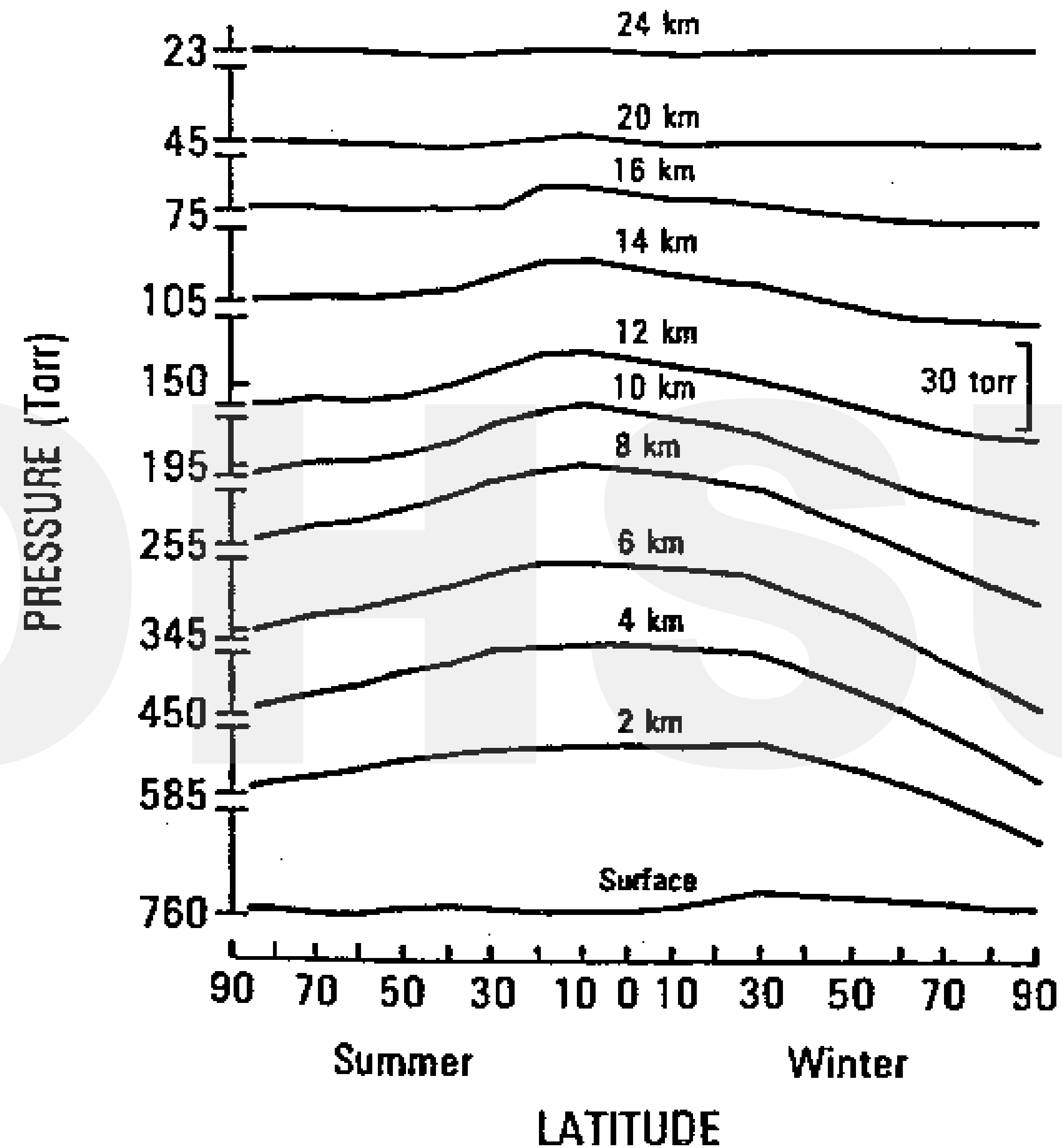
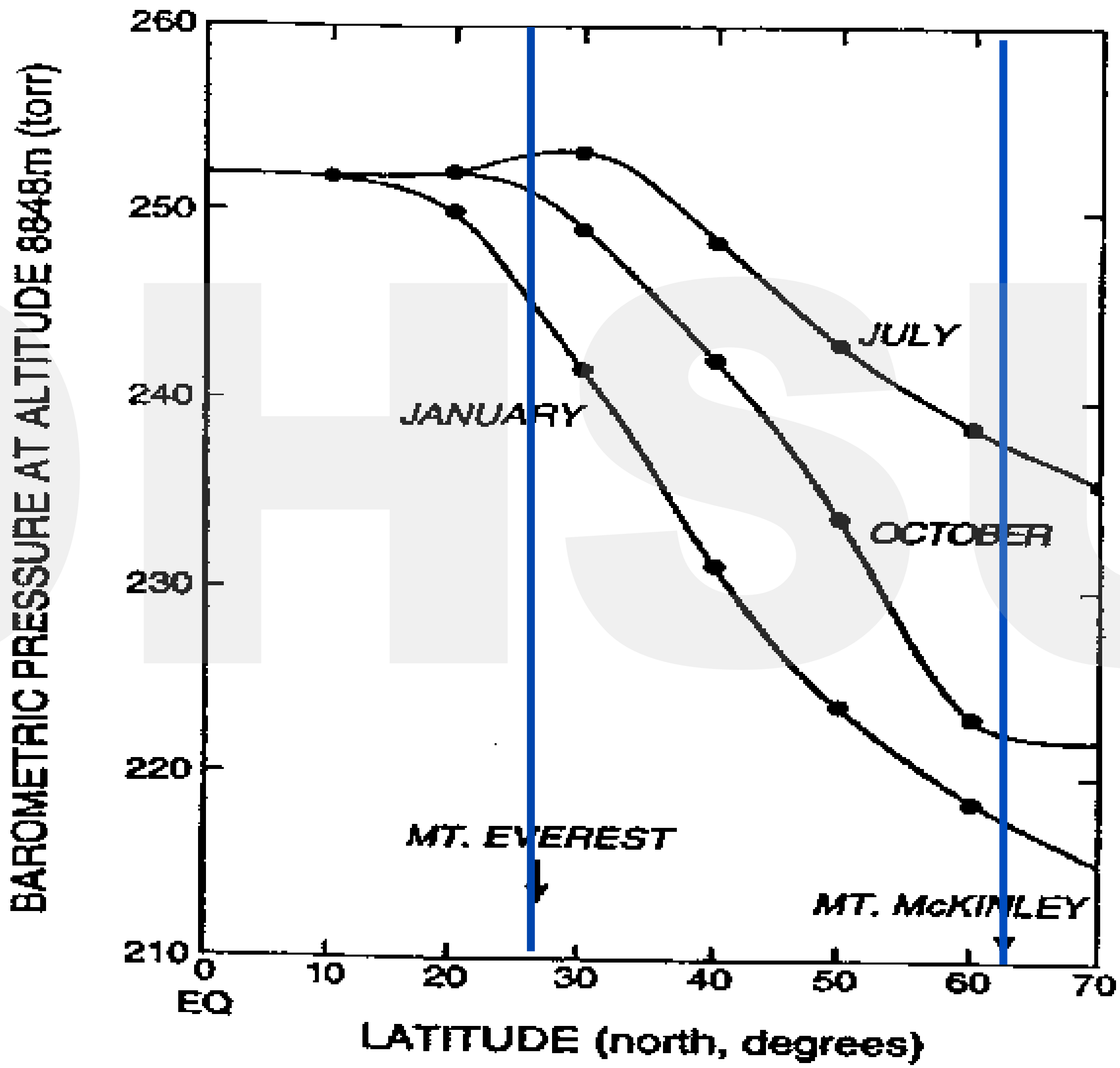
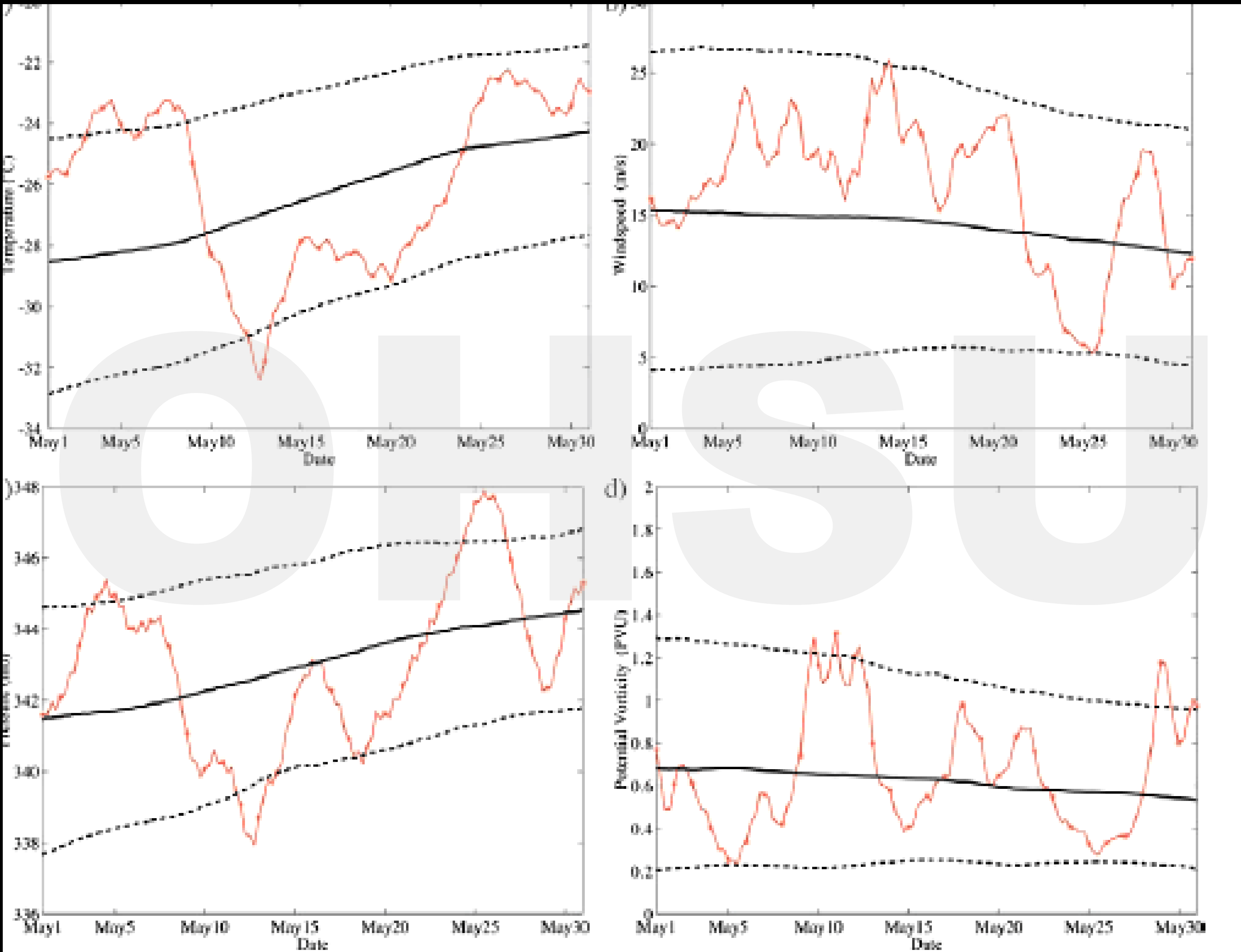


24 km
20 km
16 km
14 km
12 km
10 km
8 km
6 km
4 km
2 km
Surface
30 torr
PRESSURE (Torr)
23
45
75
105
150
195
255
345
450
585
760
90 70 50 30 10 0 10 30 50 70 90
Summer
Winter
LATITUDE


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


-22
-24
-26
-28
-30
-32
-34
May1
May5
May10
May15
May20
May25
May30
Date
25
20
15
10
5
0
Windspeed (m/s)
d)
348
346
344
342
340
338
336
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

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.

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Photo: Lindsey Fell

How do we Adapt to Hypoxia???

Increase oxygen delivery to tissues

Chain of Oxygen

- Lungs
- Blood
- Tissue

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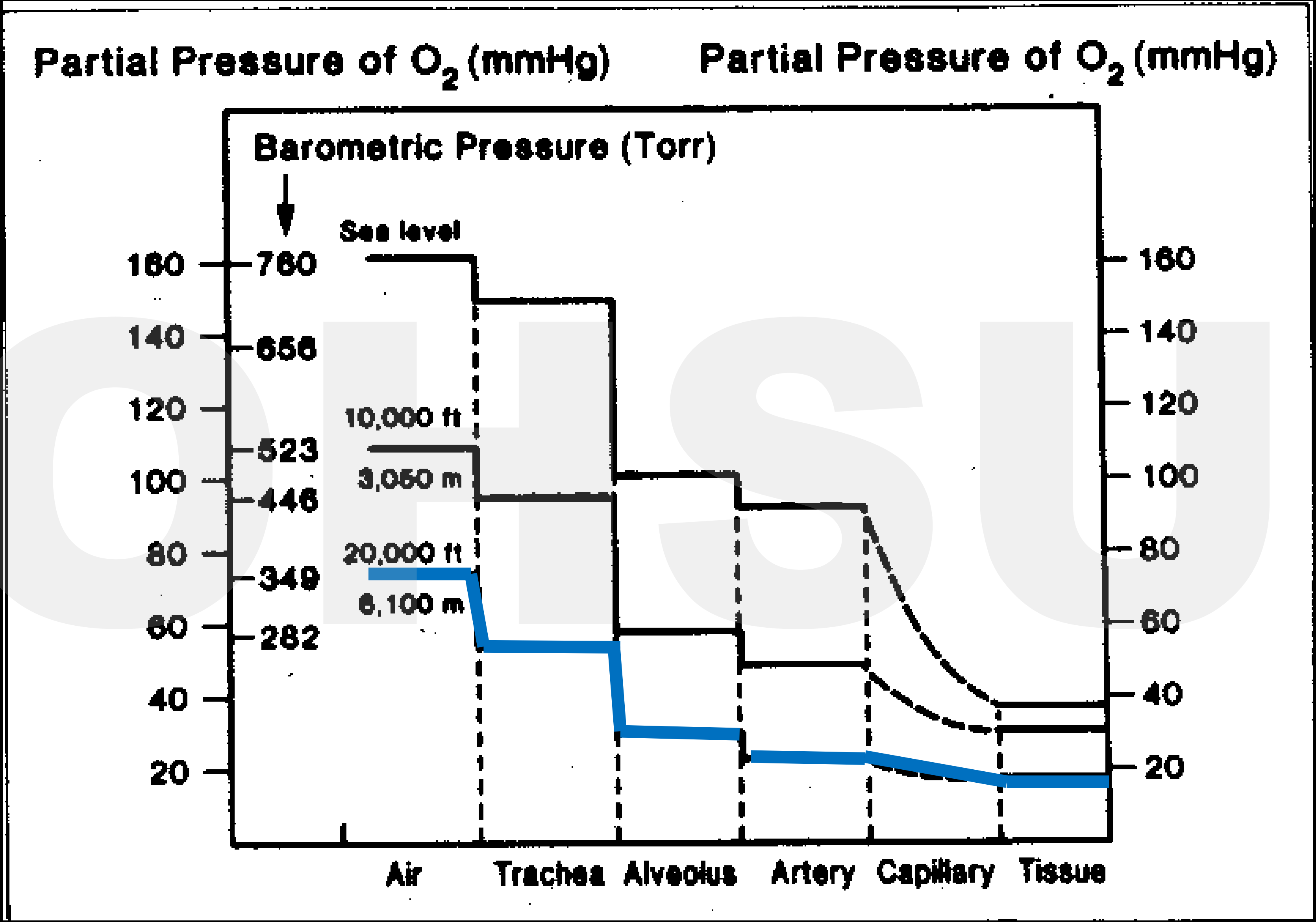
Partial Pressure of O_2 (mmHg)
Partial Pressure of O_2 (mmHg)
Barometric Pressure (Torr)
Sea level
10,000 ft
3,050 m
20,000 ft
6,100 m
160
140
120
100
80
60
40
20
760
656
523
446
349
282
Air
Trachea
Alveolus
Artery
Capillary
Tissue
OHSU

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

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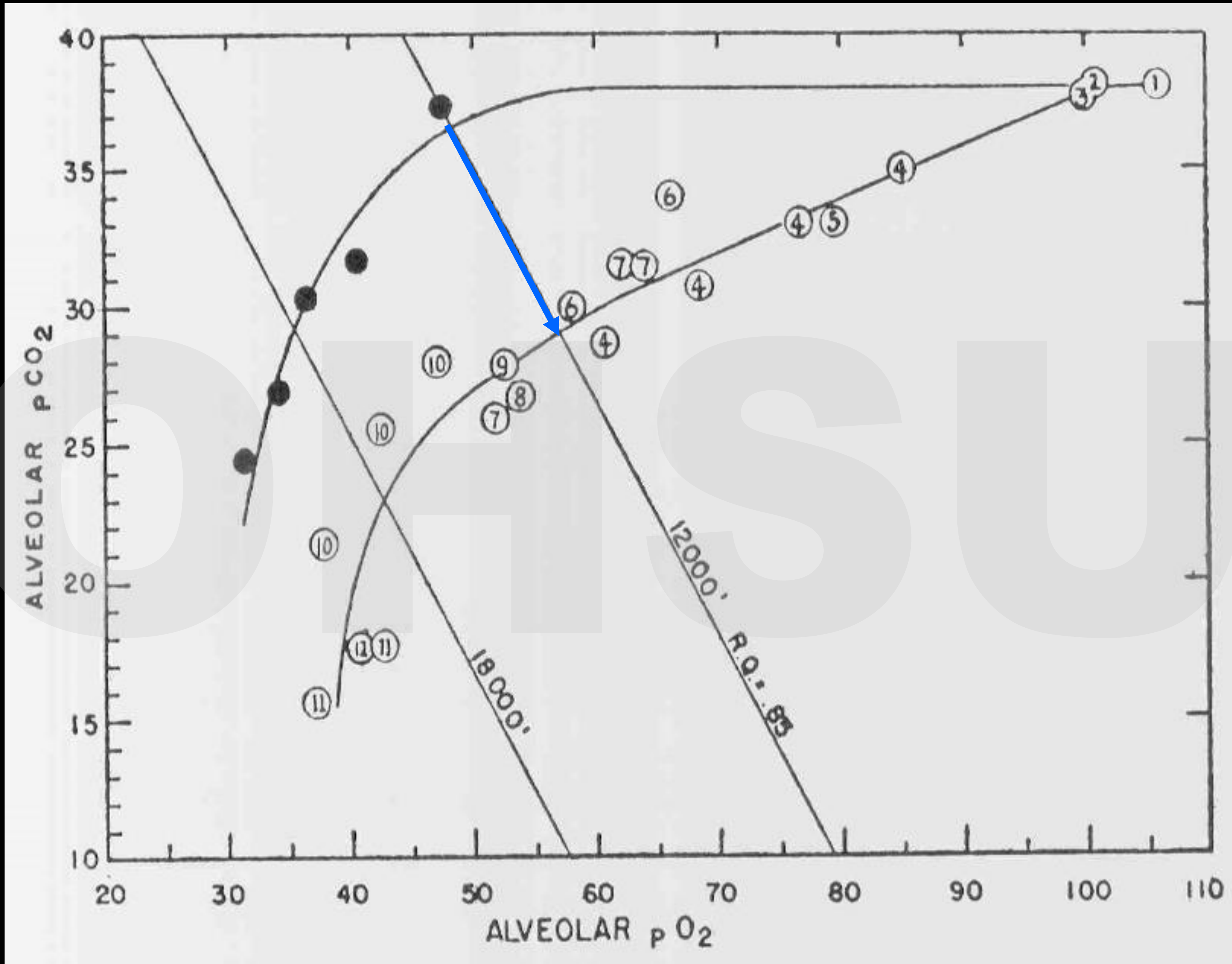
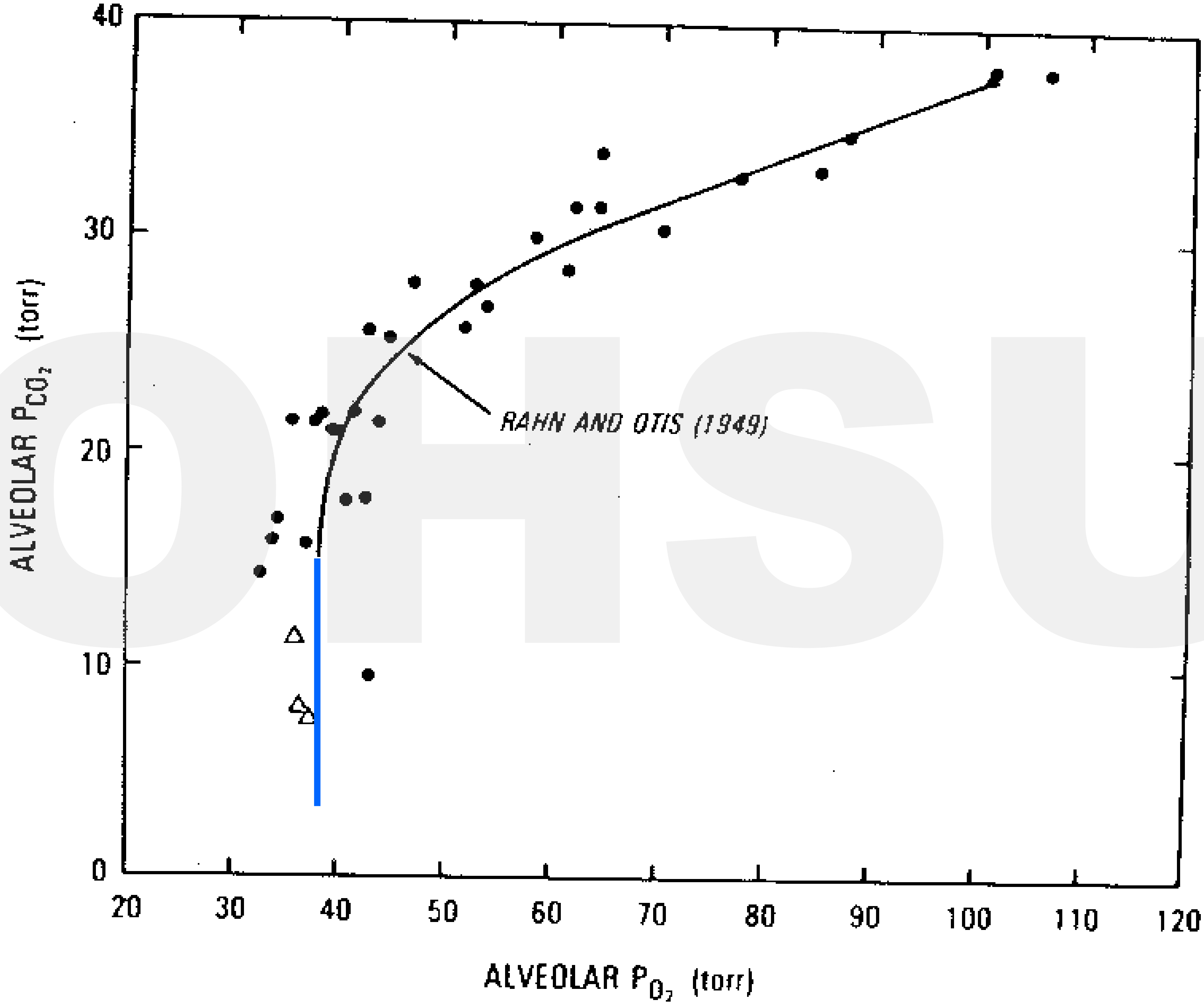


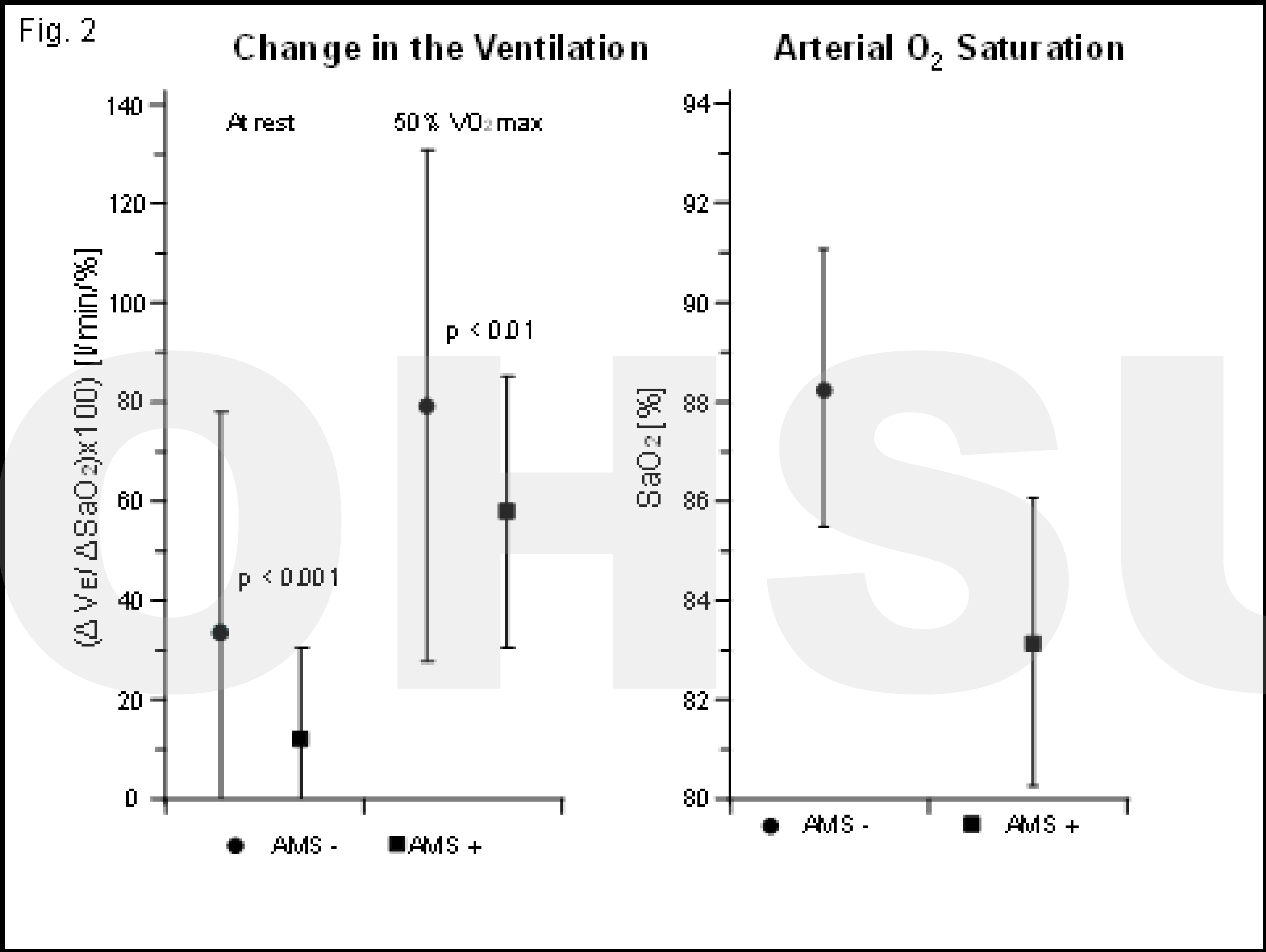
40
35
30
25
20
15
10
20
30
40
50
60
70
80
90
100
110
ALVEOLAR pCO2
ALVEOLAR pO2
12000'
R.Q. = .85
18000'
OHSU



ALVEOLAR P_{CO_2} (torr)
40
30
20
10
0
RAHN AND OTIS (1949)
20
30
40
50
60
70
80
90
100
110
120
ALVEOLAR P_{O_2} (torr)

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

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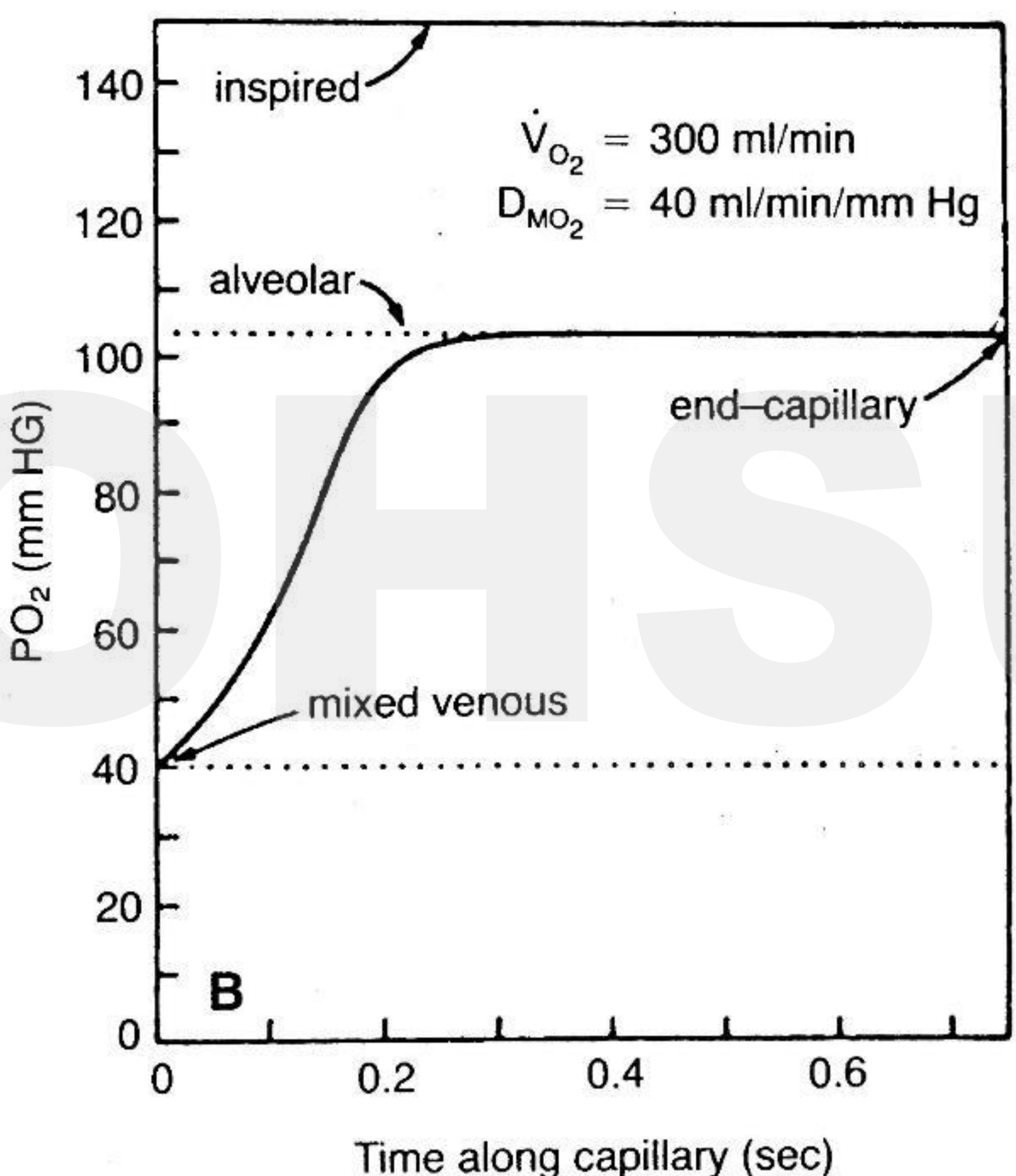
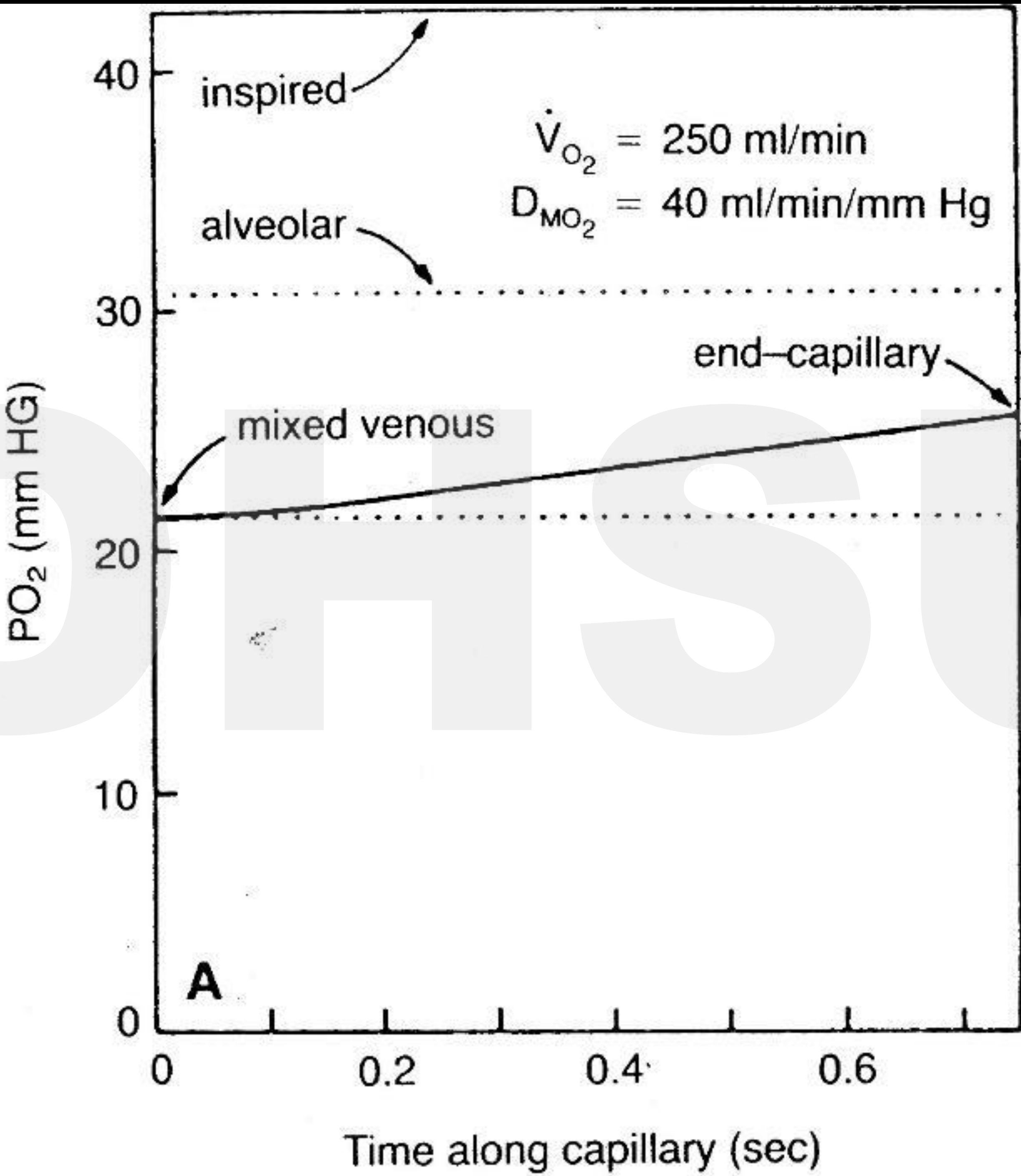


inspired
$\dot{V}_{O_2}$ = 300 ml/min
D_{MO_2} = 40 ml/min/mm Hg
alveolar
end–capillary
mixed venous
B
PO_2 (mm HG)
140
120
100
80
60
40
20
0
0
0.2
0.4
0.6
Time along capillary (sec)

OHSU



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
0.2
0.4
0.6
PO2 (mm HG)
Time along capillary (sec)

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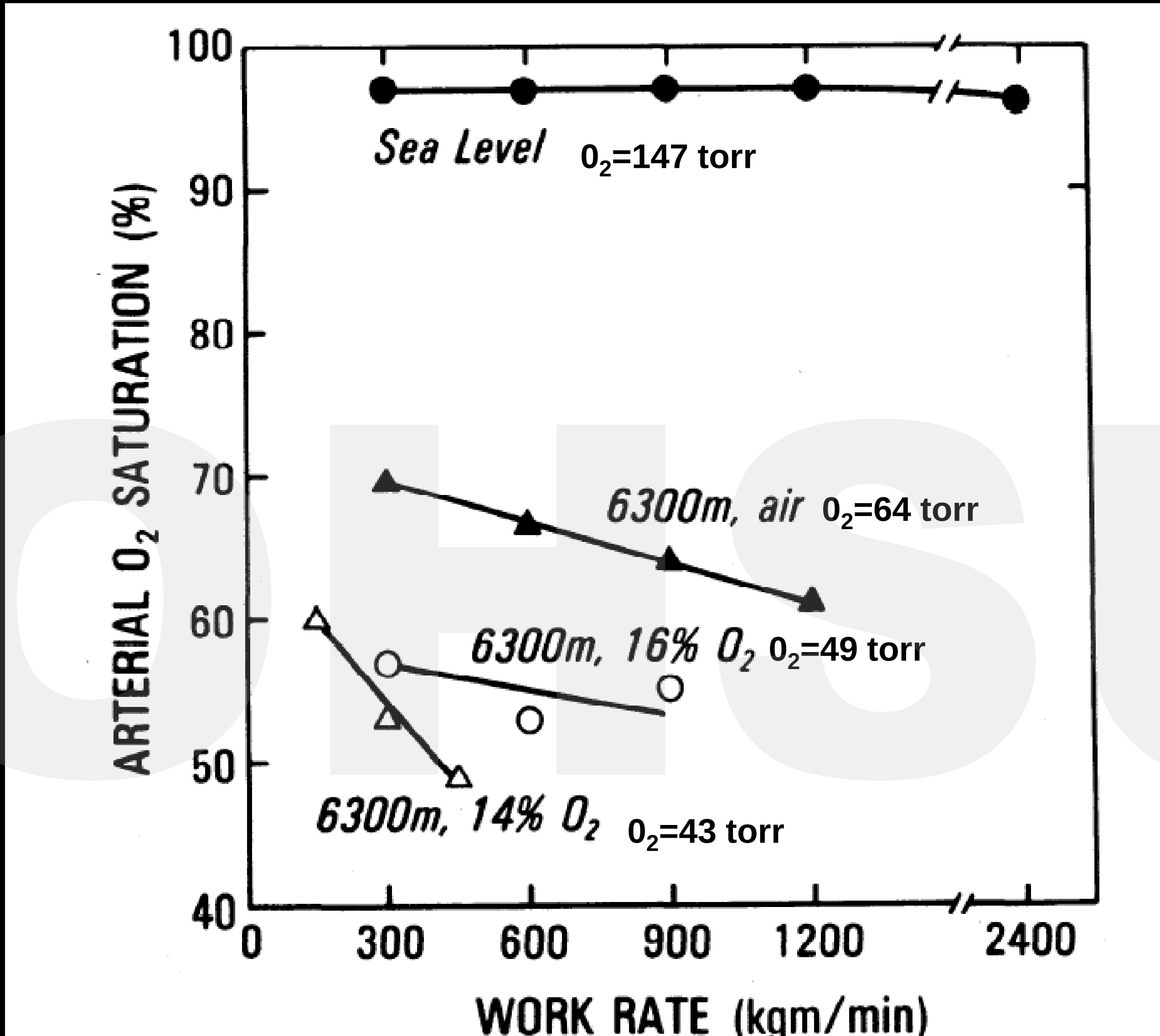

J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 55(3): 688–698, 1983.

Blood

- Changes in hematocrit
- Changes in oxygen disassociation curve

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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

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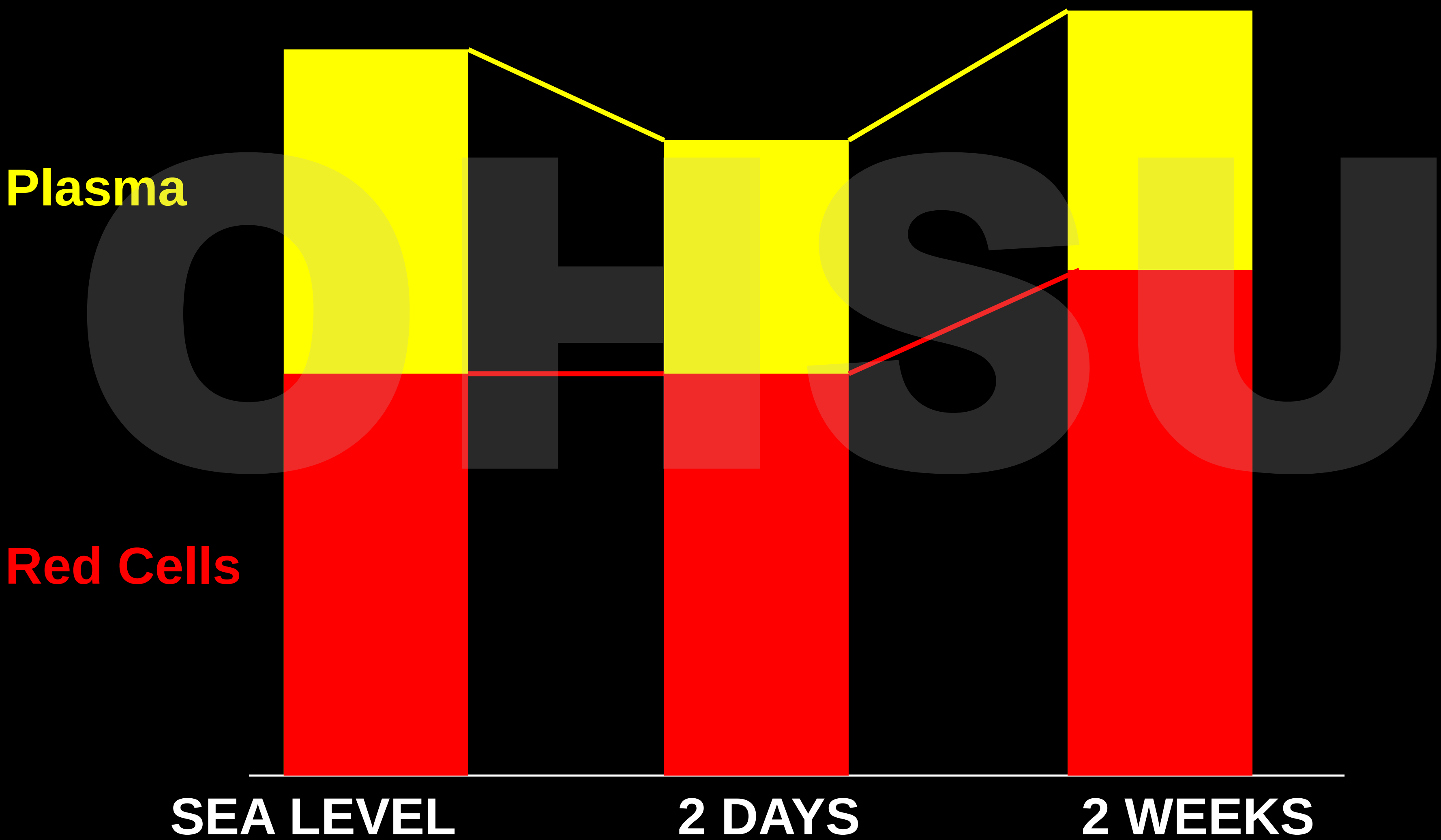

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Hematocrit at Heights

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

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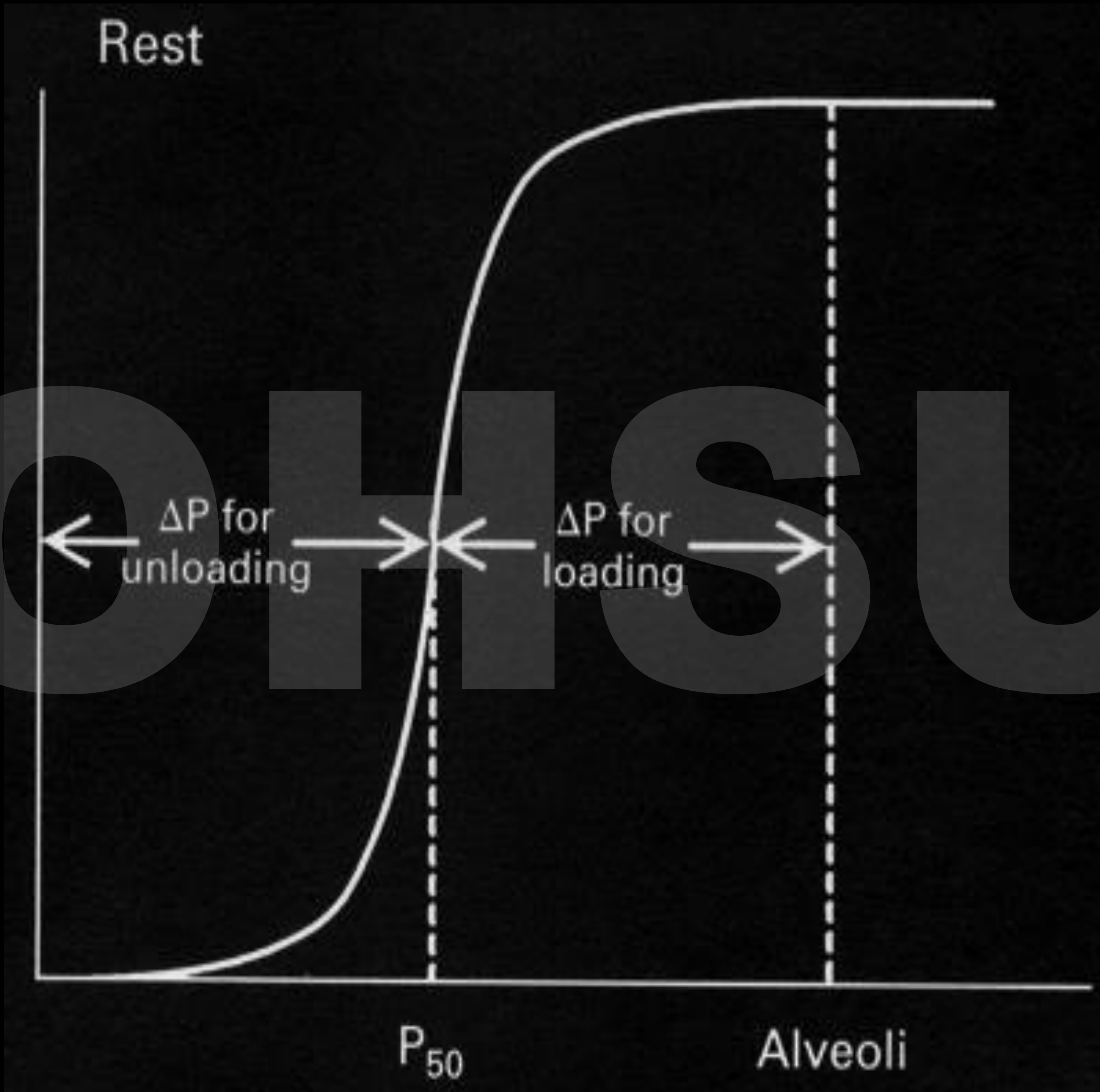
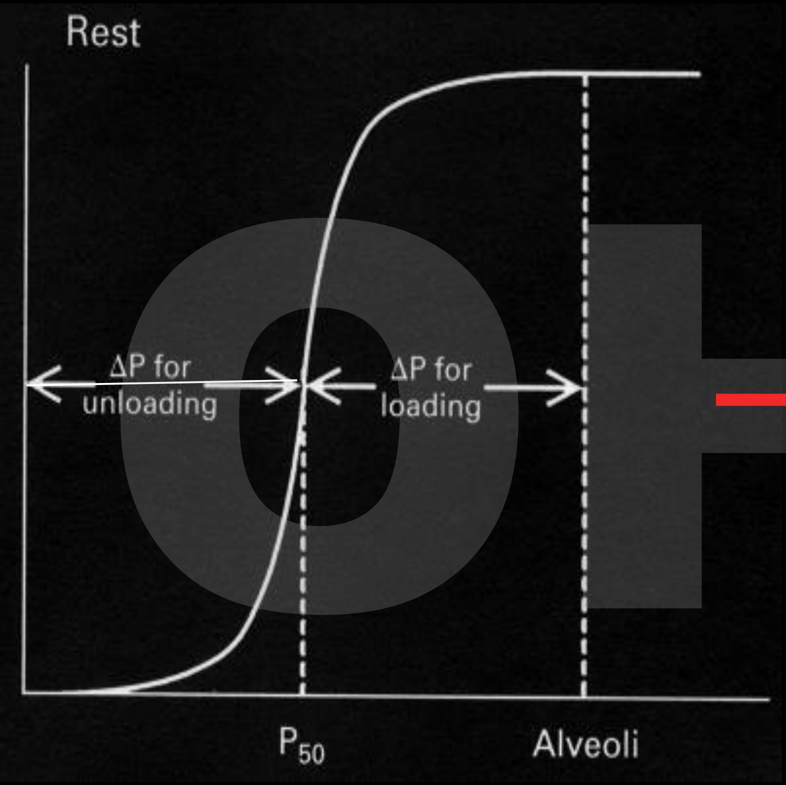
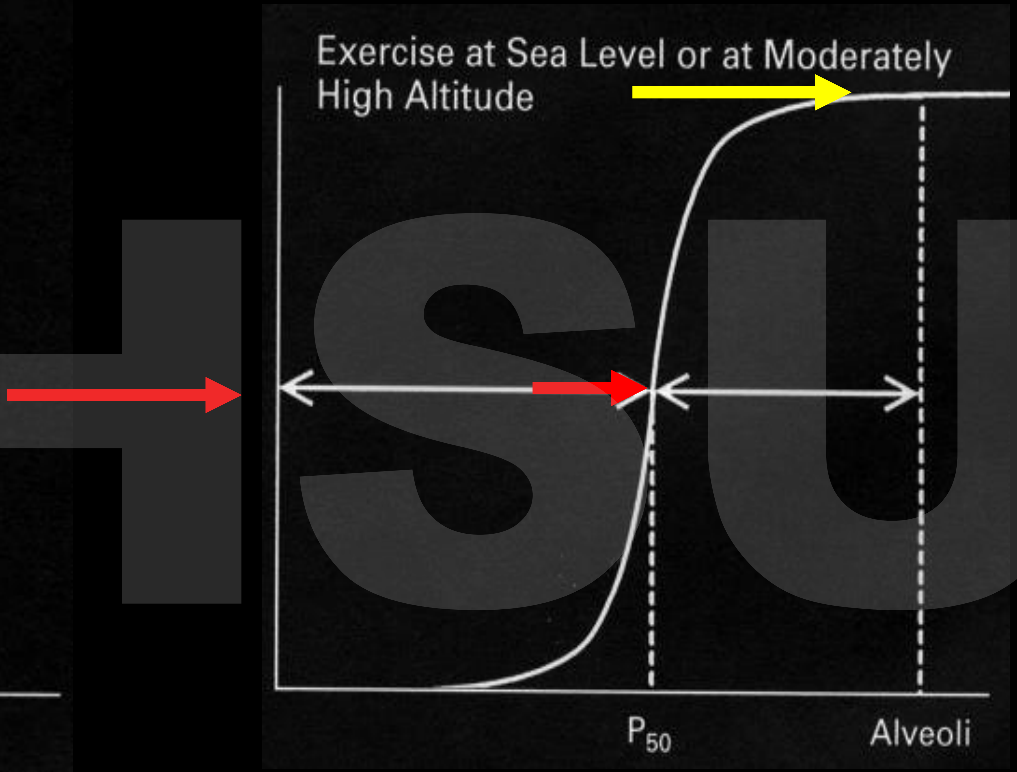
O_2 Disassociation Curve Changes

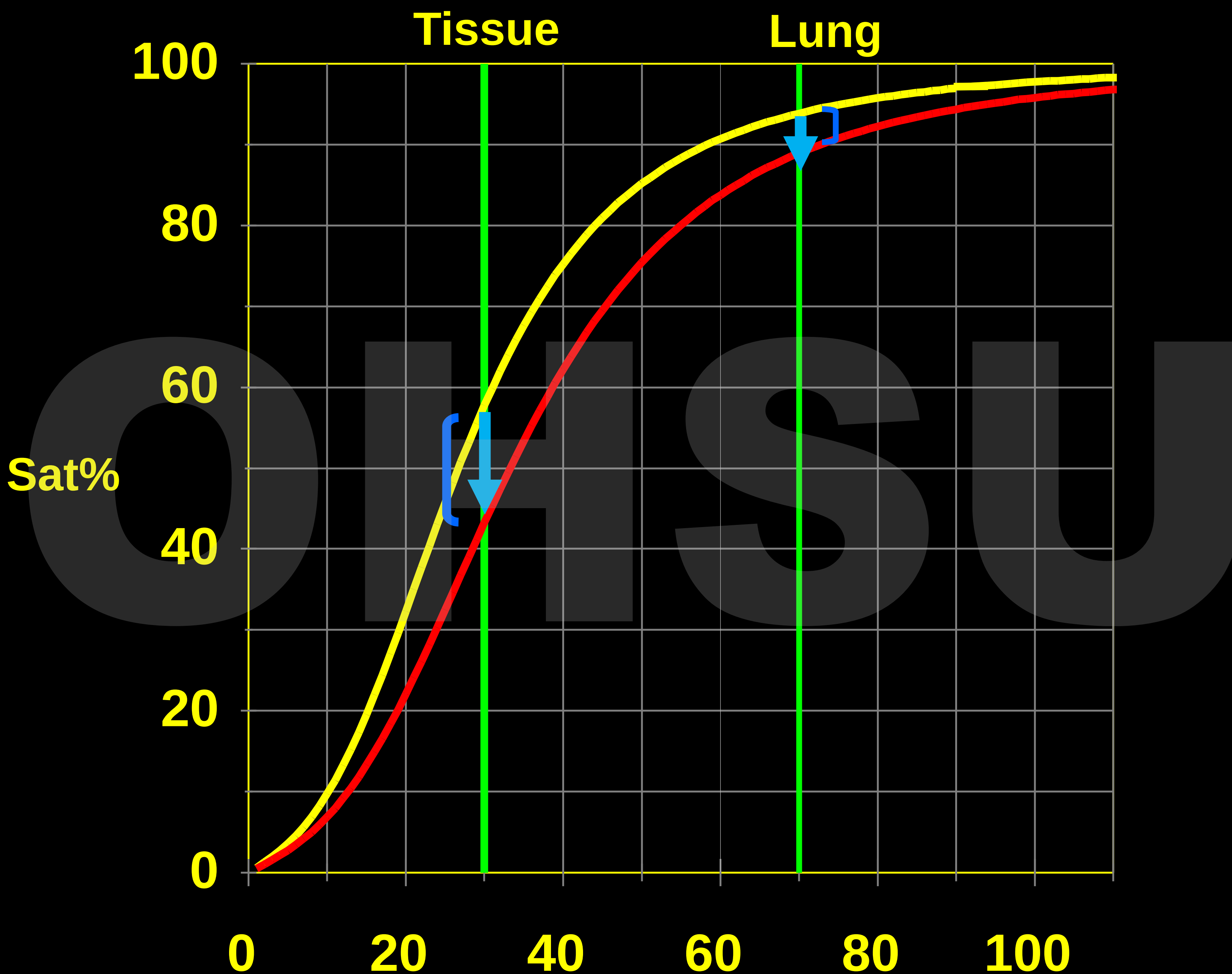


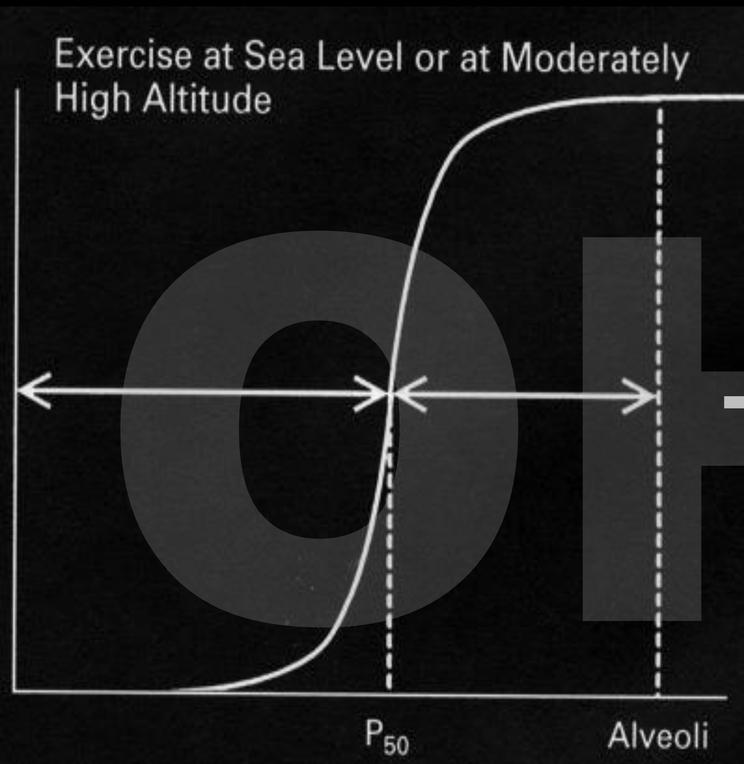
Rest
ΔP for unloading
ΔP for loading
P50
Alveoli
OHSU

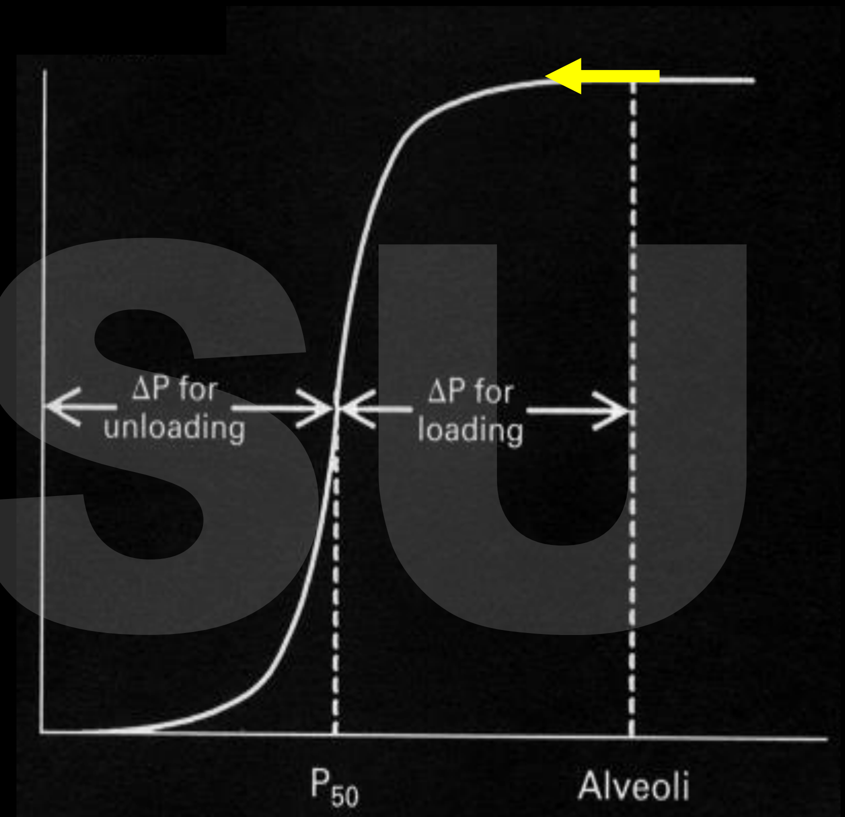




Decreased affinity for Oxygen


Tissue
Lung
100
80
60
40
20
0
Sat%
0
20
40
60
80
100
OHSU





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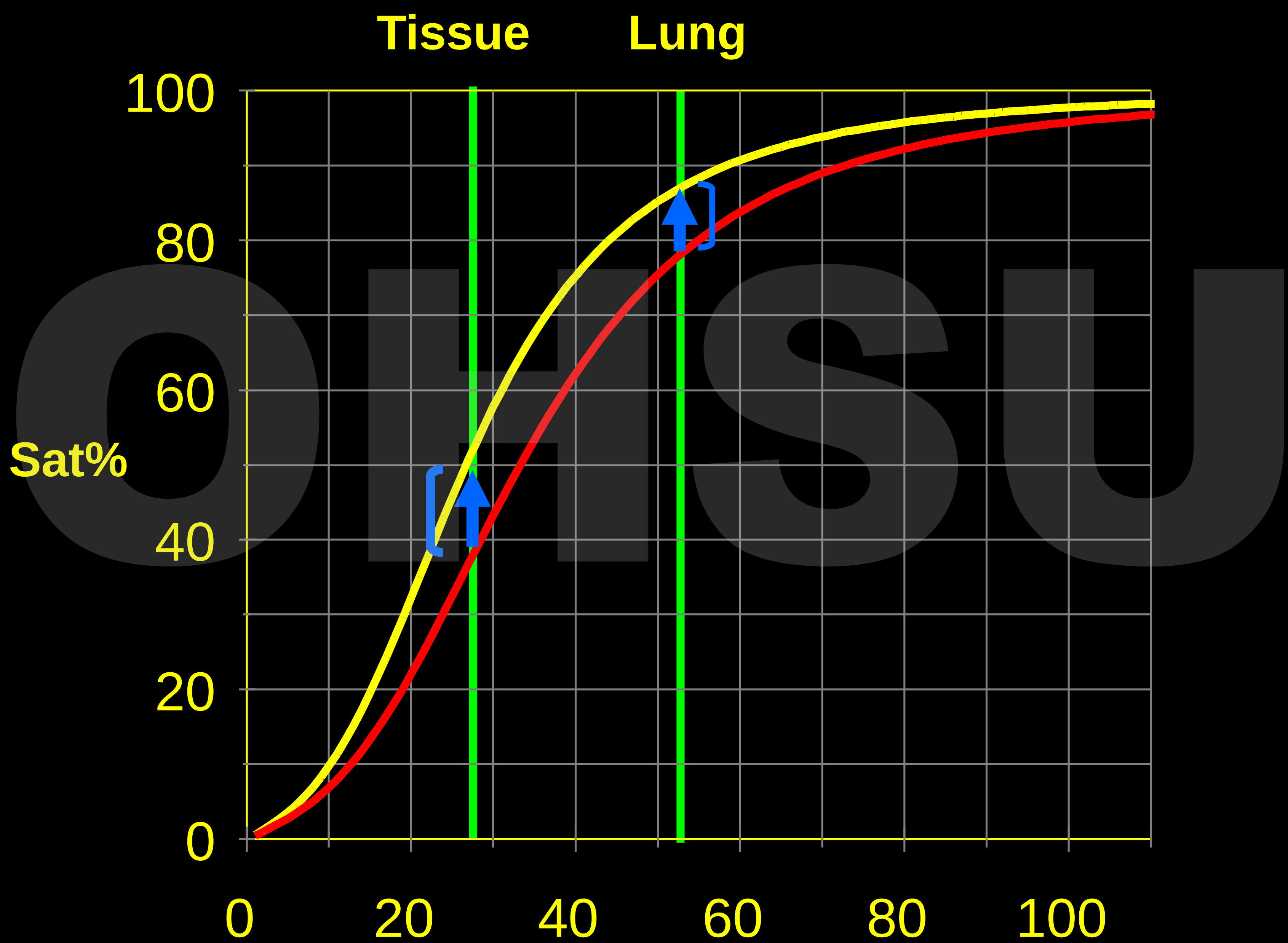
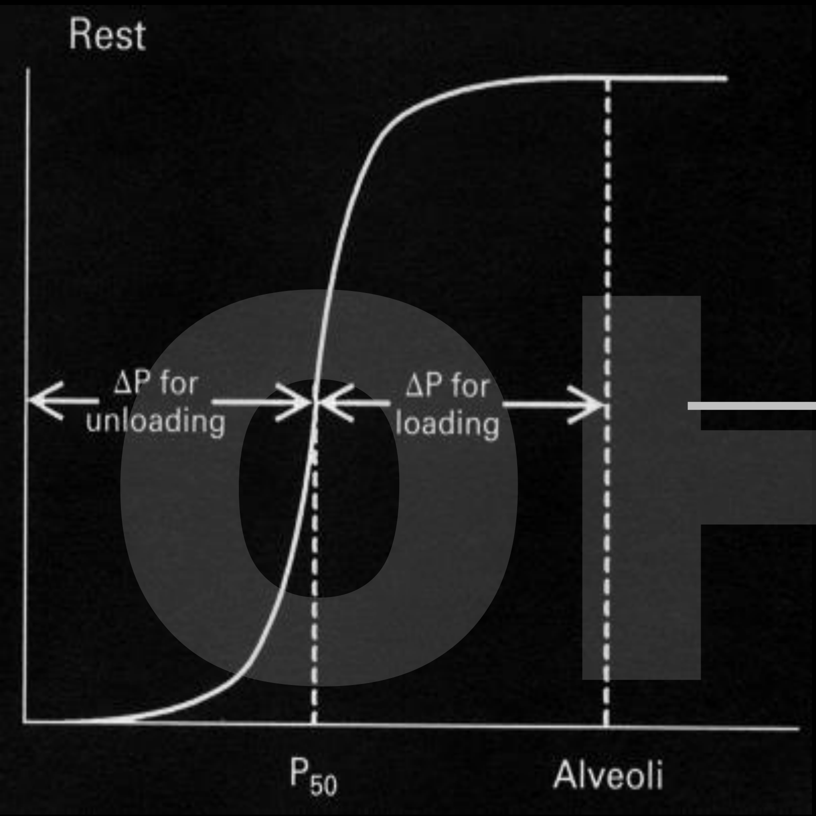
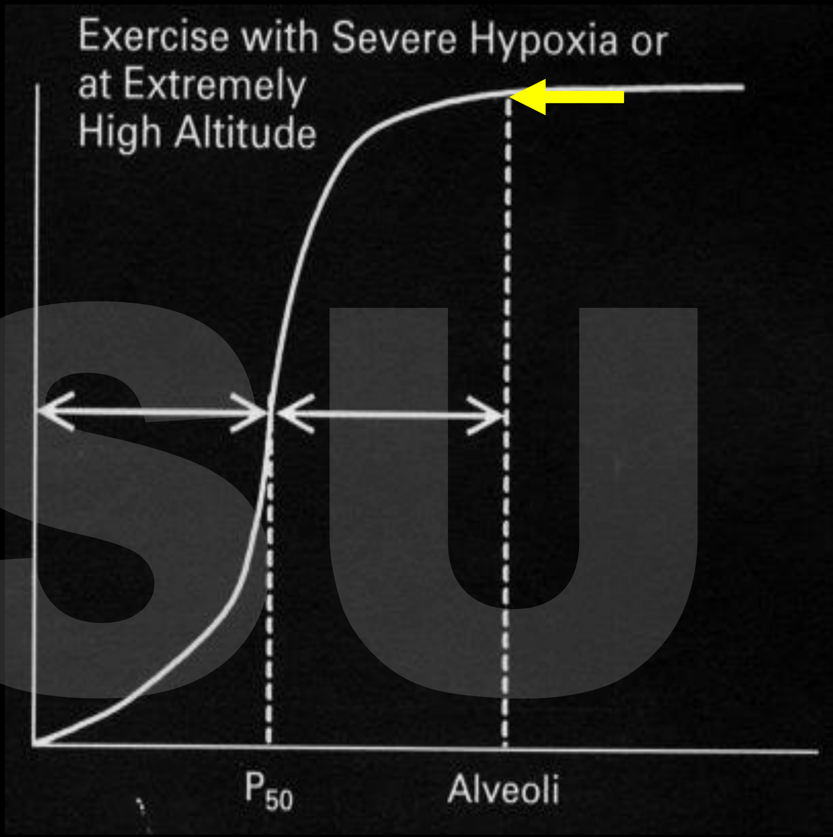
Baseline affinity for Oxygen



Tissue
Lung
100
80
60
40
20
0
Sat%
0
20
40
60
80
100

Photo: Tom Deitz





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Increased affinity for Oxygen

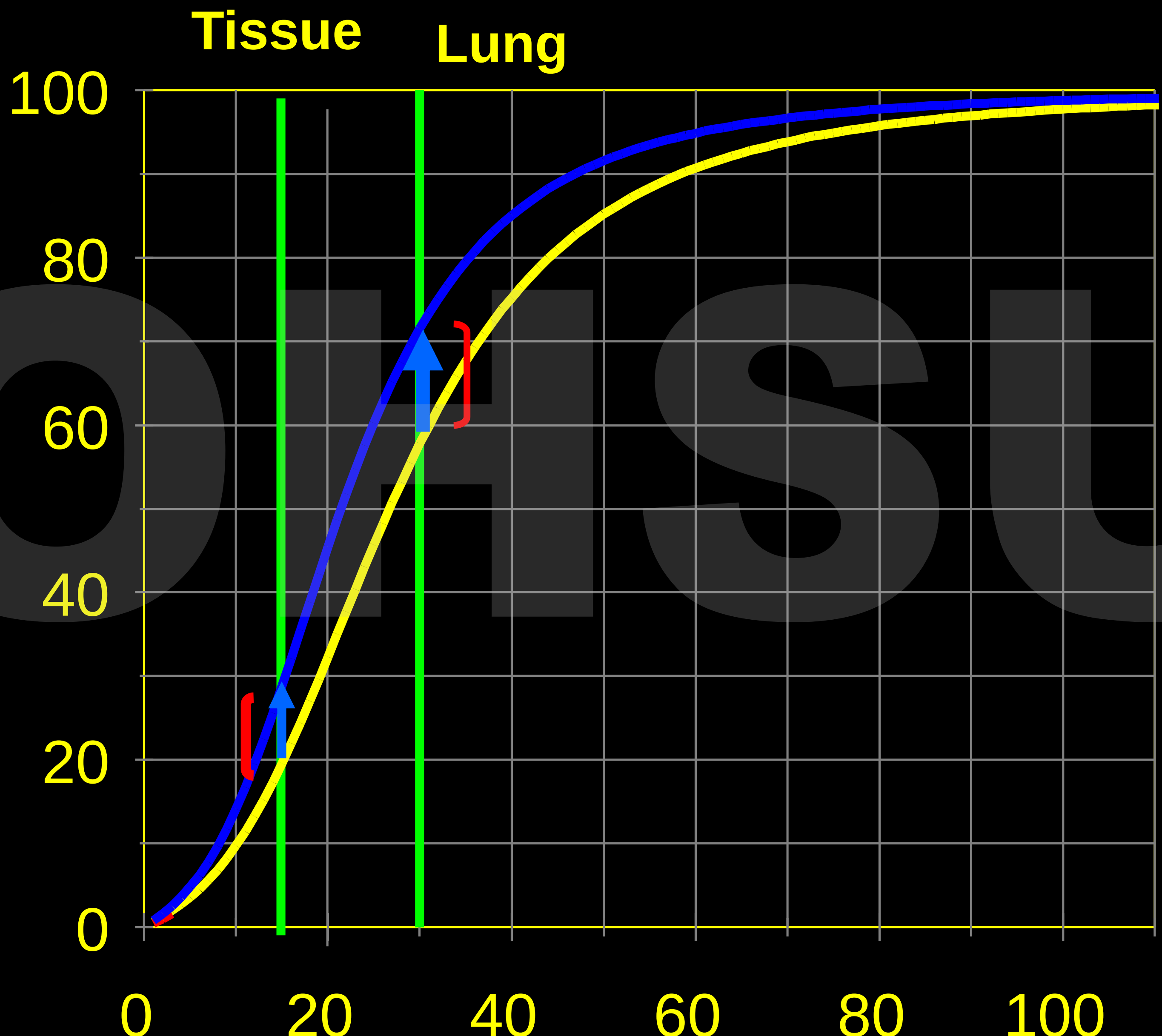

Tissue
Lung
100
80
60
40
20
0
0
20
40
60
80
100

Photo: Deb Robertson

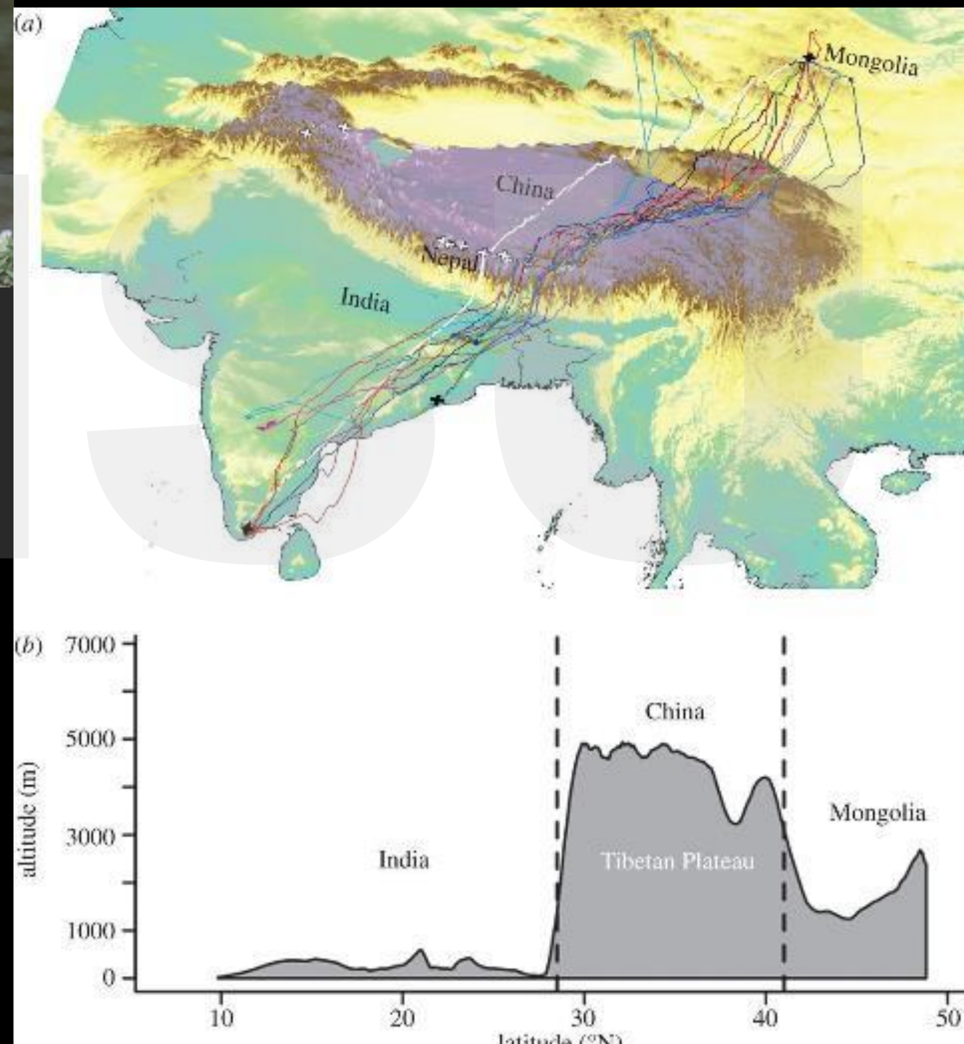
Evidence Increase O_2 Affinity is Beneficial

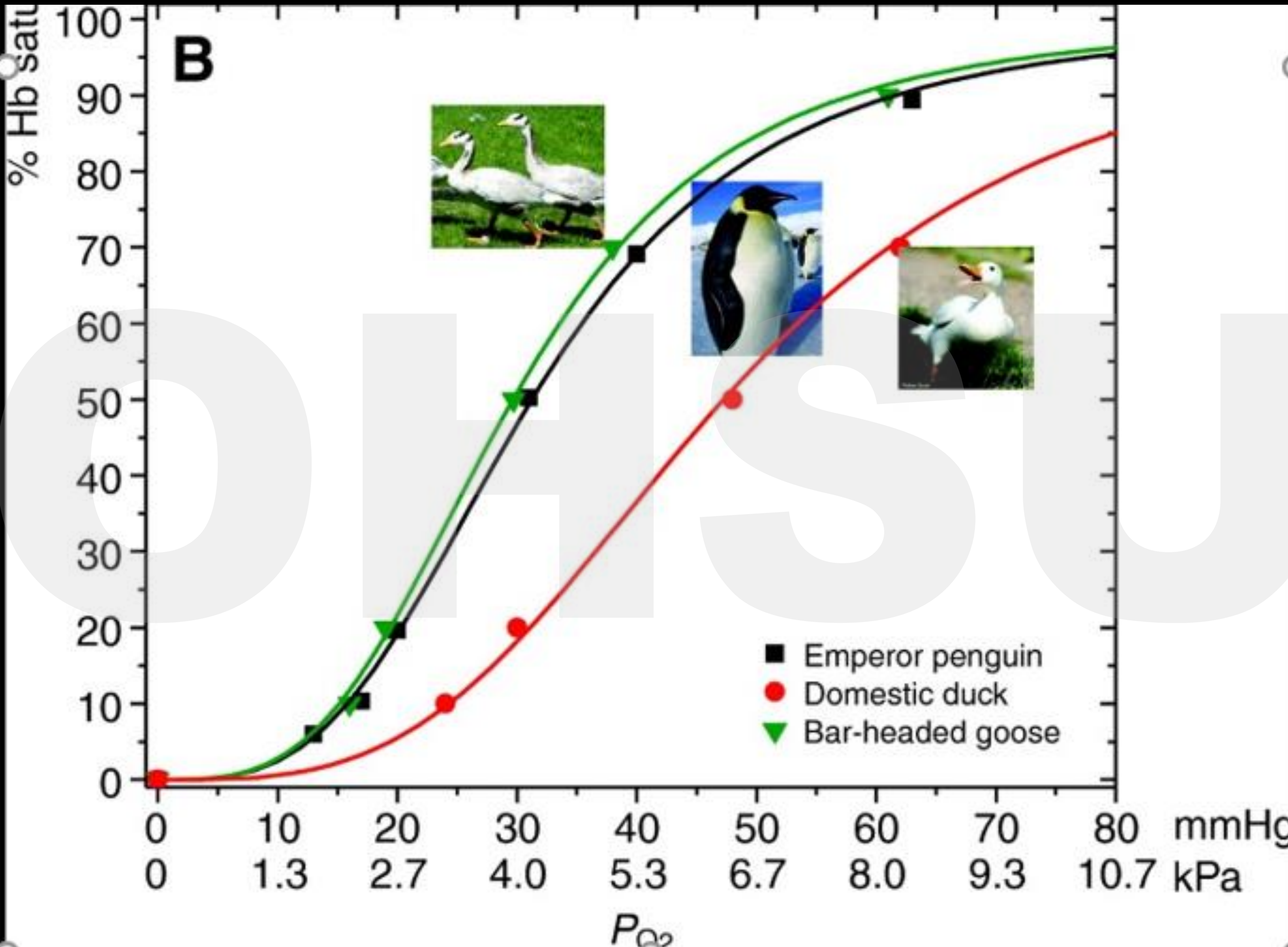
- High altitude animals
  - Sheep with high affinity polymorphism
- Human studies
- "Human llamas" study

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)



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_{O2}
Emperor penguin
Domestic duck
Bar-headed goose
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Tibetans

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

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EPAS1 (HIF-2α)

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

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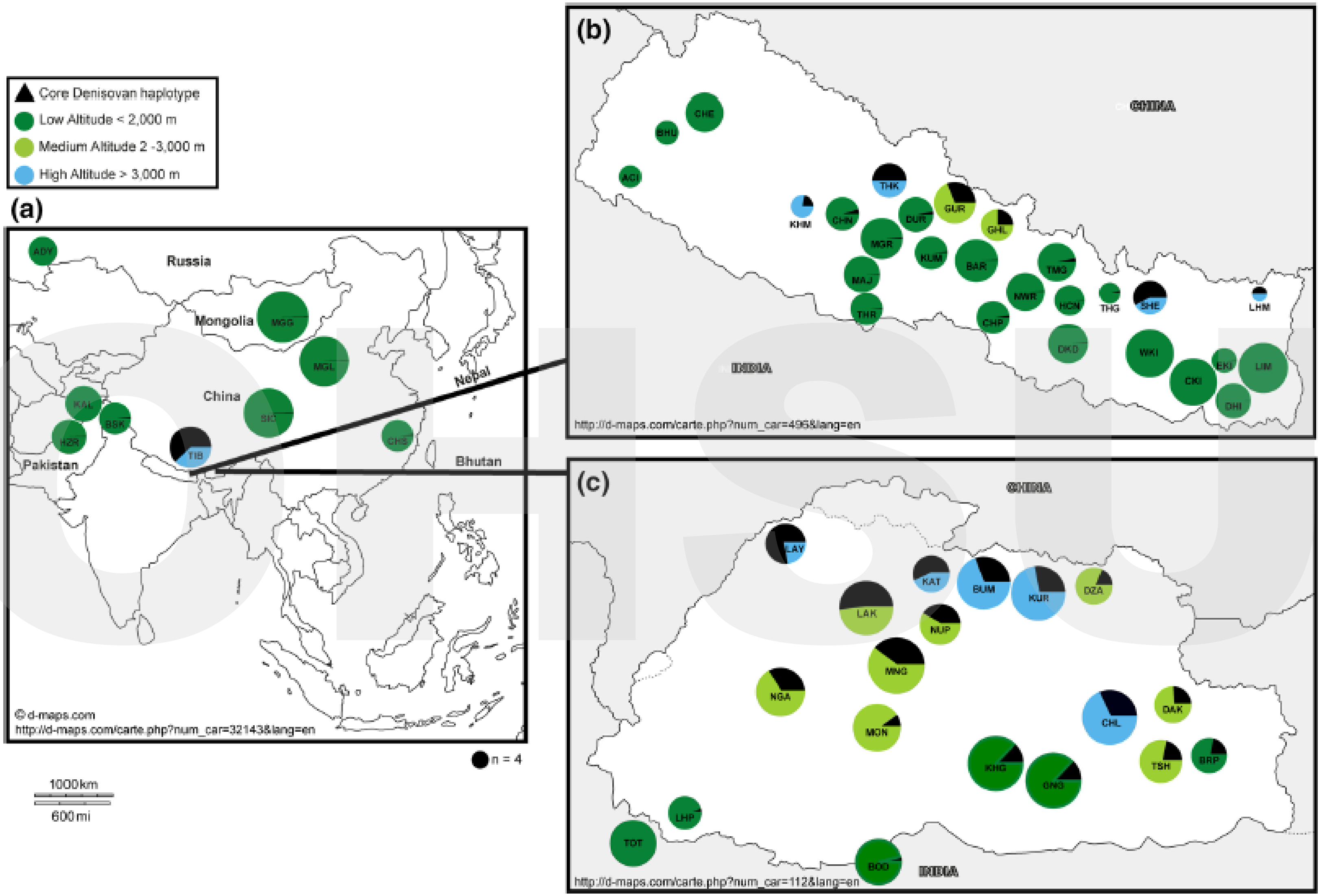
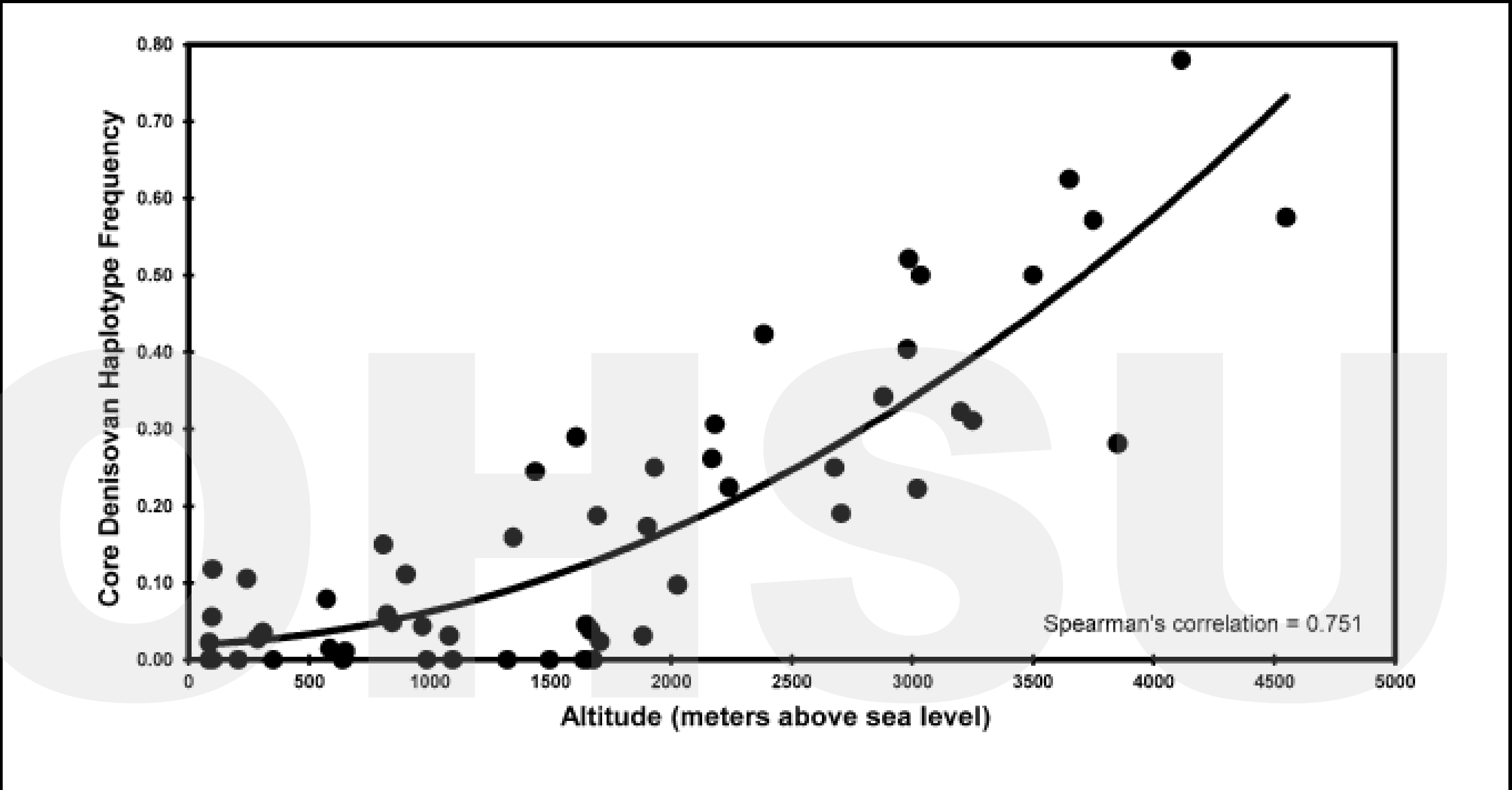


Hum Genet (2016) 135:393–402



Hum Genet (2016) 135:393–402

Other Mutations

- EGLN1 (PHD)
  - Reduced HIF pathway sensitivity to hypoxia

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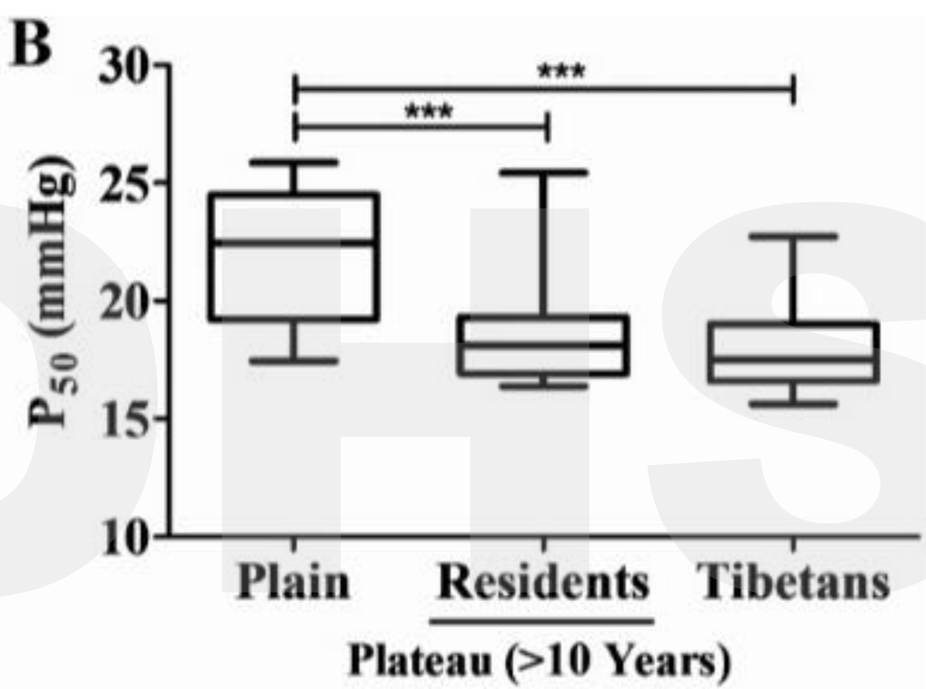

HEMATOLOGY, 2018
VOL. 23, NO. 5, 309–313

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Tissues

- Increase capillary density
- Decrease muscle mass

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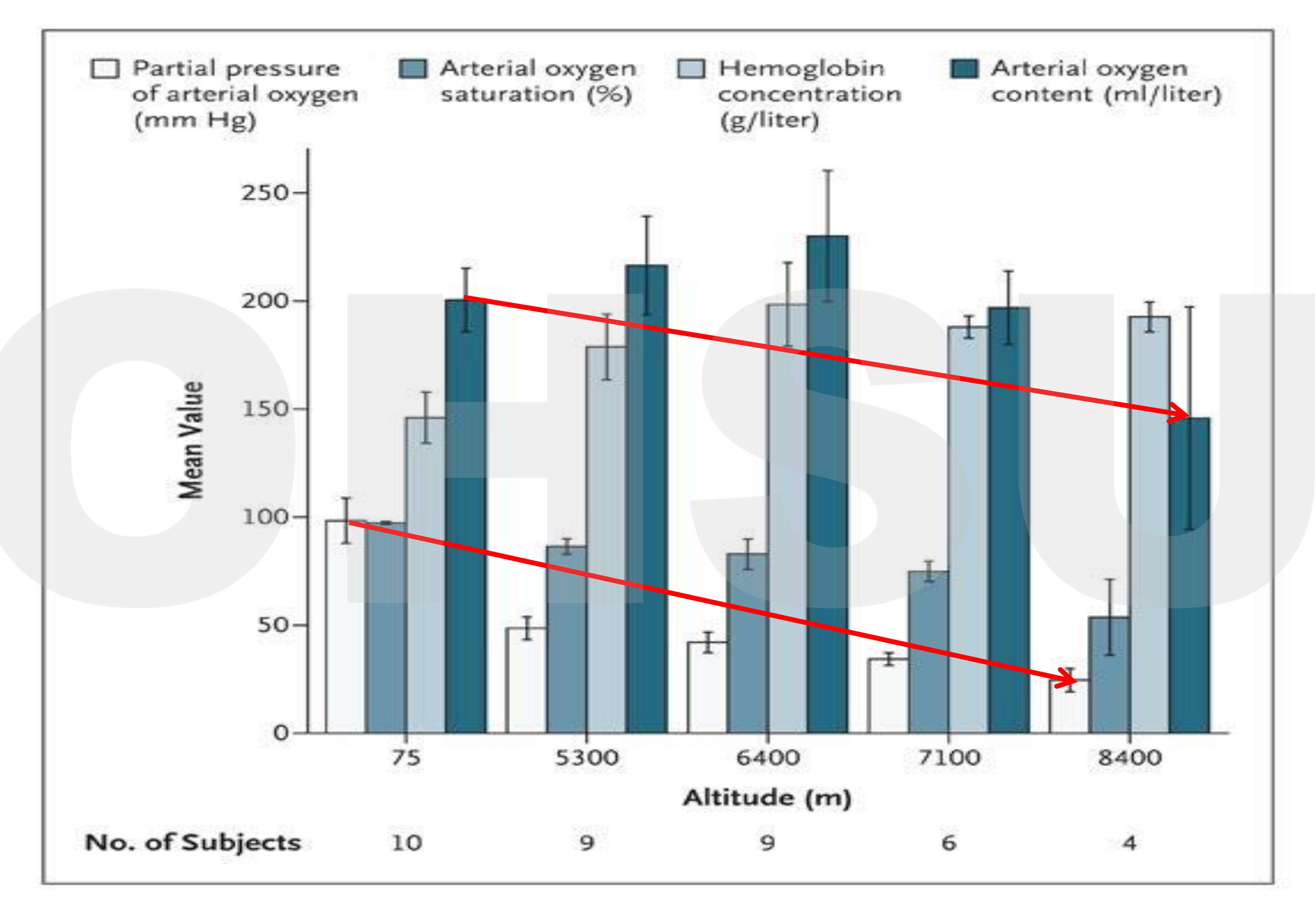
Photo: Lindsey Fell



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. 1	2	3	4	Group Mean
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)

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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

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Acute Mountain Sickness

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

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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

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Grading of AMS

- <u>Lake Louise criteria</u>
  - 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)

<u>AMS:</u>

Headache plus:

Self-reported $\geq$ 4

Total > 5

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Therapy

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

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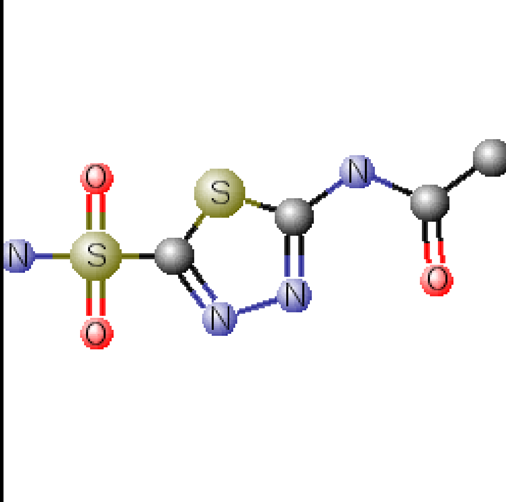
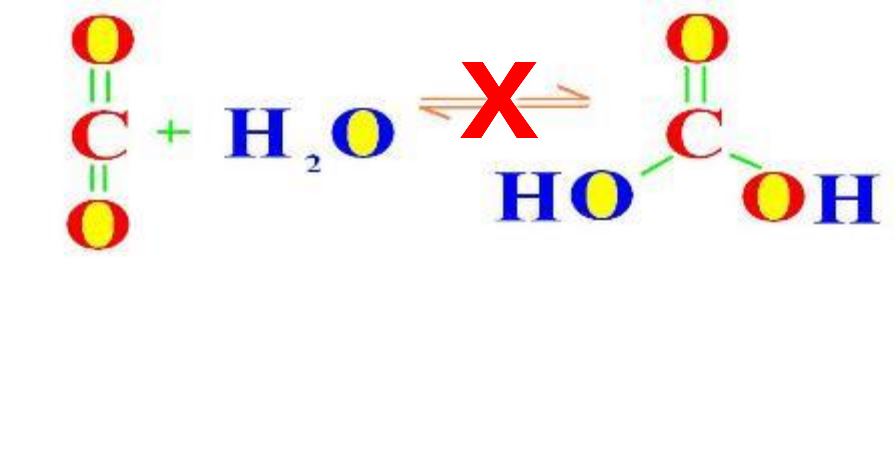
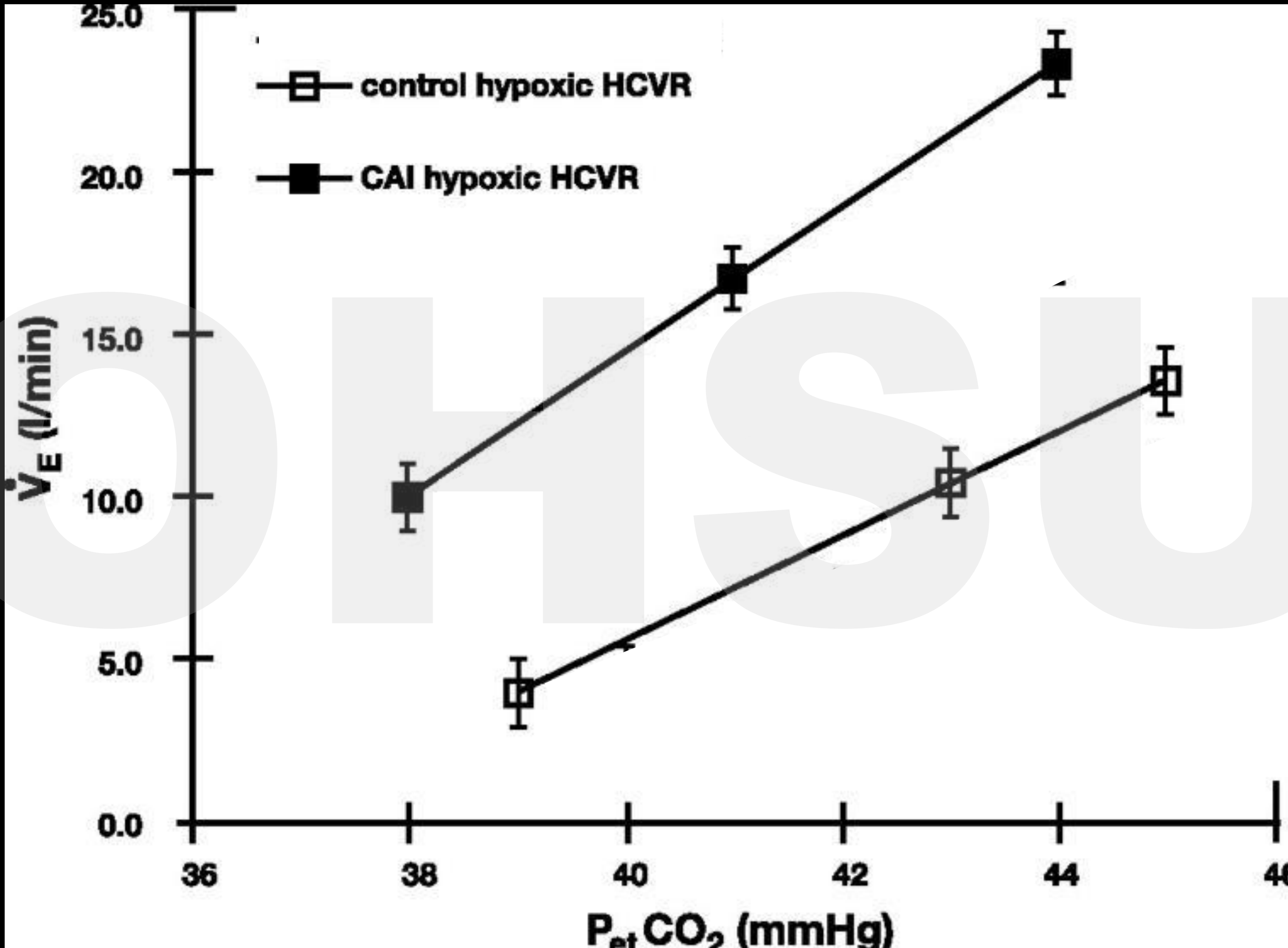
Acetazolamide



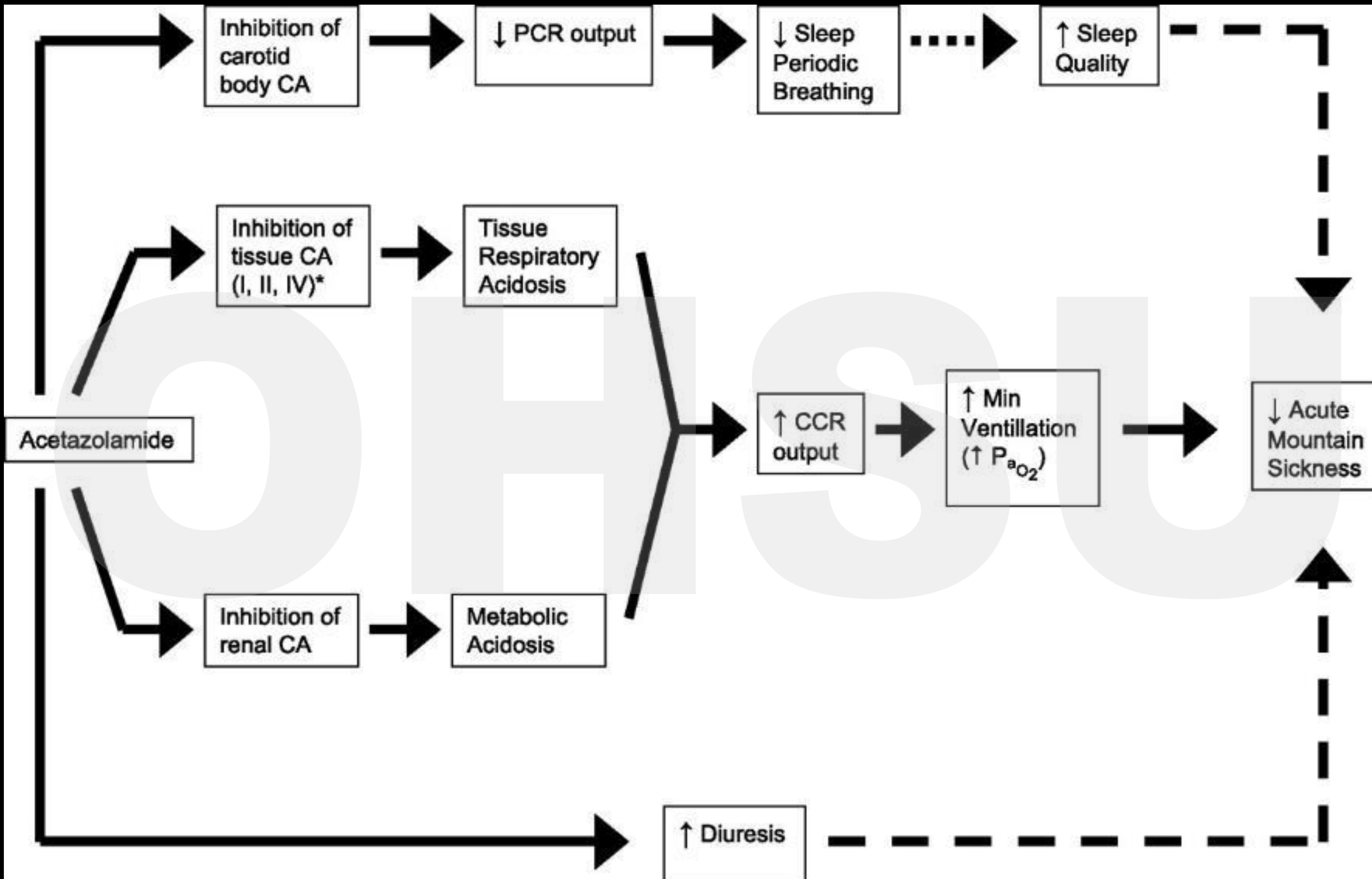
- Carbonic anhydrase inhibitor
  - Increases ventilation
  - Diuresis
- Speeds acclimatization
- Maintains oxygenation
- Treatment/prophylaxis



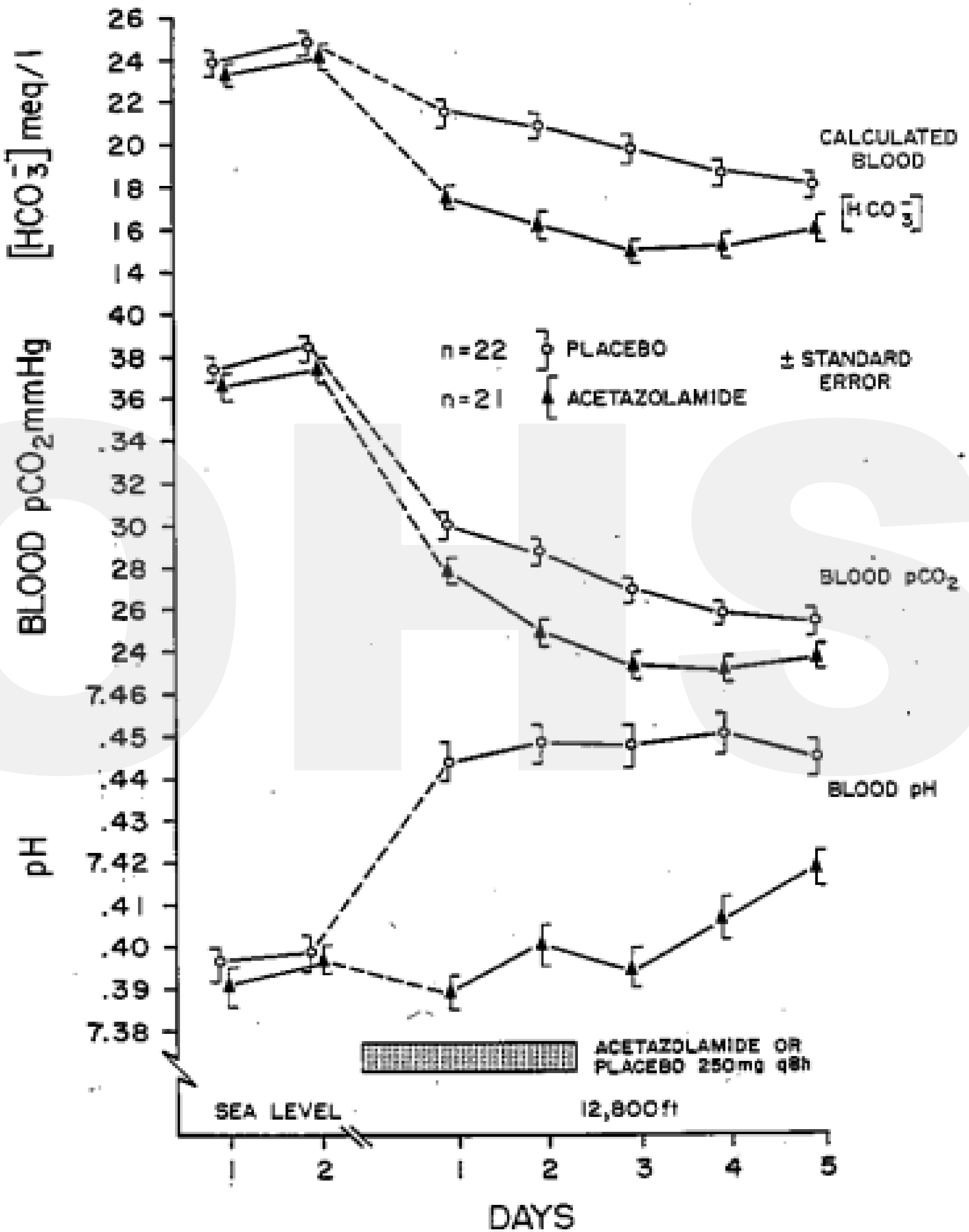
OHSU



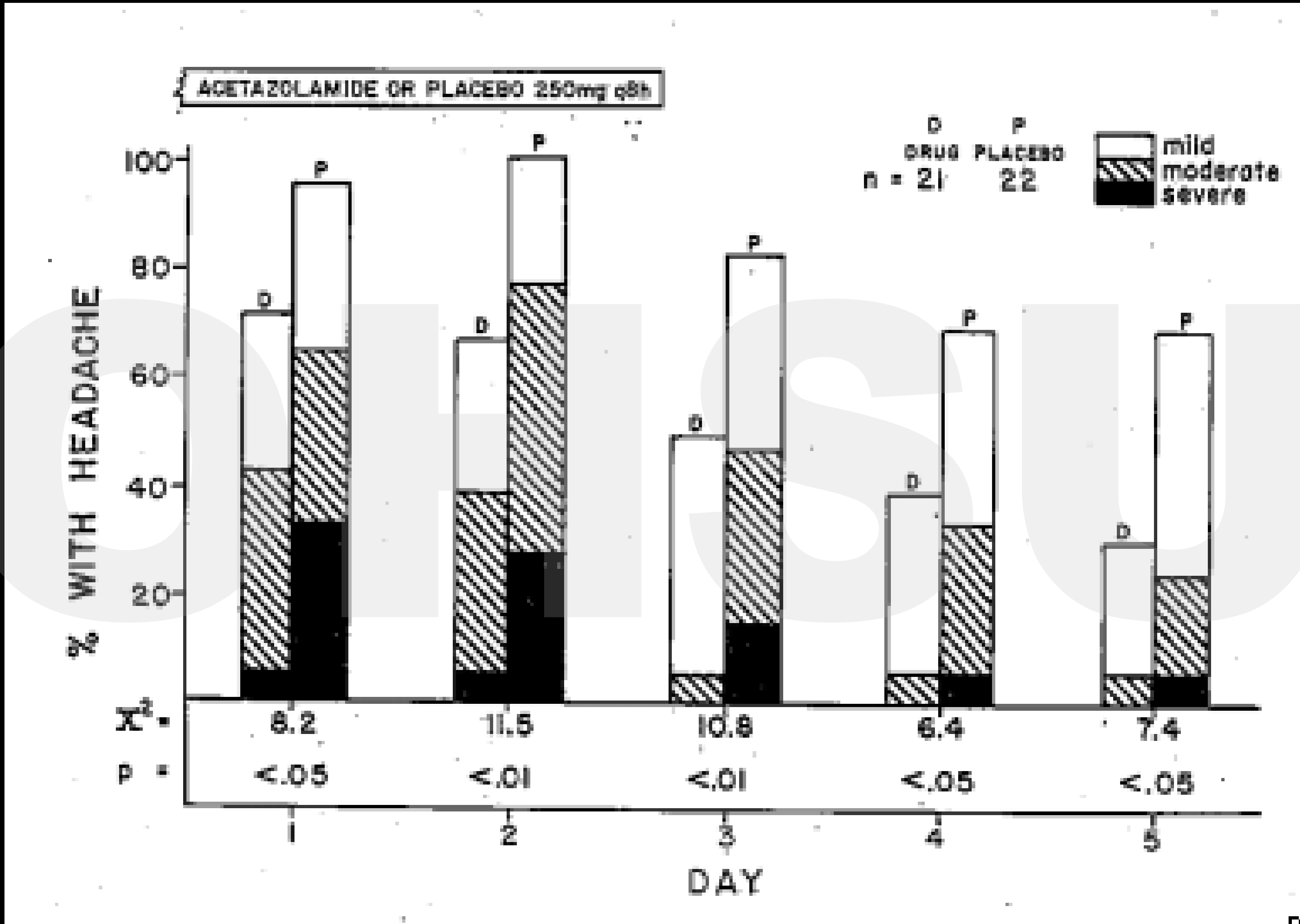
control hypoxic HCVR
CAI hypoxic HCVR
25.0
20.0
15.0
10.0
5.0
0.0
$\dot{V}_E$ (l/min)
36
38
40
42
44
46
$P_{et}CO_2$ (mmHg)
OHSU



Inhibition of carotid body CA
↓ PCR output
↓ Sleep Periodic Breathing
↑ Sleep Quality
Inhibition of tissue CA (I, II, IV)*
Tissue Respiratory Acidosis
Acetazolamide
↑ CCR output
↑ Min Ventillation (↑ $P_{a_{O_2}}$)
↓ Acute Mountain Sickness
Inhibition of renal CA
Metabolic Acidosis
↑ Diuresis
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

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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.

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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

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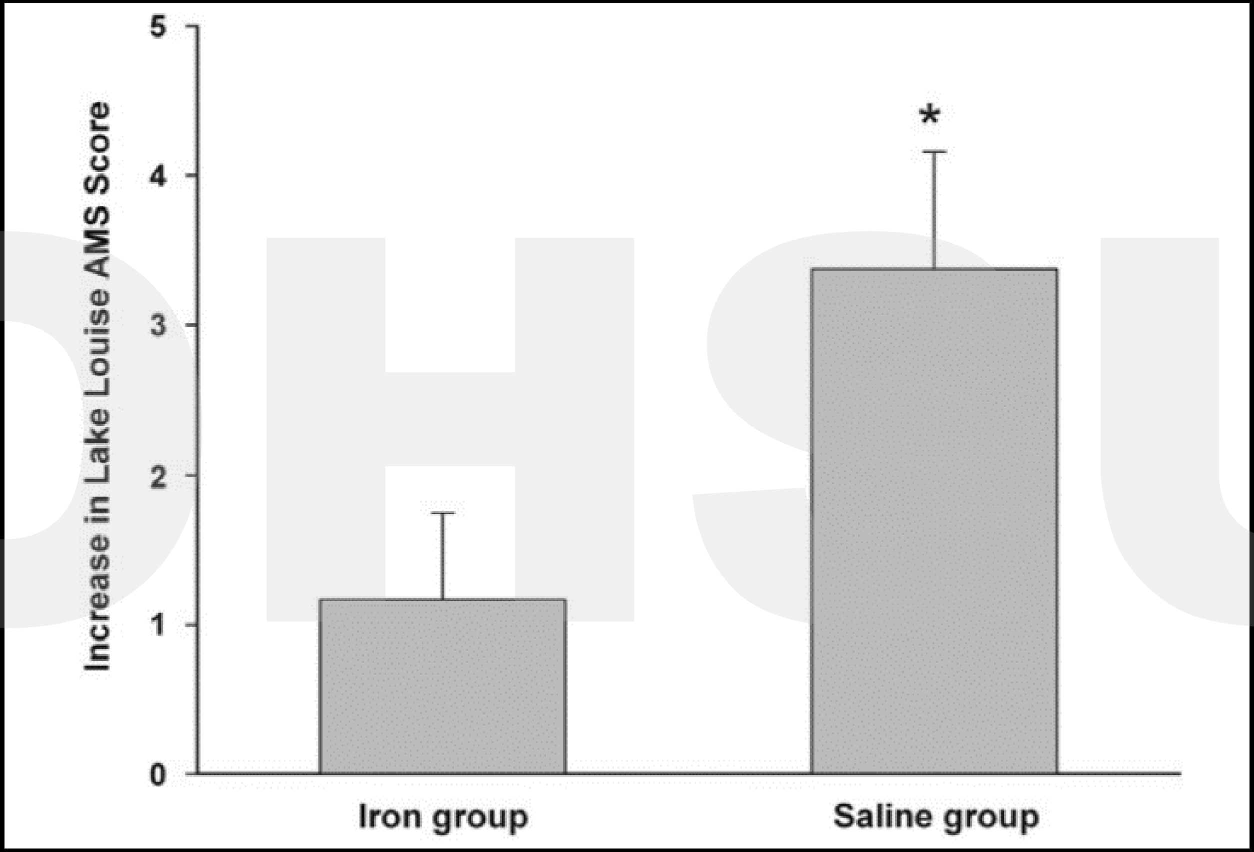
IV Iron



High Alt Med Biol. 2011 Fall;12(3):265-269

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

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Sleep Disturbances

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

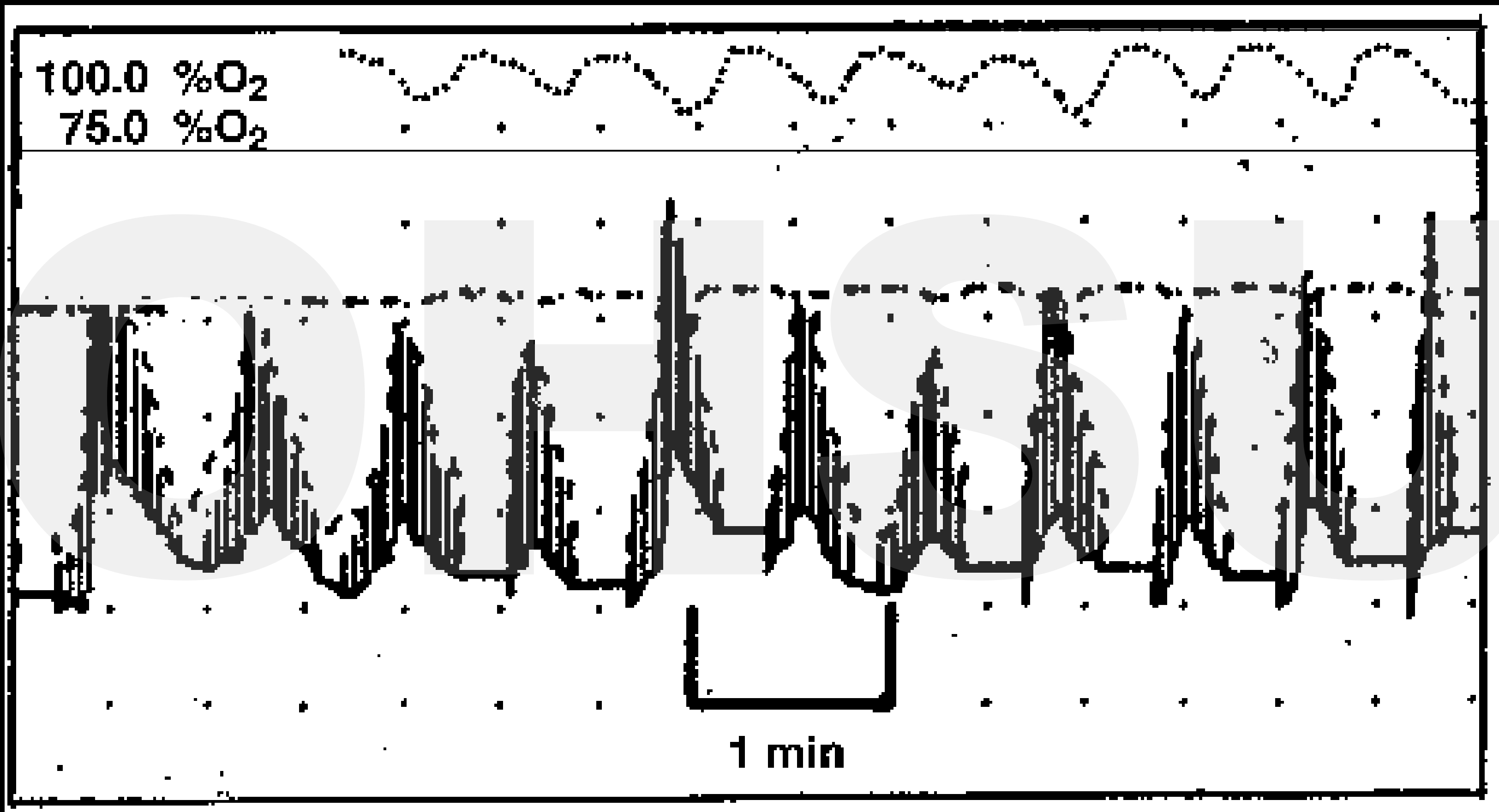
100.0 %O2
75.0 %O2
1 min

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

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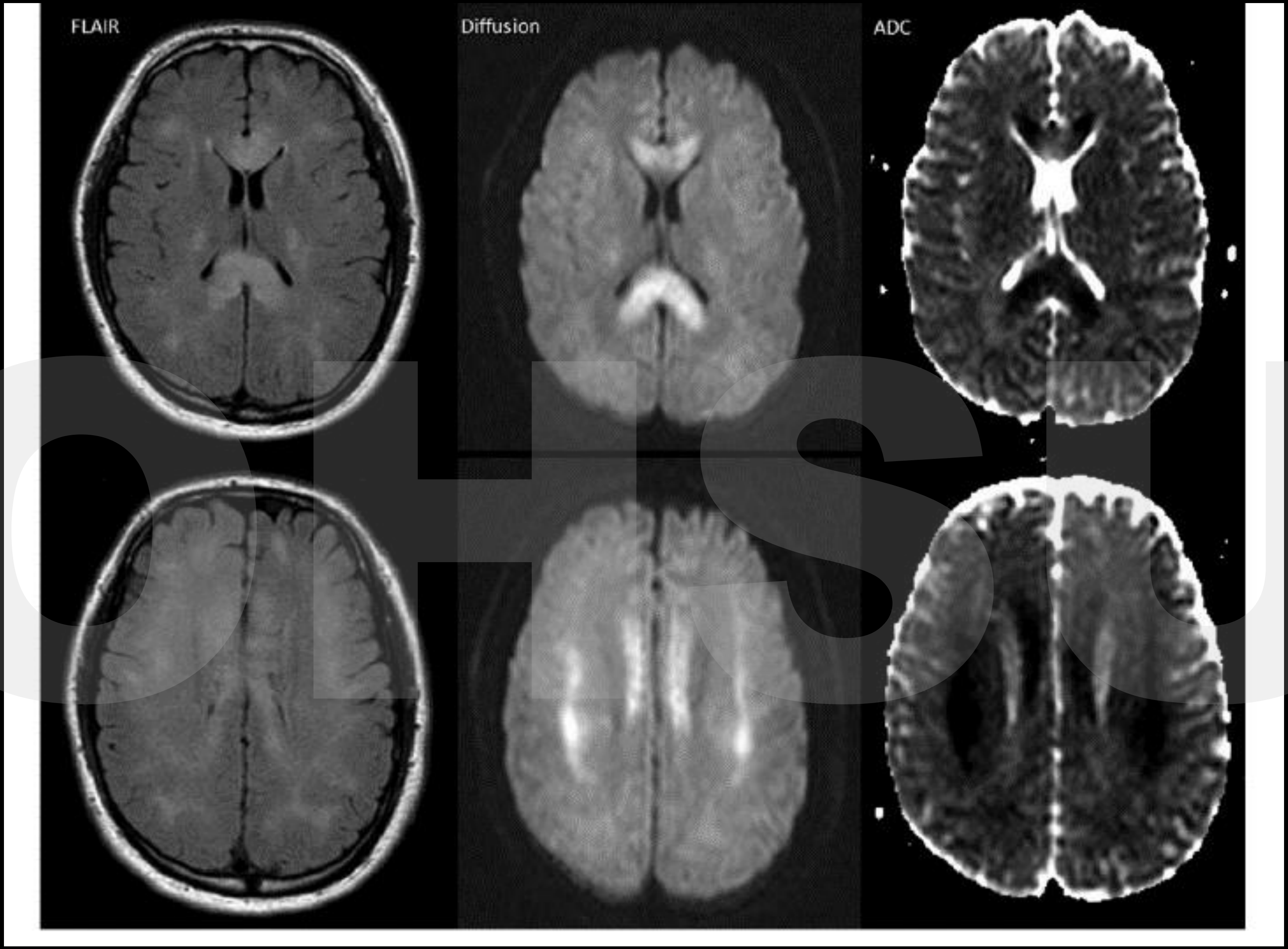
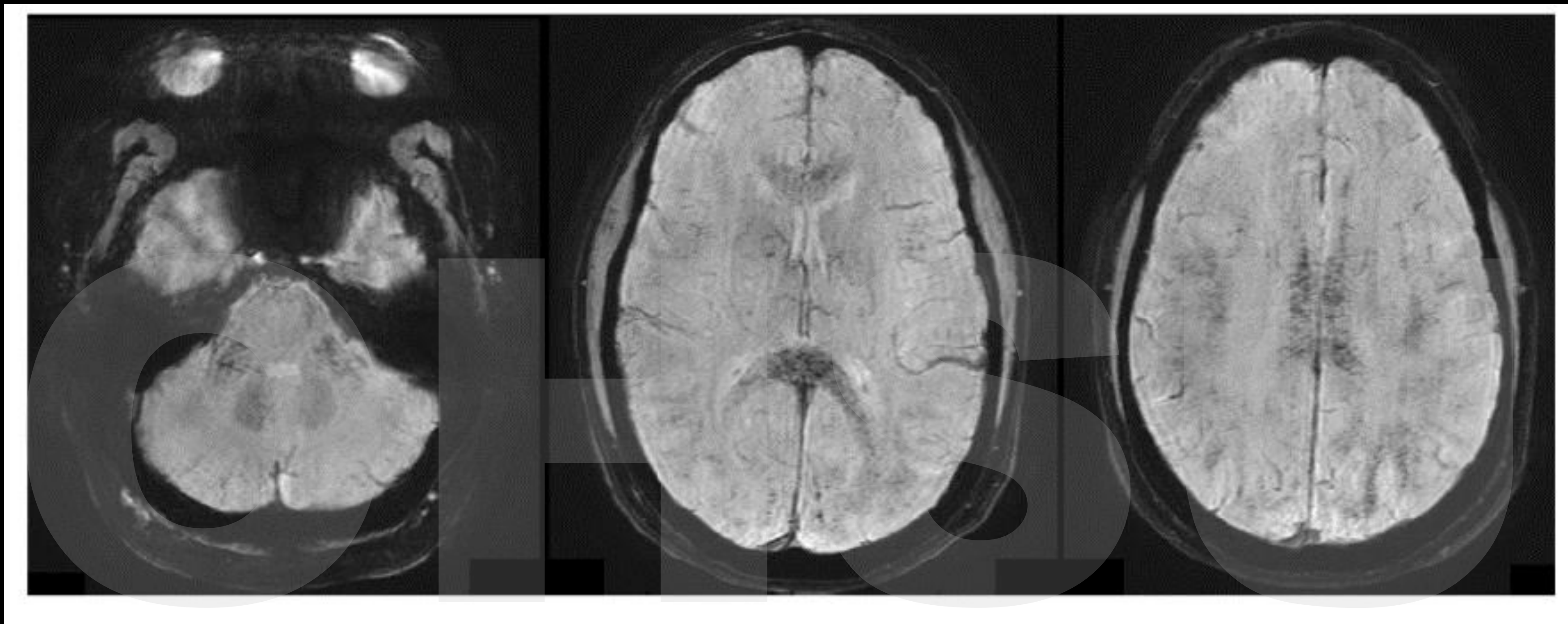
HACE:

- 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

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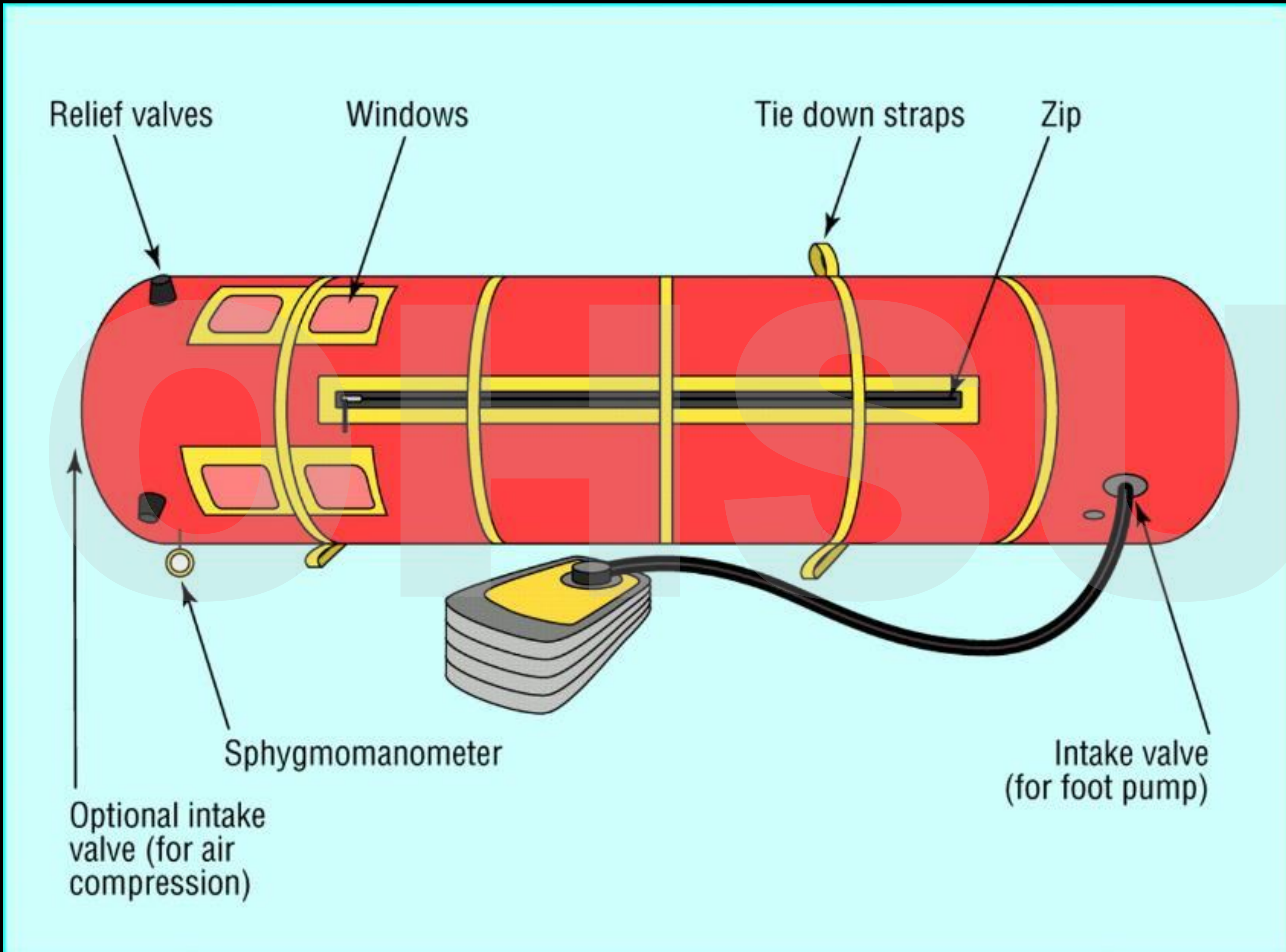
Relief valves
Windows
Tie down straps
Zip
Sphygmomanometer
Intake valve
(for foot pump)
Optional intake
valve (for air
compression)
CHSU

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AMS: Pathogenesis

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

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Disorder of Fluid Regulation?

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

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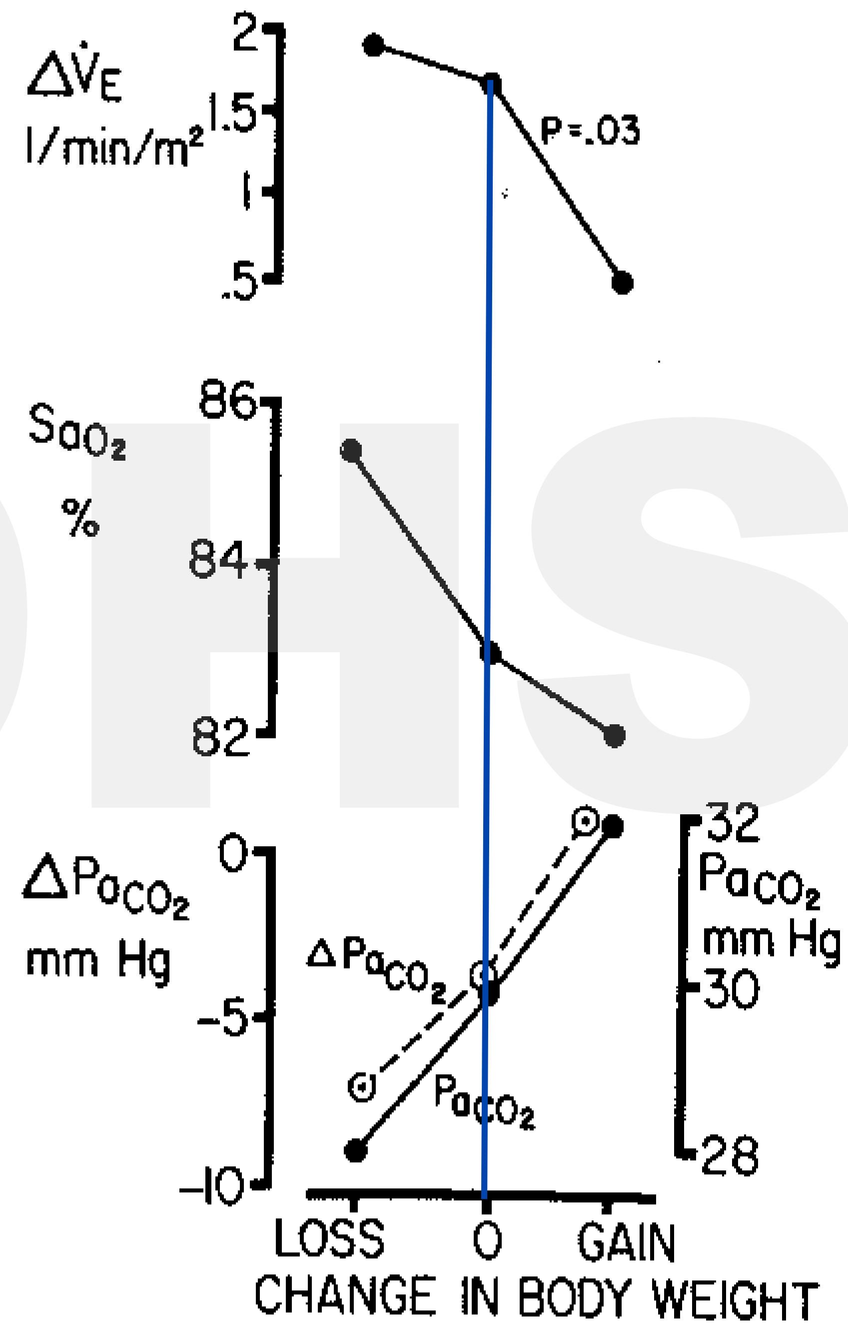

ΔV̇E
l/min/m²
2
1.5
1
.5
P=.03
SaO2
%
86
84
82
ΔPaCO2
mm Hg
0
-5
-10
ΔPaCO2
PaCO2
PaCO2
mm Hg
32
30
28
LOSS
O
GAIN
CHANGE IN BODY WEIGHT

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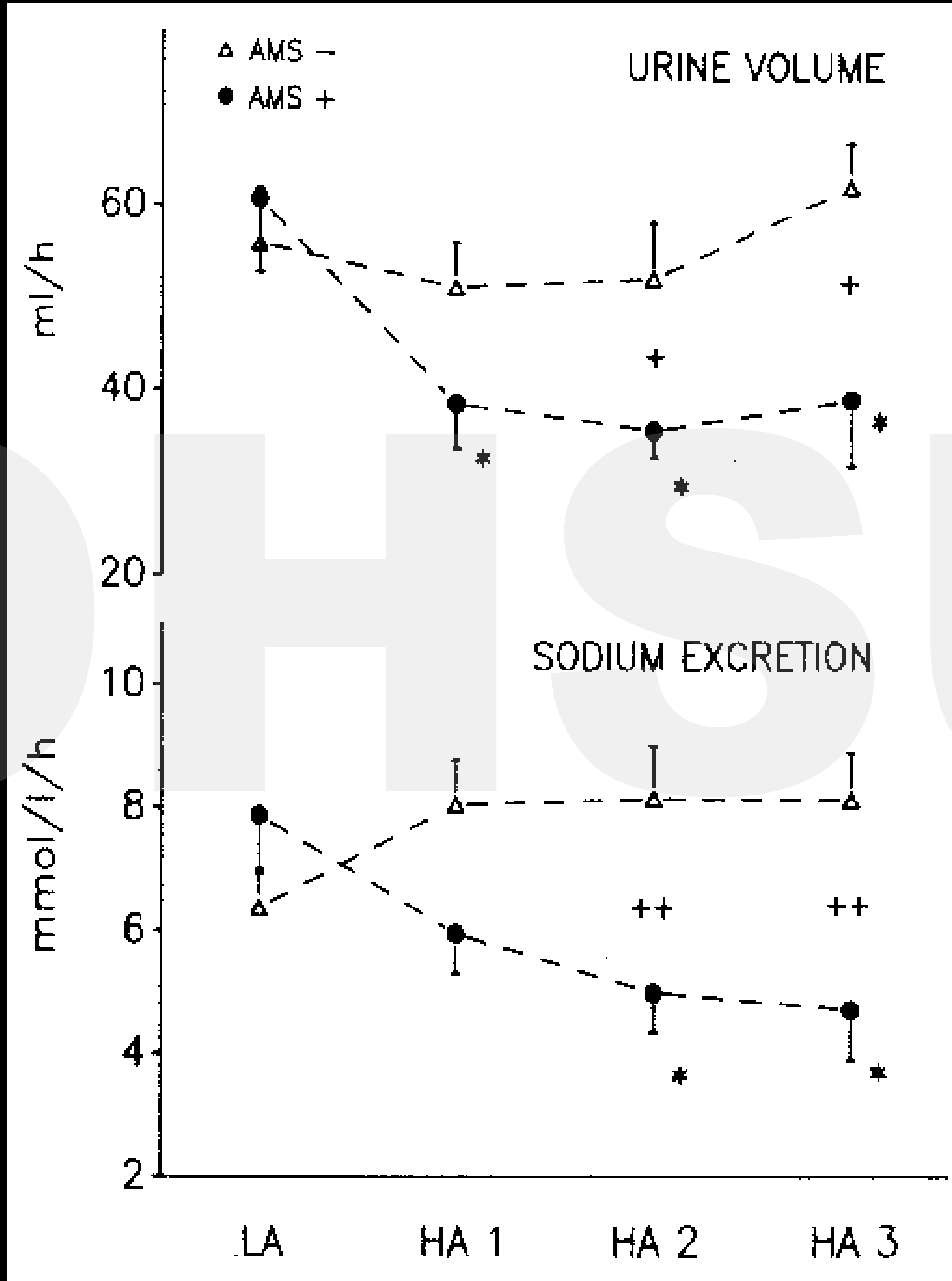

AMS −
AMS +
URINE VOLUME
ml/h
60
40
20
SODIUM EXCRETION
mmol/l/h
10
8
6
4
2
LA
HA 1
HA 2
HA 3

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“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

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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

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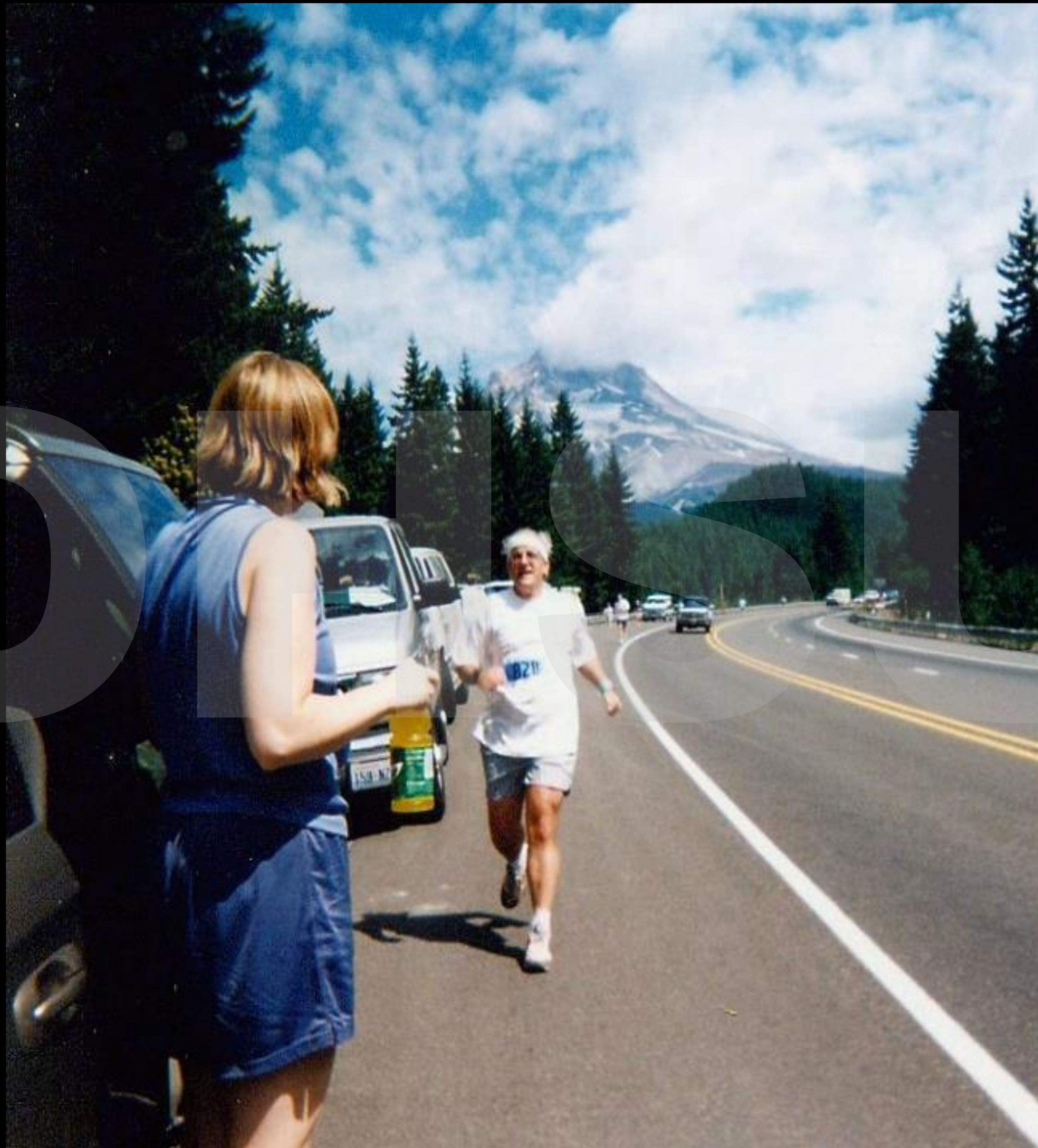
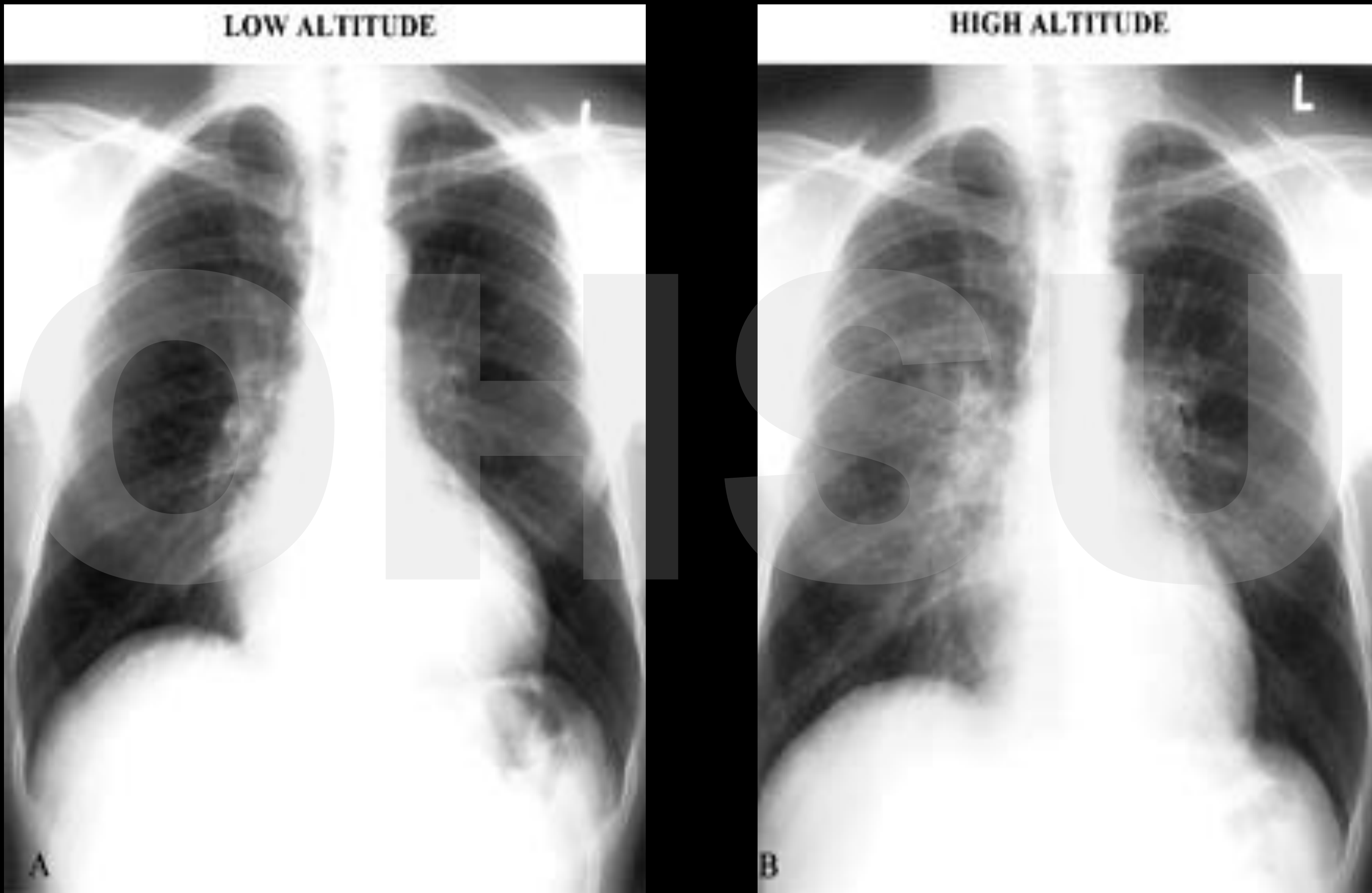
HAPE: Incidence and Risk Groups

- 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)





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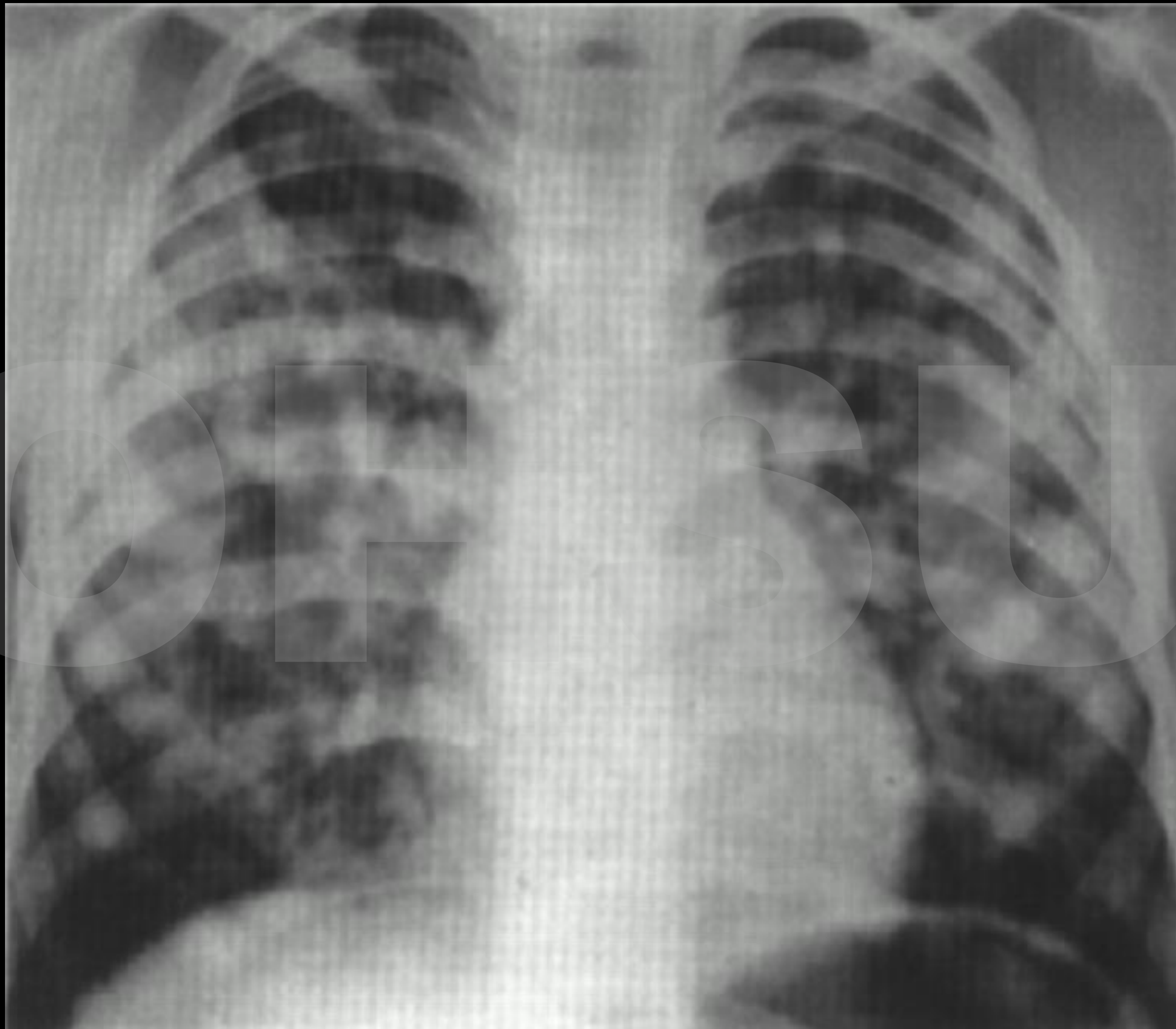
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HAPE: Treatment

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

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HAPE: Prophylaxis

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

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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

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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

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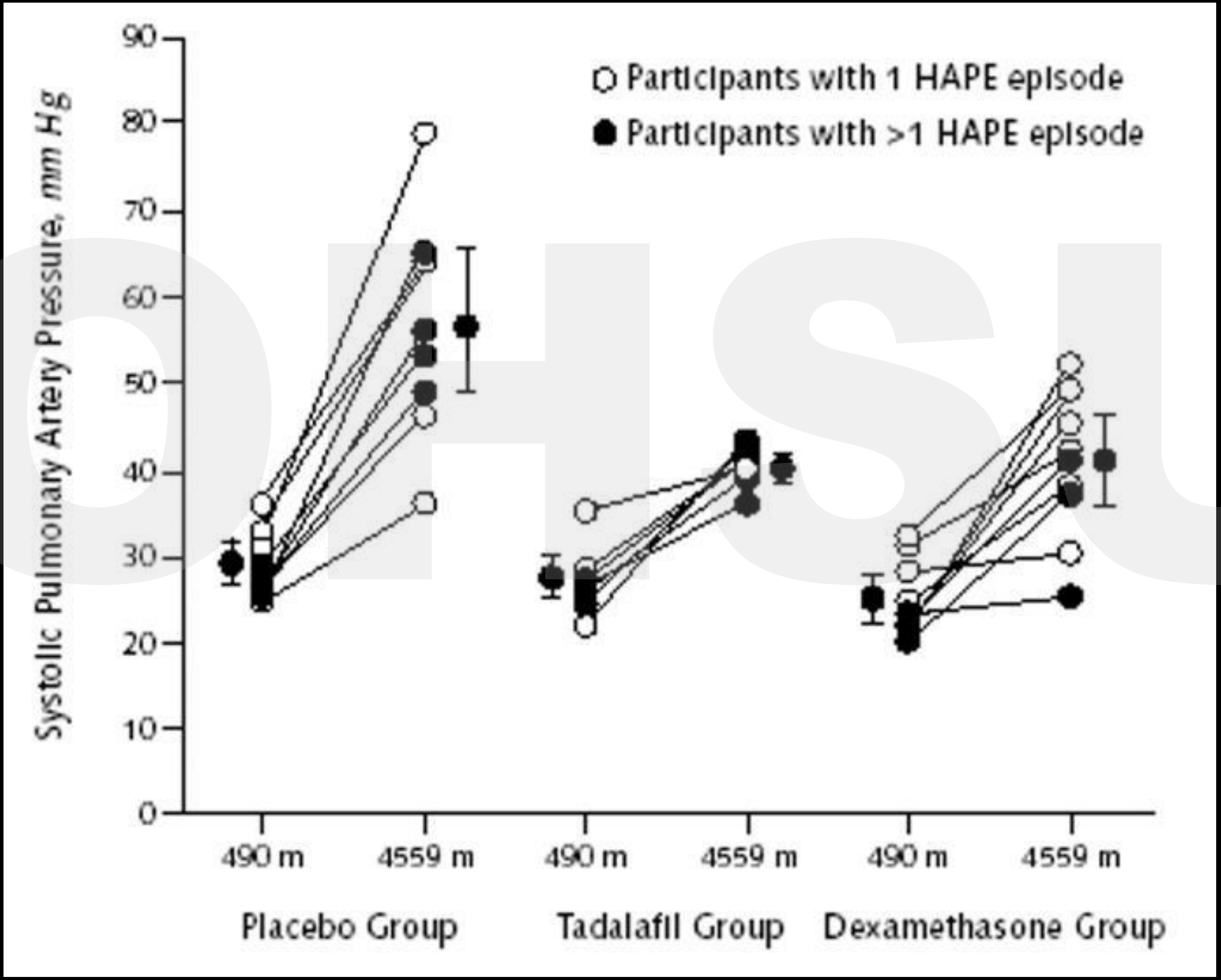
PDE-5 Inhibitors

- Fading because of cost and concerns about increased AMS incidence

Dexamethasone



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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

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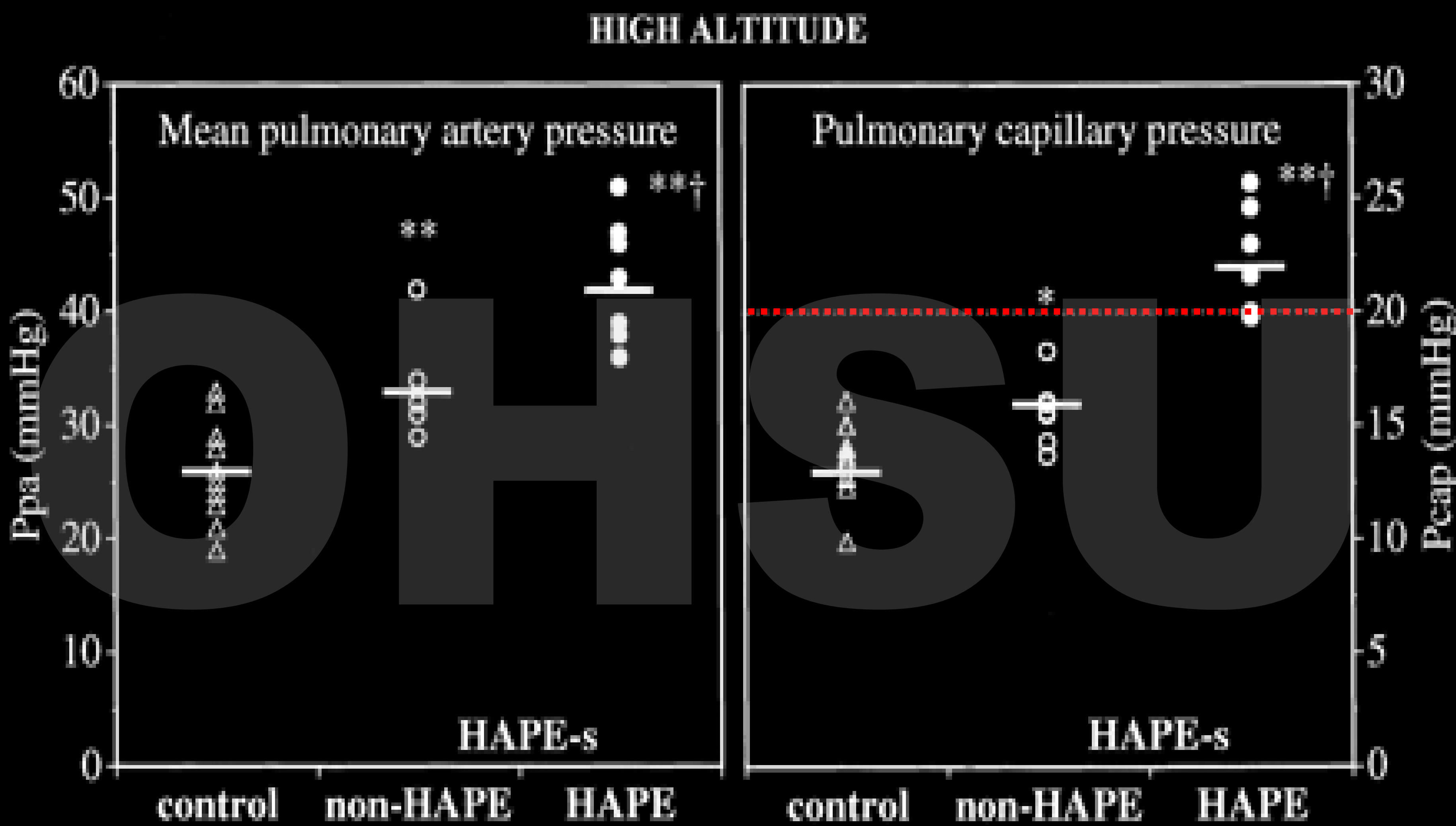
HIGH ALTITUDE
Mean pulmonary artery pressure
Pulmonary capillary pressure
Ppa (mmHg)
Pcap (mmHg)
60
50
40
30
20
10
0
30
25
20
15
10
5
0
**
**†
*
**†
HAPE-s
HAPE-s
control
non-HAPE
HAPE
control
non-HAPE
HAPE
OHSU


LASKA
4323

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

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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

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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

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Photo: Deb Robertson

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