

Don't Hold Your Breath

Mammalian Adaptations to High Altitudes & Deep Sea

Emily Jones, Brooke Lubinski, & Gautam Rao
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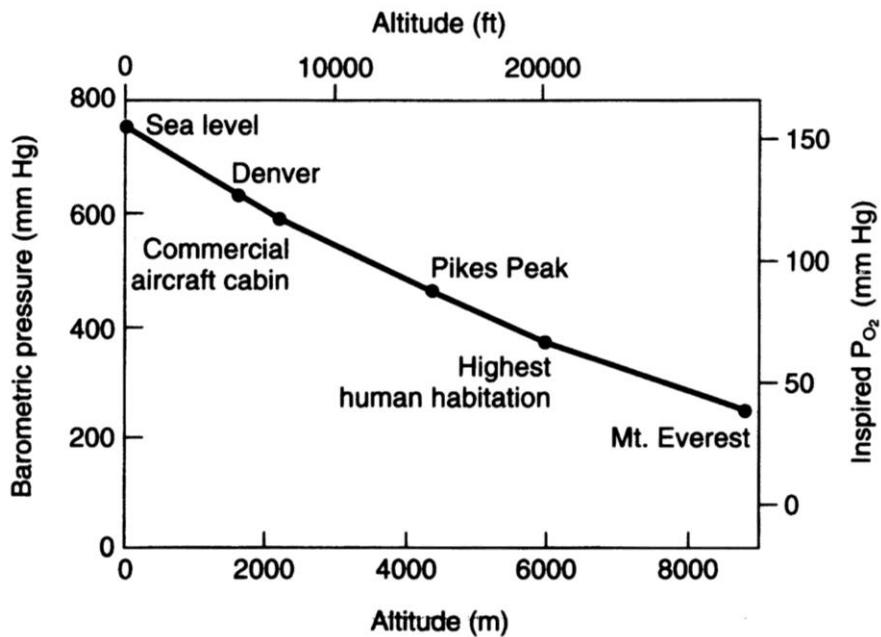
Outline

- High altitudes
 - What can go wrong: acute mountain sickness, HAPE, & HACE
 - Human adaptations: Tibetans & Andeans
 - Animal adaptations: yak & deer mouse
- Deep Sea
 - What can go wrong: decompression sickness & raptures of the deep
 - Human “adaptations”: Japanese pearl divers
 - Animal adaptations: Weddel seals & sea otters

A photograph of a snowy mountain peak. In the foreground, a climber in dark gear and a white helmet stands on a steep, snow-covered slope. They are looking towards the left. The background shows more mountain peaks and a vast expanse of white clouds under a blue sky.

High Altitude Humans

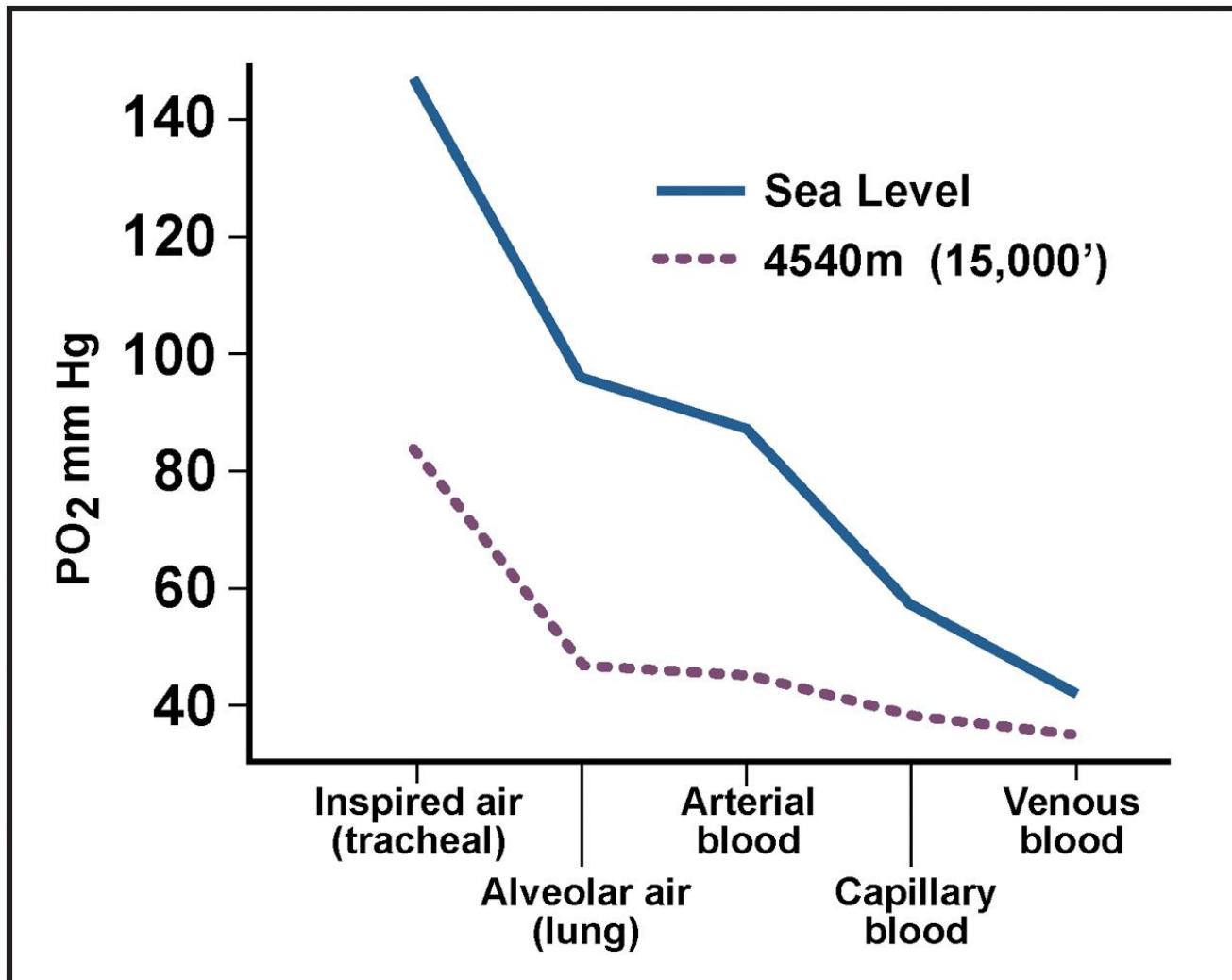
Atmospheric Gases



Dalton's Law: $P_t = P_{O_2} + P_{N_2} + P_x$

Altitude (feet)	Atmospheric Pressure (mm/Hg)	PAO ₂ (mm/Hg)	PVO ₂ (mm/Hg)	Pressure Differential (mm/Hg)	Blood Saturation (%)
Sea Level	760	100	40	60	98
10,000	523	60	31	29	87
18,000	380	38	26	12	72
22,000	321	30	22	8	60
25,000	282	7	4	3	9
35,000	179	0	0	0	0

Partial Pressure of Oxygen

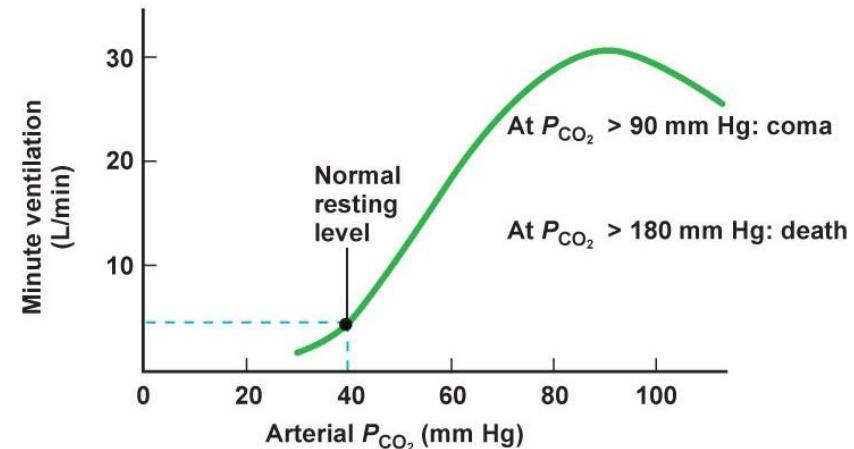
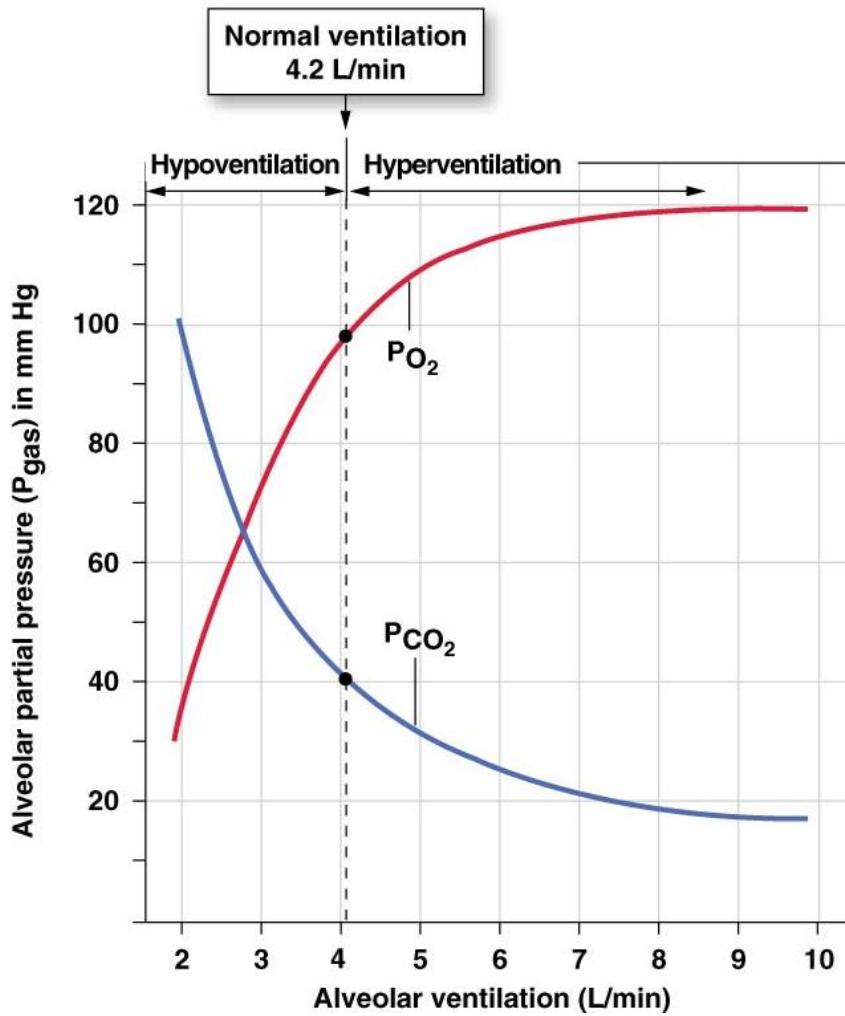


Acute Mountain Sickness

- Symptoms: fatigue, nausea, dizziness, headache, difficulty sleeping, loss of appetite, rapid pulse, shortness of breath
- Hypoxemia, hypocapnia, & alkalosis

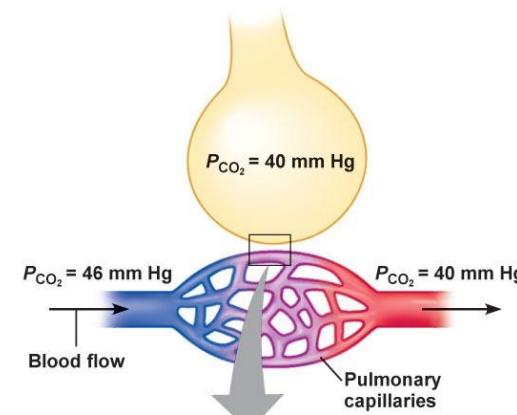
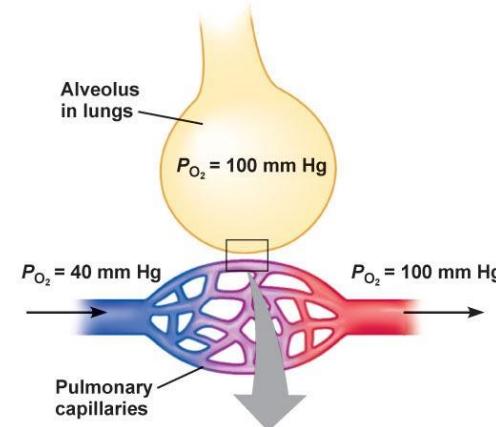
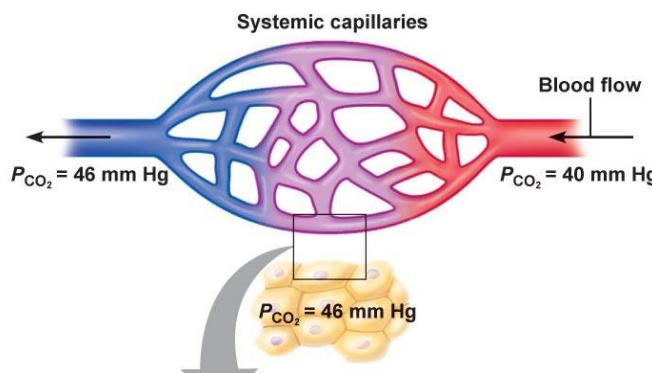
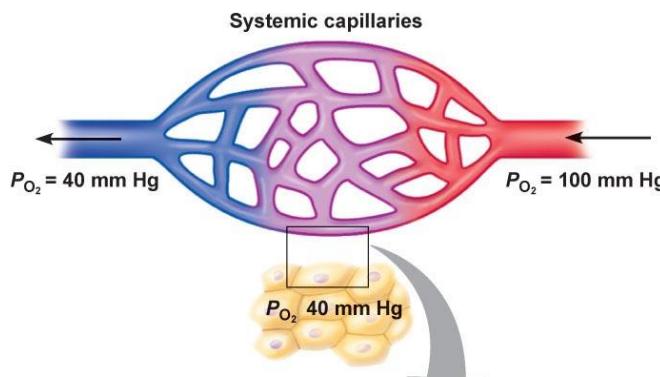


Perfusion & Peripheral Chemoreceptors



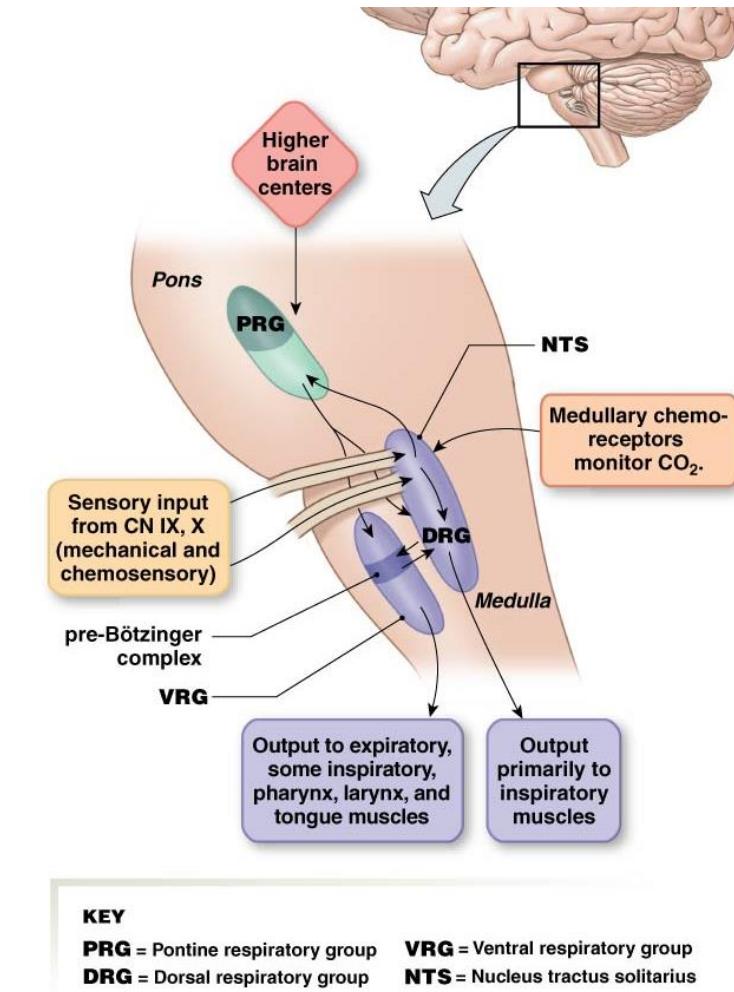
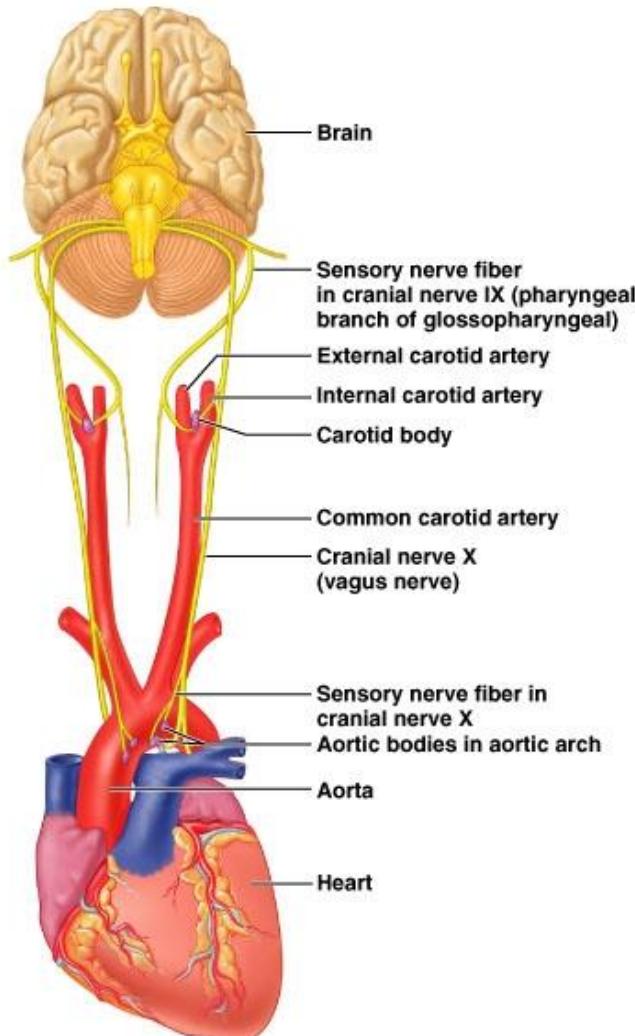
(b) Effects of arterial P_{CO_2} on ventilation

CO_2 & O_2 Pressure Differentials



$$\text{Fick's Law: } V_{\text{gas}} = A/T^*D_k(P_1 - P_2)$$

Carotid Body and Medulla



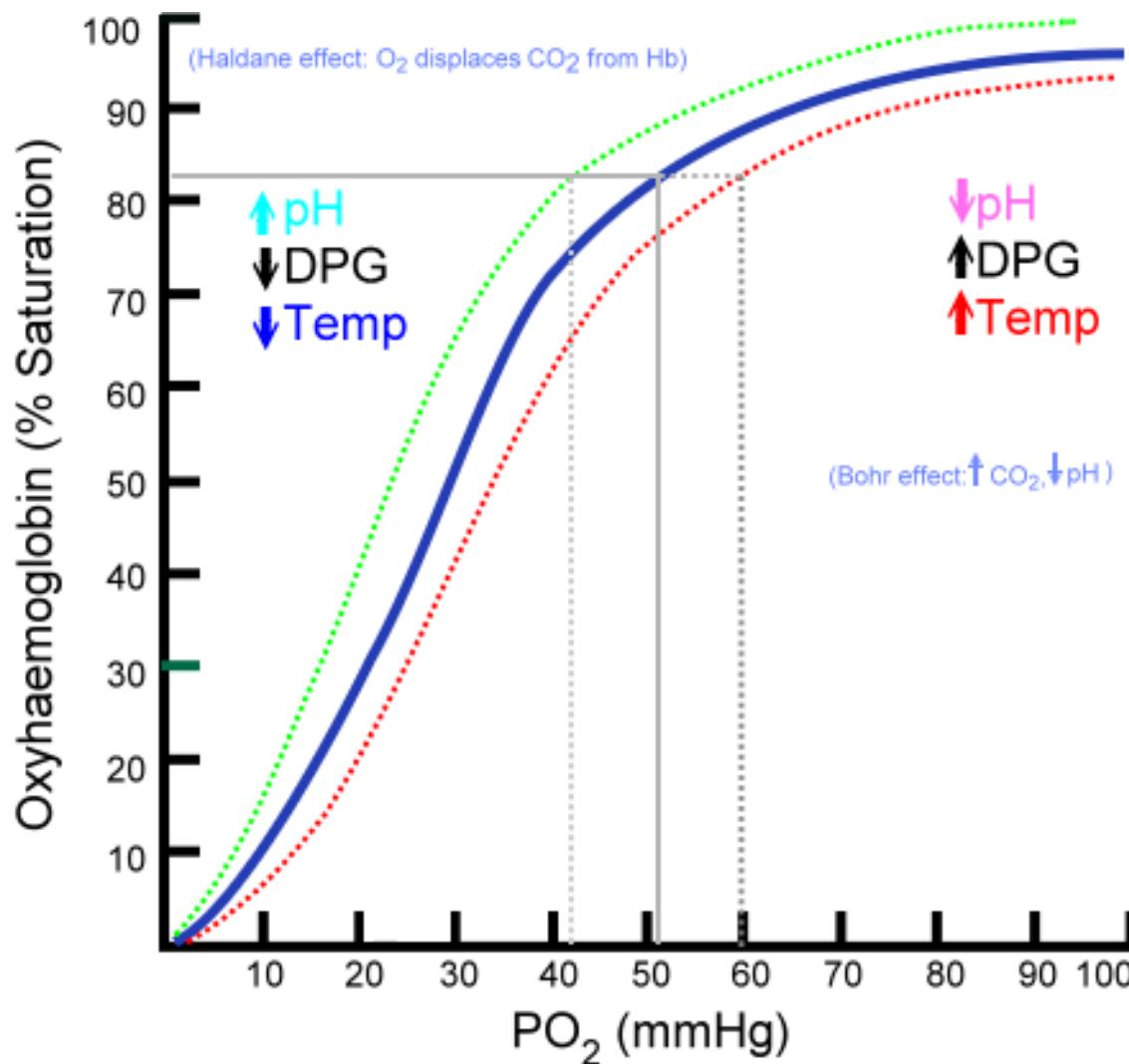
Acute Mountain Sickness

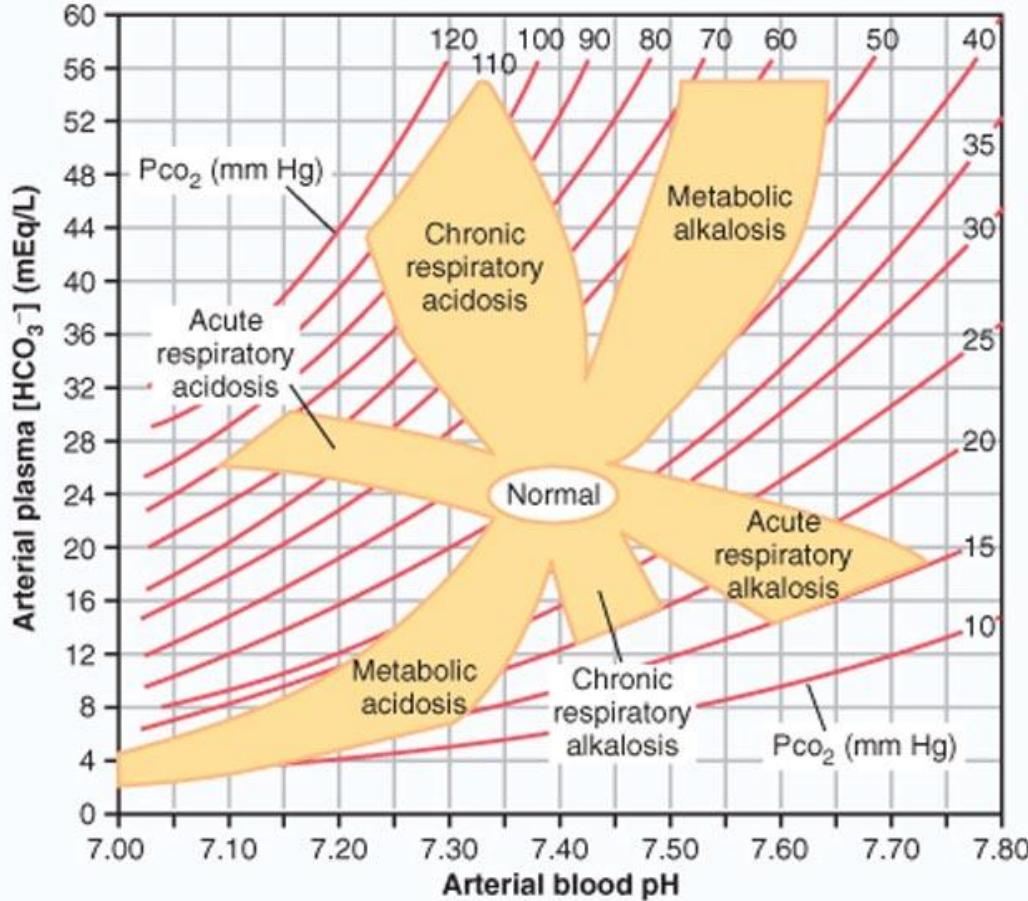
- Symptoms: fatigue, nausea, dizziness, headache, difficulty sleeping, loss of appetite, rapid pulse, shortness of breath
- Hypoxemia, hypocapnia, & alkalosis
- Caused by decreased ventilation drive & erythrocytosis
 - people with AMS have lower minute ventilation, higher expired CO₂, & lower arterial O₂
 - Hb > 200 g/L, Hct > 65%, and arterial O₂ < 85%
- Maximum oxygen intake decreases 20-30%

Acclimatization

- ↑Erythropoietin → ↑hematocrit and hemoglobin
 - at high enough concentrations, can increase blood viscosity enough to compromise vasculature & decrease tissue oxygenation
- ↑2,3-DPG  Why would this help?
- ↑renal retention of bicarbonate  Why would this help?
- Maximum oxygen intake increases to nearly normal levels over 1 year
- Proposed mechanism: ↑ carotid chemoreceptor activity

Hemoglobin





Treatment

- Stay 1 night for every 300m (1000ft) gained above 8000ft
- Acetazolamide: acidifies the blood  Why would this help?
- Myo-Inositol Trispyrophosphate could release more oxygen from hemoglobin to improve symptoms
- Oxygen

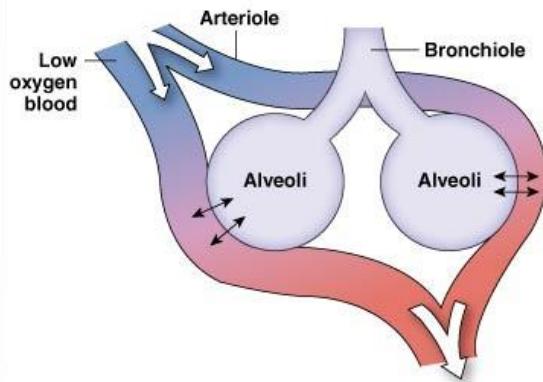
High Altitude Cerebral & Pulmonary Edema (HACE/HAPE)

- Symptoms: confusion, decreased consciousness, grey complexion, coughing
- Pulmonary edema from vaso [REDACTED]
- Cerebral edema from vaso [REDACTED]
- Treat with anti-inflammatory (dexamethasone) & phosphodiesterase (reduces pulmonary artery pressure)

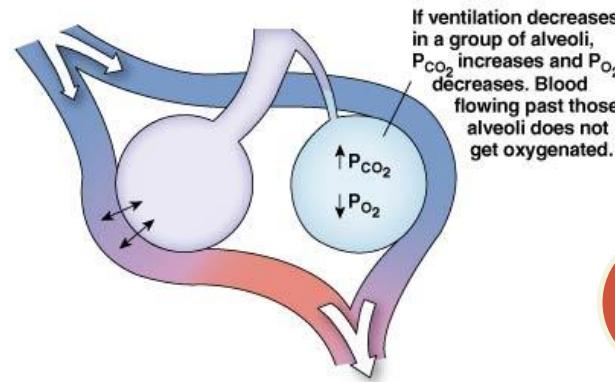
Pulmonary Vasoconstriction

Local control mechanisms attempt to match ventilation and perfusion.

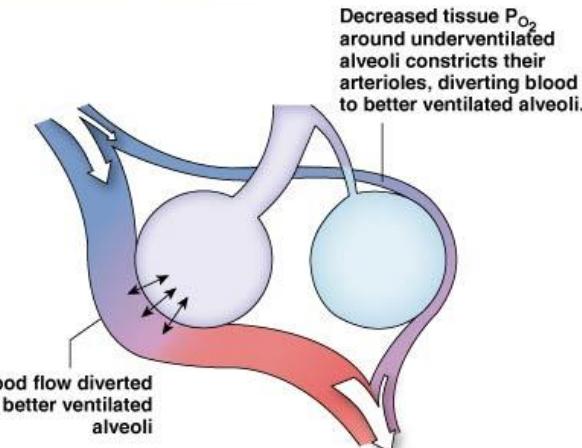
(a) Normally perfusion of blood past alveoli is matched to alveolar ventilation to maximize gas exchange.



(b) Ventilation-perfusion mismatch caused by under-ventilated alveoli.



(c) Local control mechanisms try to keep ventilation and perfusion matched.



(d) Bronchiole diameter is mediated primarily by CO_2 levels in exhaled air passing through them.

Local Control of Arterioles and Bronchioles by Oxygen and Carbon Dioxide

Gas composition	Bronchioles	Pulmonary arteries	Systemic arteries
P_{CO_2} increases	Dilate	(Constrict)*	Dilate
P_{CO_2} decreases	Constrict	(Dilate)	Constrict
P_{O_2} increases	(Constrict)	(Dilate)	Constrict
P_{O_2} decreases	(Dilate)	Constrict	Dilate

* Parentheses indicate weak responses.

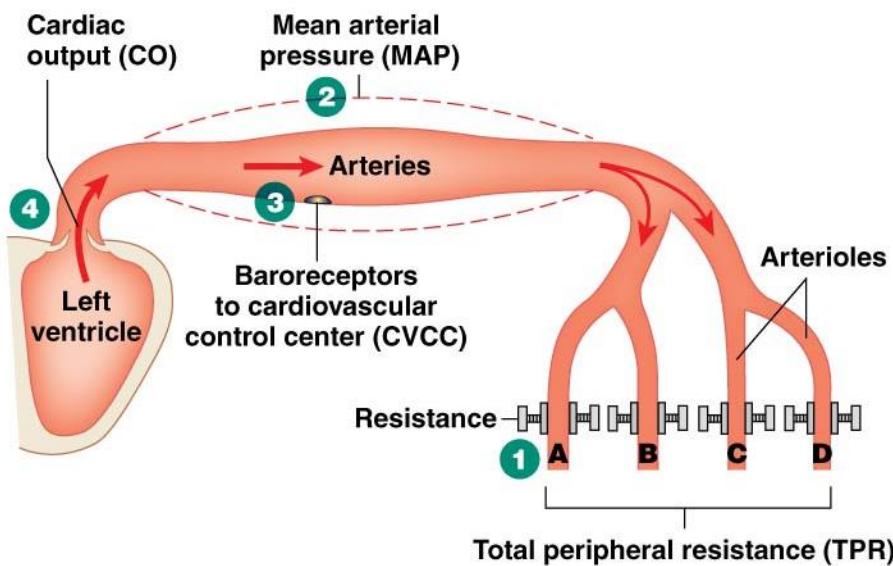
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Why?

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Heart effects?

$CO = MAP/TPR$



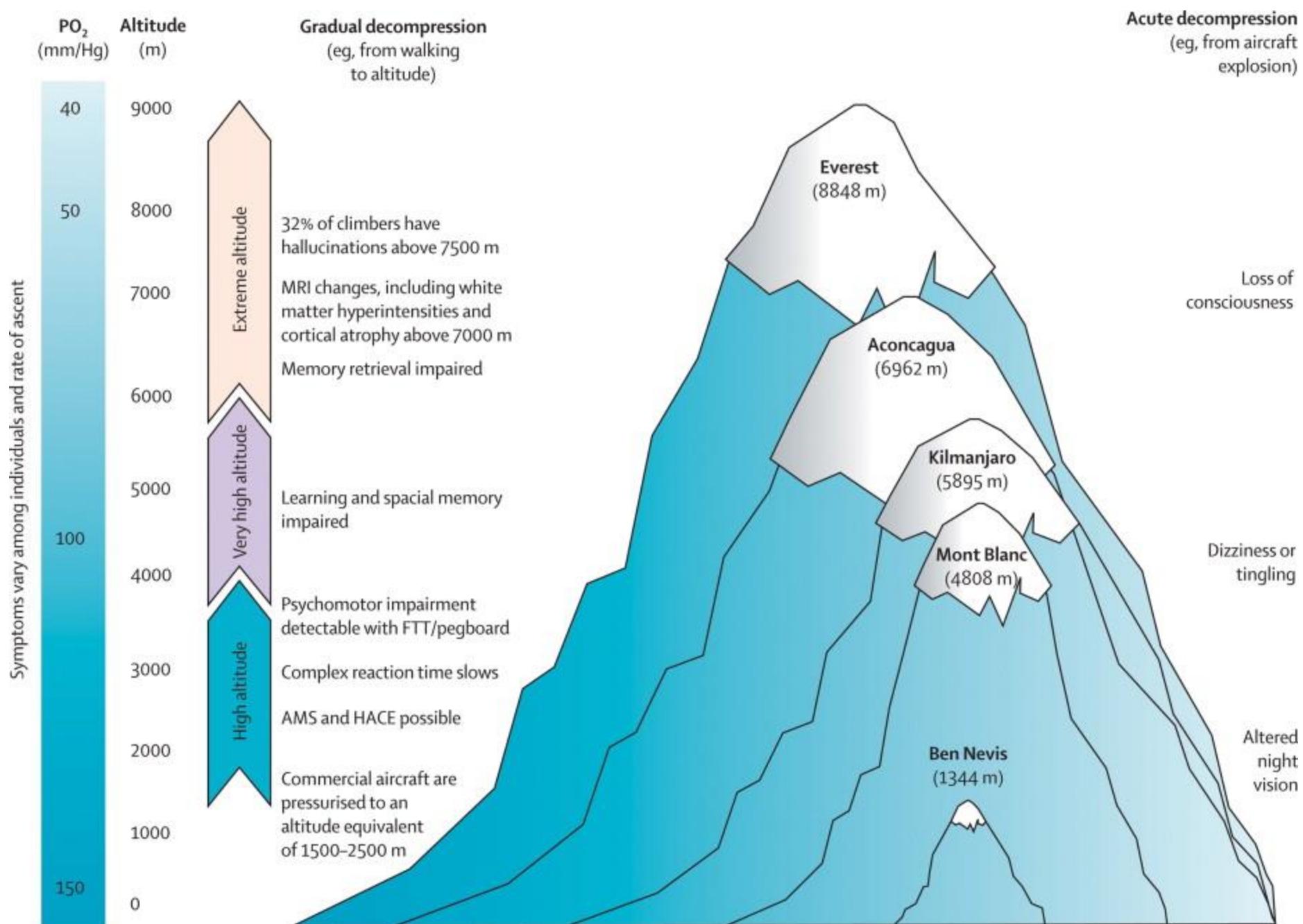
1 Arteriole A → Increased constriction → Increased total peripheral resistance ($\uparrow R_A$) → Increased total peripheral resistance ($\uparrow TPR$)

2 $\uparrow TPR \times$ Cardiac output (CO) → Increased mean arterial pressure ($\uparrow MAP$)

3 $\uparrow MAP \rightarrow$ baroreceptors fire → baroreceptor reflex

Assuming that tissue blood flow is matched to tissue need and does not need to change:

4 Baroreceptor reflex → Decreased cardiac output ($\downarrow CO$)
 $\uparrow TPR \times \downarrow CO = MAP$ restored to normal



Andeans & Tibetans



Populated since 11,000 years ago
Average elevation: 4000m (13,000ft)



Populated since 25,000 years ago
Average elevation: 4900m (16,000ft)

Highlanders

- Denser capillary beds to reduce diffusion distance
- Higher 2,3-DPG
- Exercise capacity is better than lowlanders at high elevation, but not as good as lowlanders at sea level
- Limits: no human habitation above 6000m

Andeans & Tibetans

- Andeans have higher [Hb] than lowlanders at sea level
- Tibetans have a higher ventilation rate (15 L/min vs 10.5 L/min)
- Tibetans have increased NO
- Both have heavier babies than expected due to increased NO (Tibetans) and increased gestational ventilation (Andeans), but also have high rates of diseases associated with low fetal oxygen (schizophrenia & epilepsy)
- Overall, Andeans have higher arterial O₂



Why would this help?

Hypoxia-Inducible Factor (HIF) Oxygen Signaling Pathway

- Tibetans have variants of: EPAS1 (the oxygen-sensing subunit), EGLN1 (HIF regulator), & PPARA (HIF transcriptional regulator)
 - only EGLN1 also mutated in Andeans
 - EPAS1 variants between Tibetans & Hans show the fastest allele frequency change in any human gene ever observed strongly correlated with low hemoglobin & RBC → regulation of hemoglobin rather than changing its subunits to change affinity
- Also show variants in FANCA & PKLR (RBC creation & maintenance)

High Altitude Animals



Other animals

- Various animals
- Hypobaric chamber
- Measured hypoxic response
- Smooth muscle plays a role

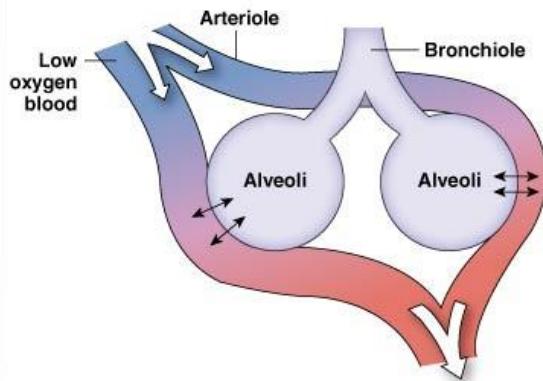
Hypoxic Response

- Pulmonary vasoconstriction
- Systemic vasodilation
- Carotid body and Medulla
- Cellular response
- Genetic response

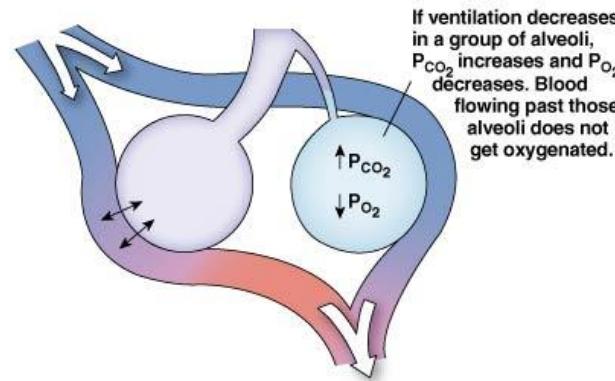
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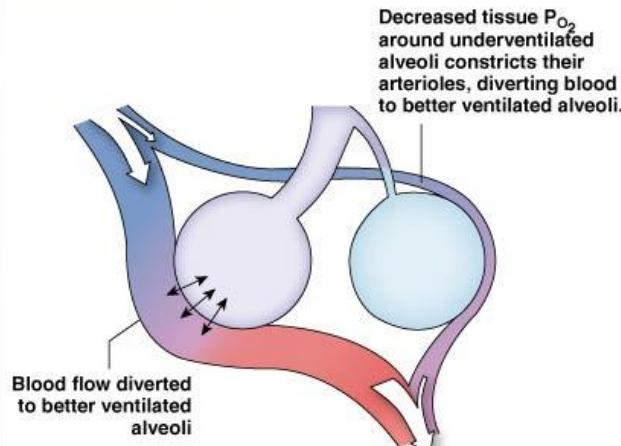
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P_{O_2} decreases	(Dilate)	Constrict	Dilate

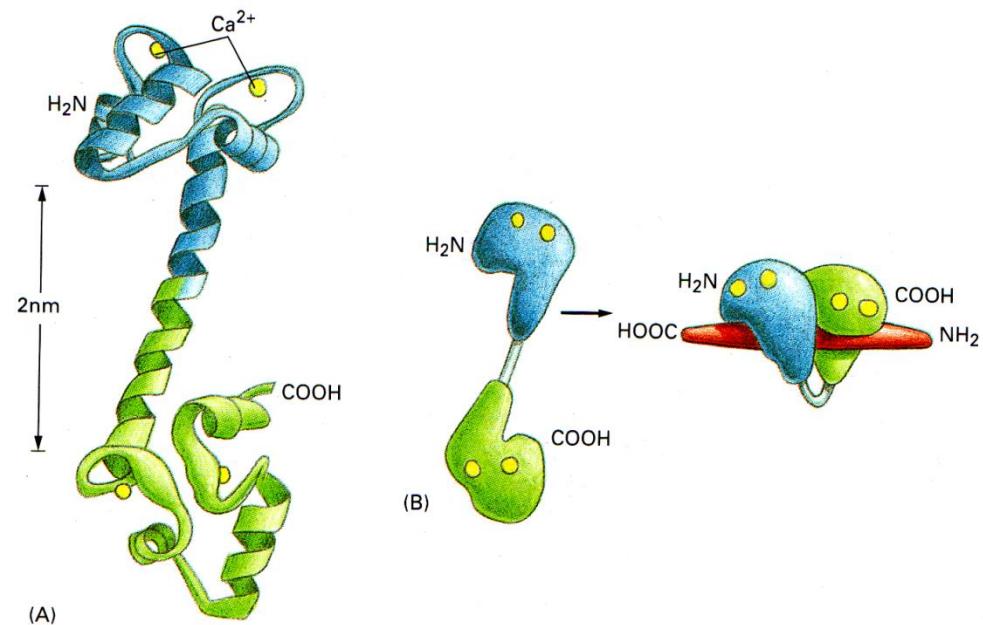
* Parentheses indicate weak responses.

Smooth muscle contraction

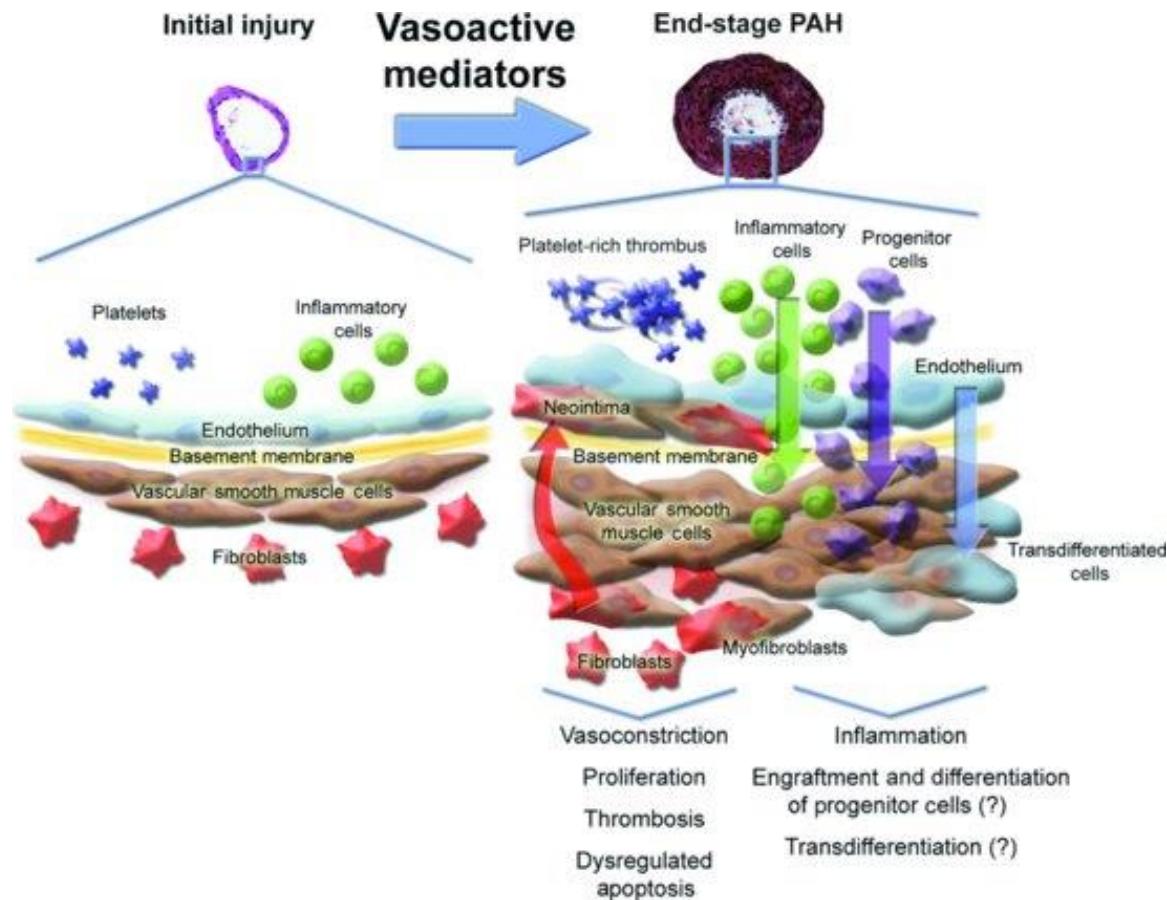
- Membrane depolarizes
- Ca⁺² influx
- Ca⁺² and calmodulin complex
- MLCK
- Contraction



Compare with skeletal

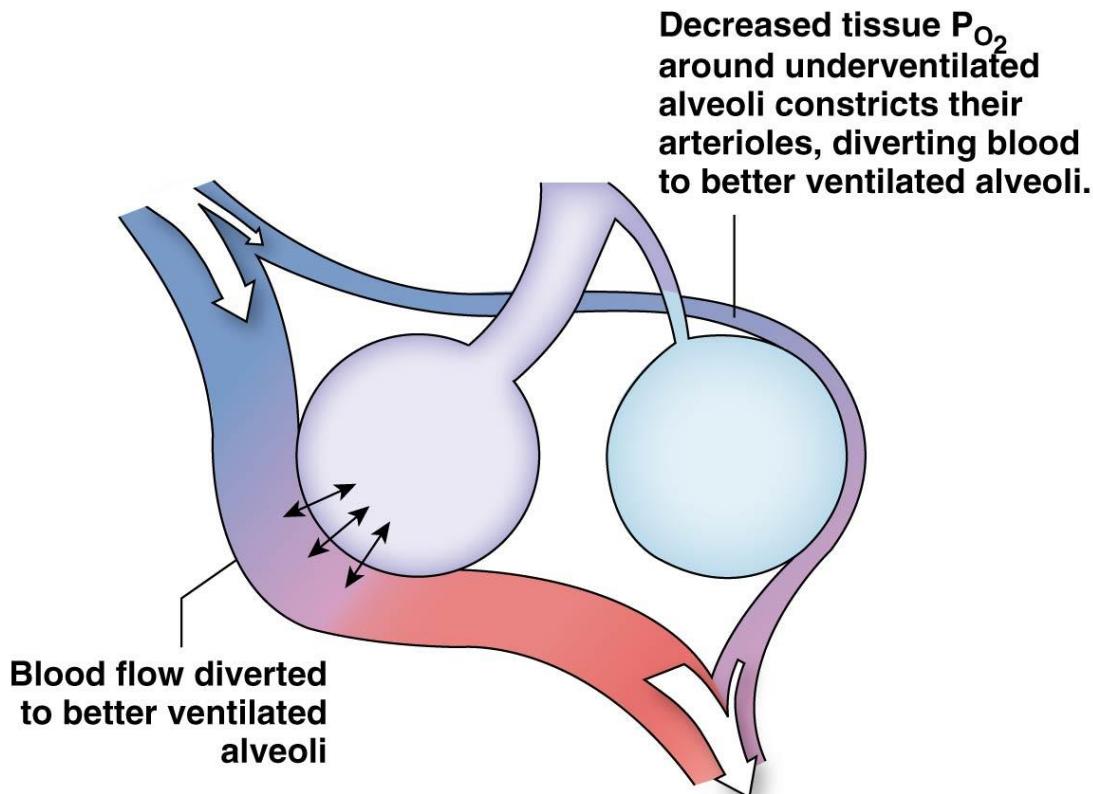


Pulmonary Hypertension



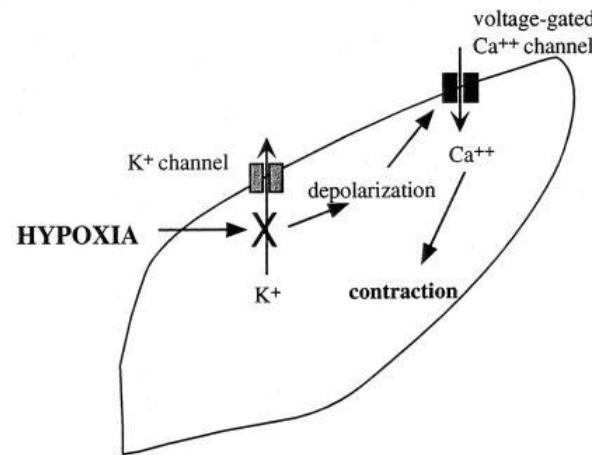
Systemic Vasodilation

(c) Local control mechanisms try to keep ventilation and perfusion matched.

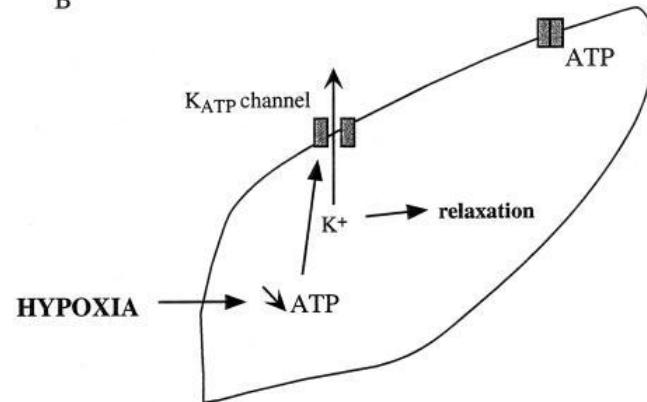


Difference between two

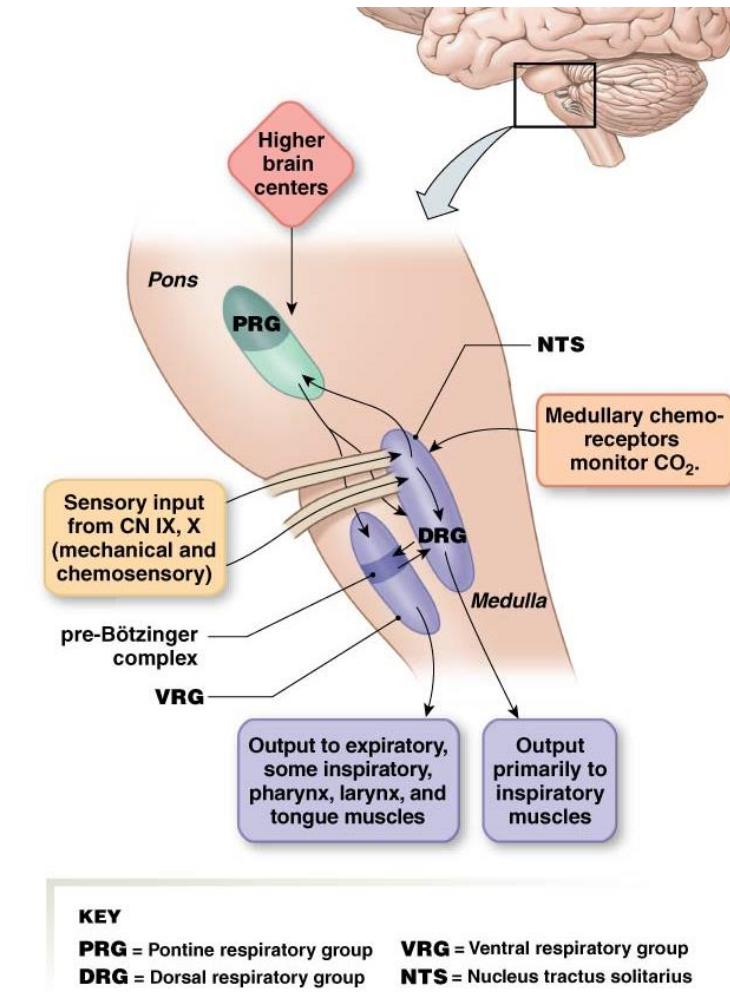
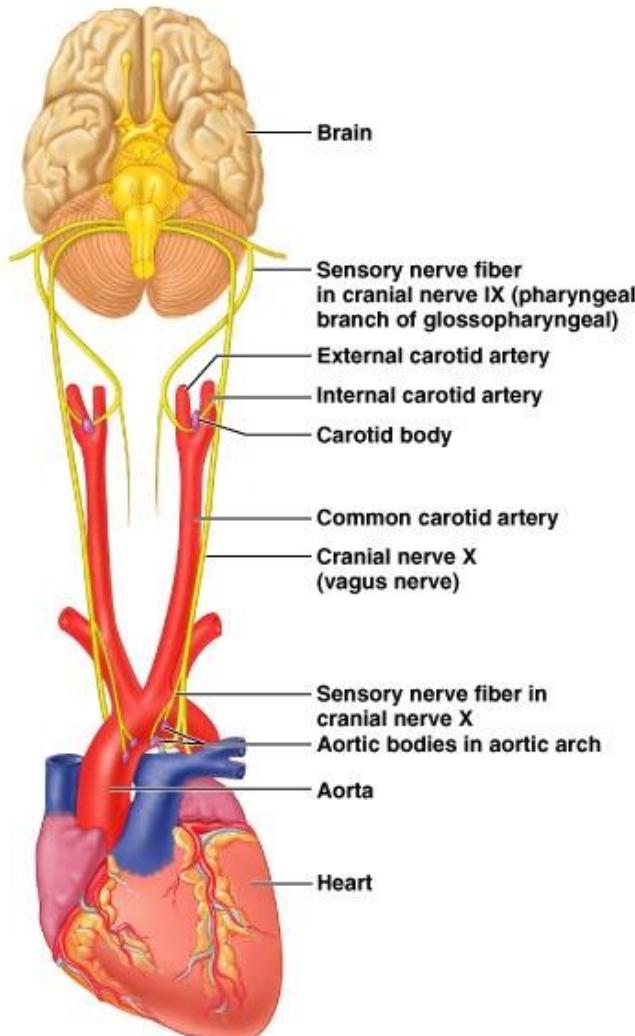
A



B

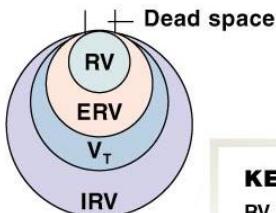


Carotid Body and Medulla



Respiration

The four lung volumes



KEY

RV = Residual volume
ERV = Expiratory reserve volume
V_T = Tidal volume
IRV = Inspiratory reserve volume

Capacities are sums of 2 or more volumes.

$$\text{Inspiratory capacity} = V_T + \text{IRV}$$

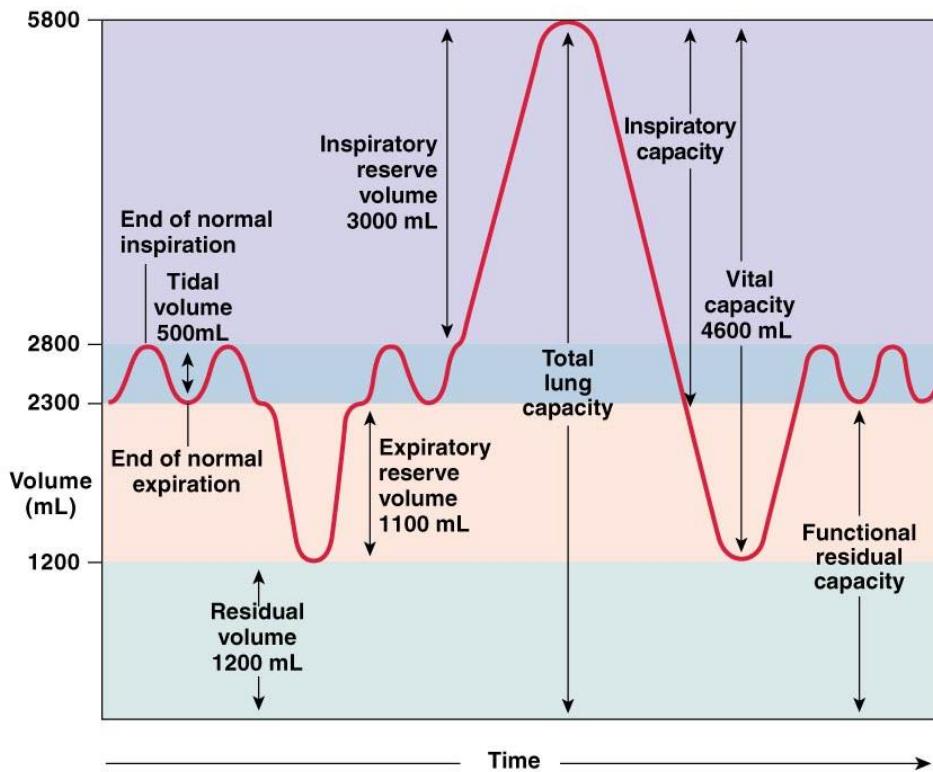
$$\text{Vital capacity} = V_T + \text{IRV} + \text{ERV}$$

$$\text{Total lung capacity} = V_T + \text{IRV} + \text{ERV} + \text{RV}$$

$$\text{Functional residual capacity} = \text{ERV} + \text{RV}$$

Pulmonary Volumes and Capacities*		
	Males	Females
Vital capacity	IRV 3000	1900
	V _T 500	500
	ERV 1100	700
Residual volume	1200	1100
Total lung capacity	5800 mL	4200 mL

A spirometer tracing showing lung volumes and capacities.



*Pulmonary volumes are given for a normal 70-kg man or a 50-kg woman, 28 years old.

Respiration Rate

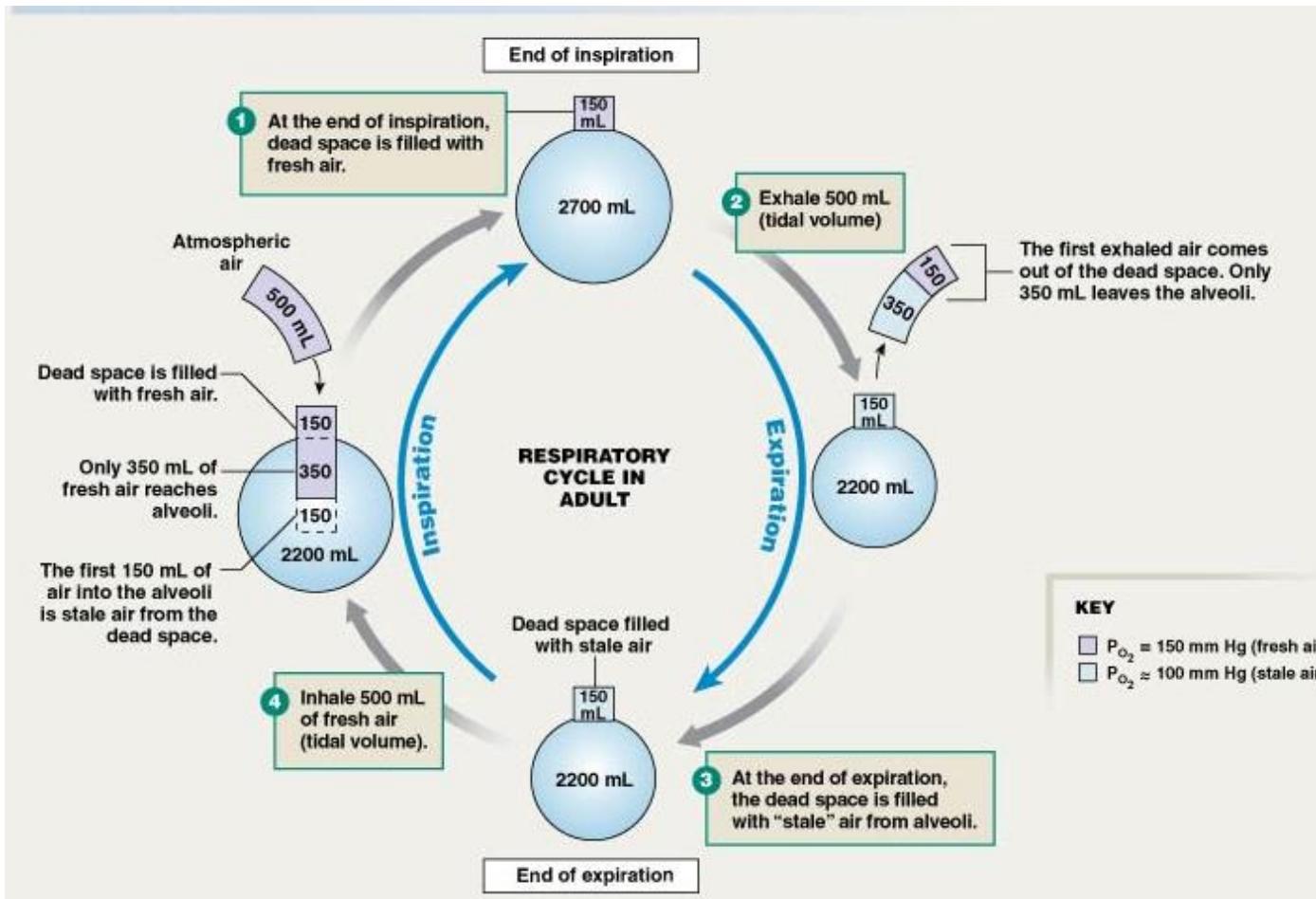
- Minute Ventilation = Tidal Volume X Respiratory Rate



Which is better?

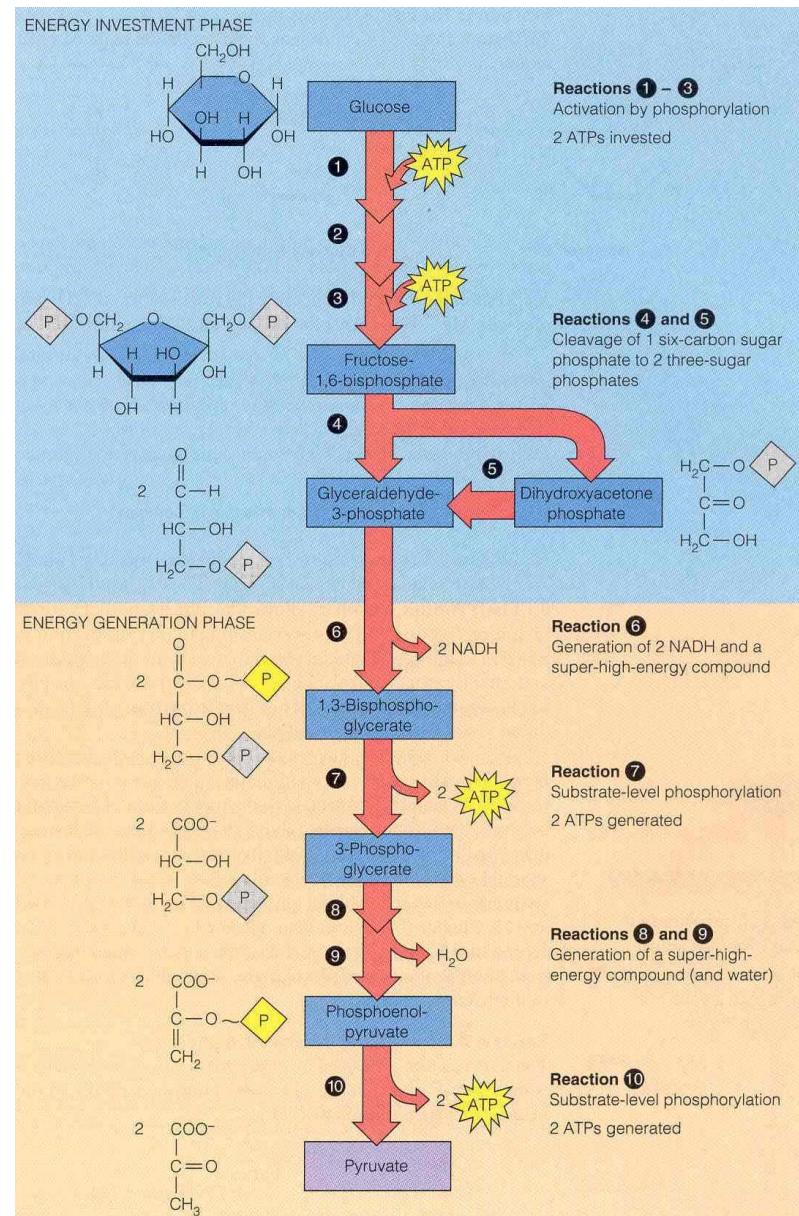
- Alveolar Ventillation
- $VA = (VT \times RR) - (DSV \times RR)$
- This gives a measure of how much gas exchange can occur
- It's more efficient to increase VT than RR

DSV



Cellular Response

- Glycolysis
- Shift processes
- Necrosis



Genetic response

- VEGF
- NO
- Erythropoietin

Yak vs. Cattle



Varying altitude

- Switch conditions
- Brisket Disease
 - Right side heart failure
 - Pulmonary hypertension



What is different in Yaks?

Yaks

- Hypoxic response is reduced in yaks vs cattle



- Larger heart
- Large lungs
- Large chest

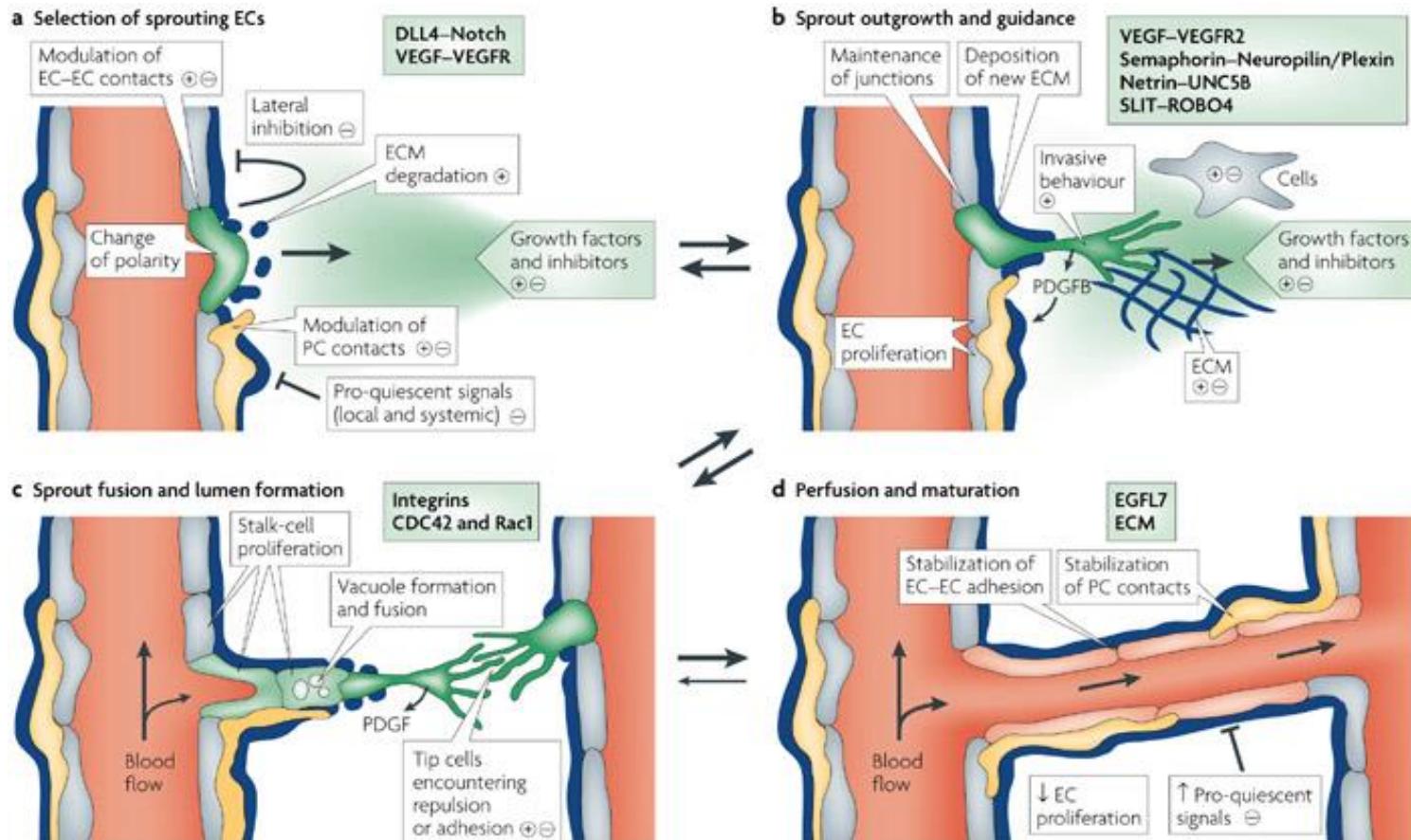
HIF-1

- Hypoxia-inducing factor 1
- Heterodimeric
- Produced in normoxia and hypoxia
- Normoxia: polyubiquitinylated
- Hydroxylase destroys HIF- α in presence of O₂
- Stimulates:
 - VEGF
 - Erythropoietin

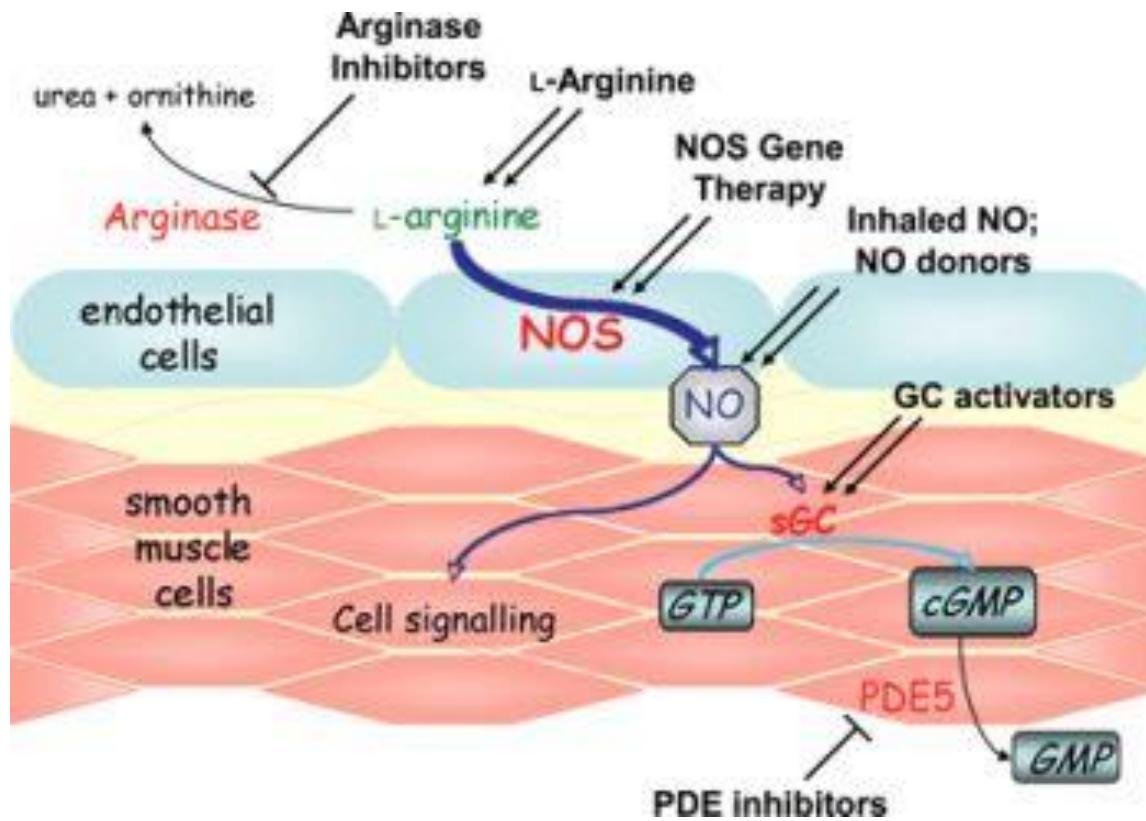
VEGF

- Vascular Endothelial Growth Factor
- Angiogenesis
- NO synthesis

Angiogenesis



NO



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How?

Erythropoietin

- Released by kidney under hypoxic conditions
- Bone marrow
- Increases red blood cell count

LDH-1

- Lactate dehydrogenase
- Pyruvate → Lactate
- LDH-1 variant
- Higher Km value



Deer mouse



High vs. Low

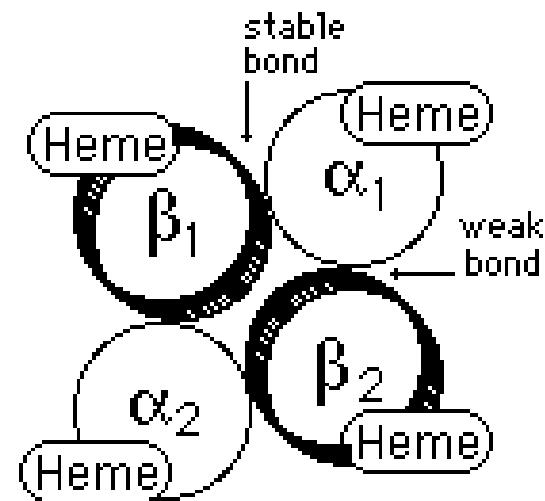
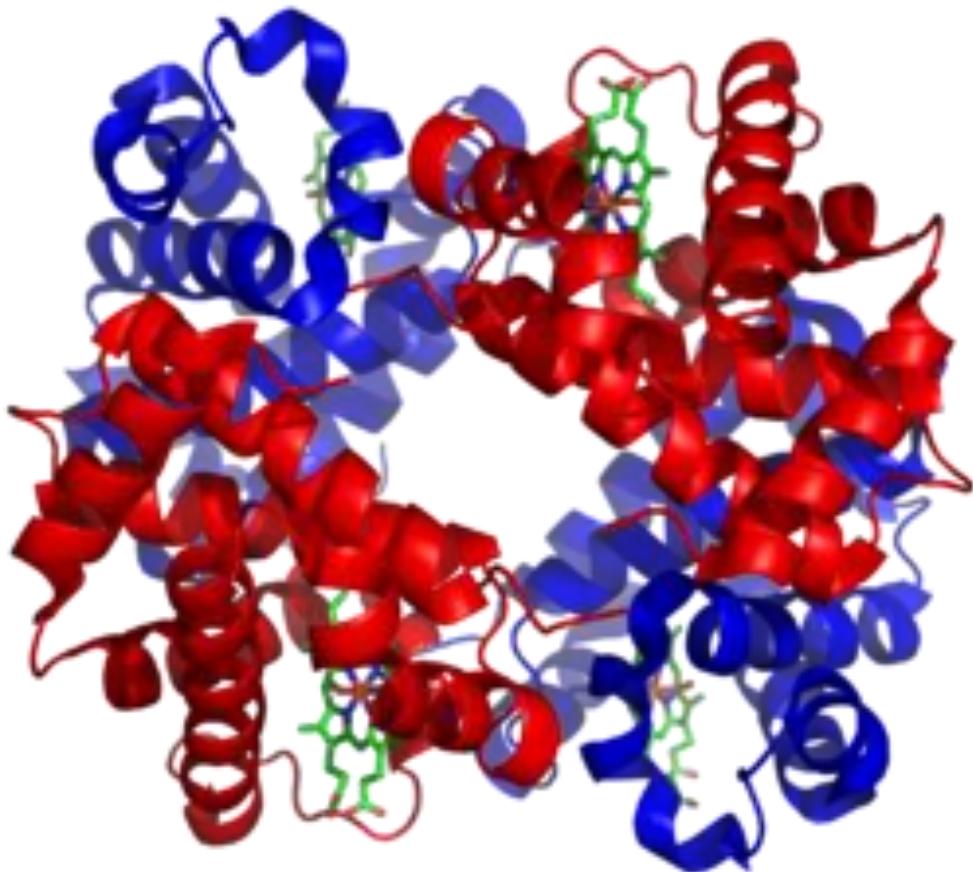
- Slight variation
- Organs
- Energy Demands



Hemoglobin

- Heterotetrameric
- T and R state
- 2,3 DPG

Heterotetrameric



Conformations



Figure 7-5a
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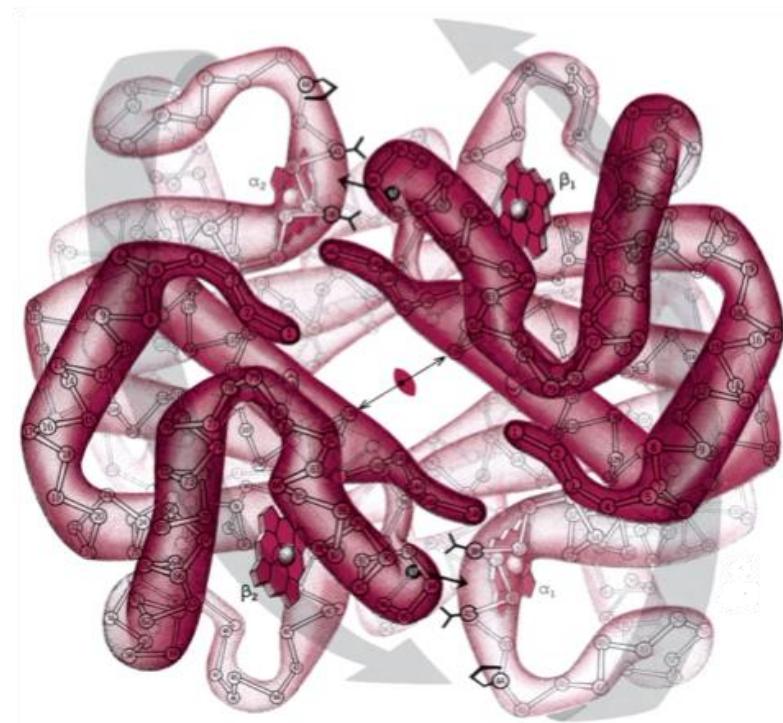


Figure 7-5b
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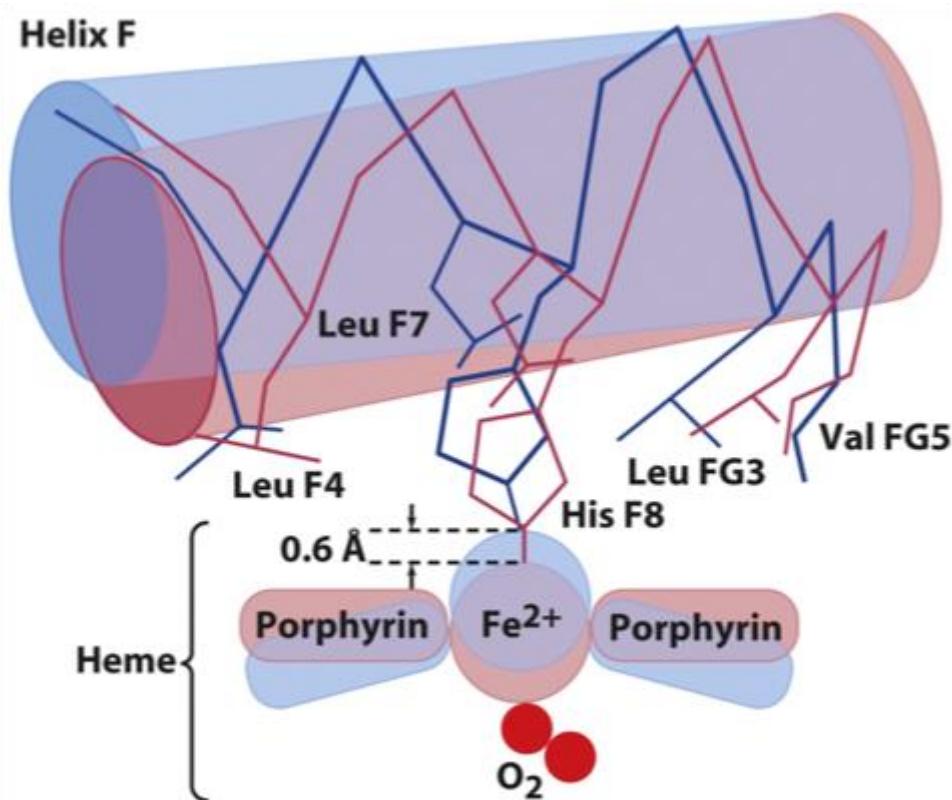


Figure 7-8
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2,3 DPG

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Why?

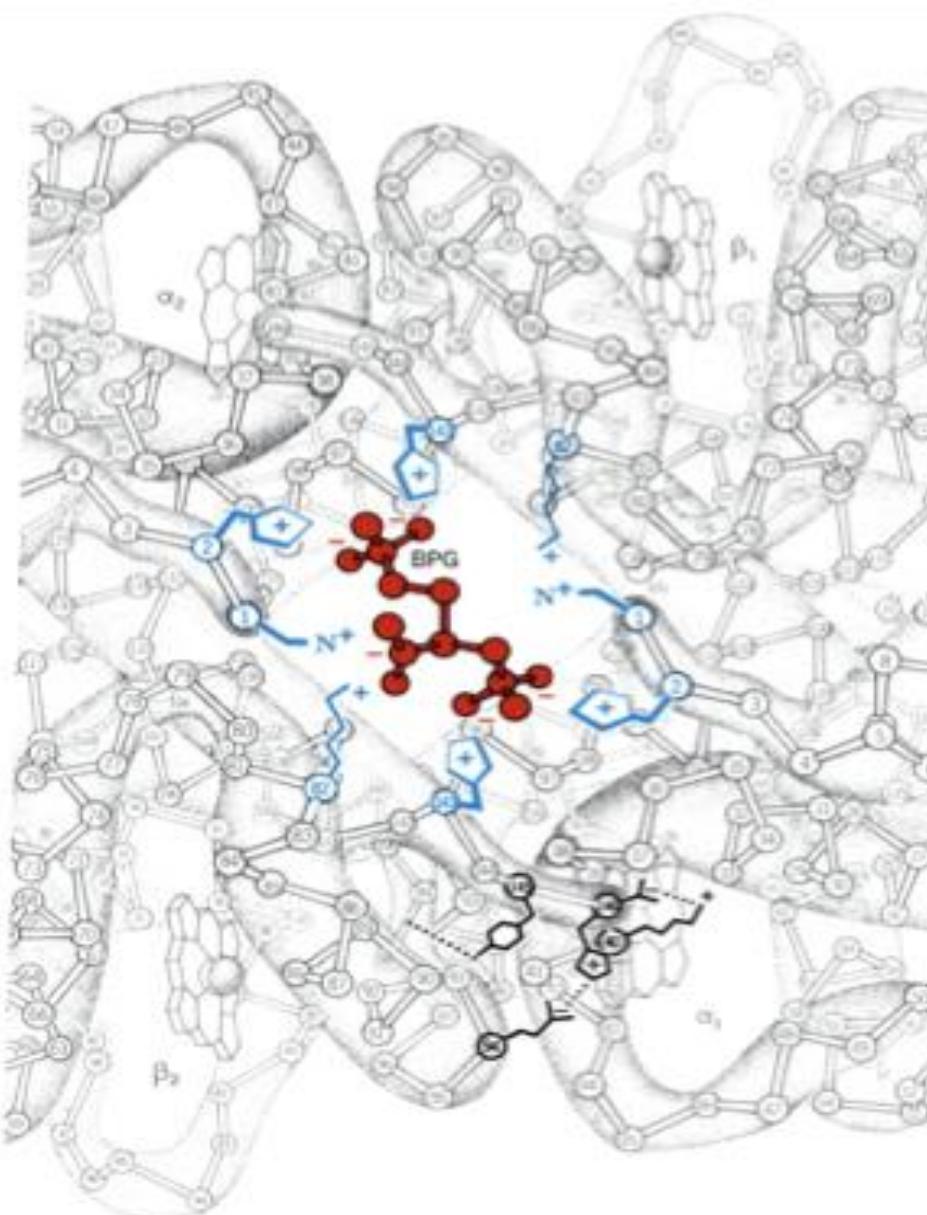
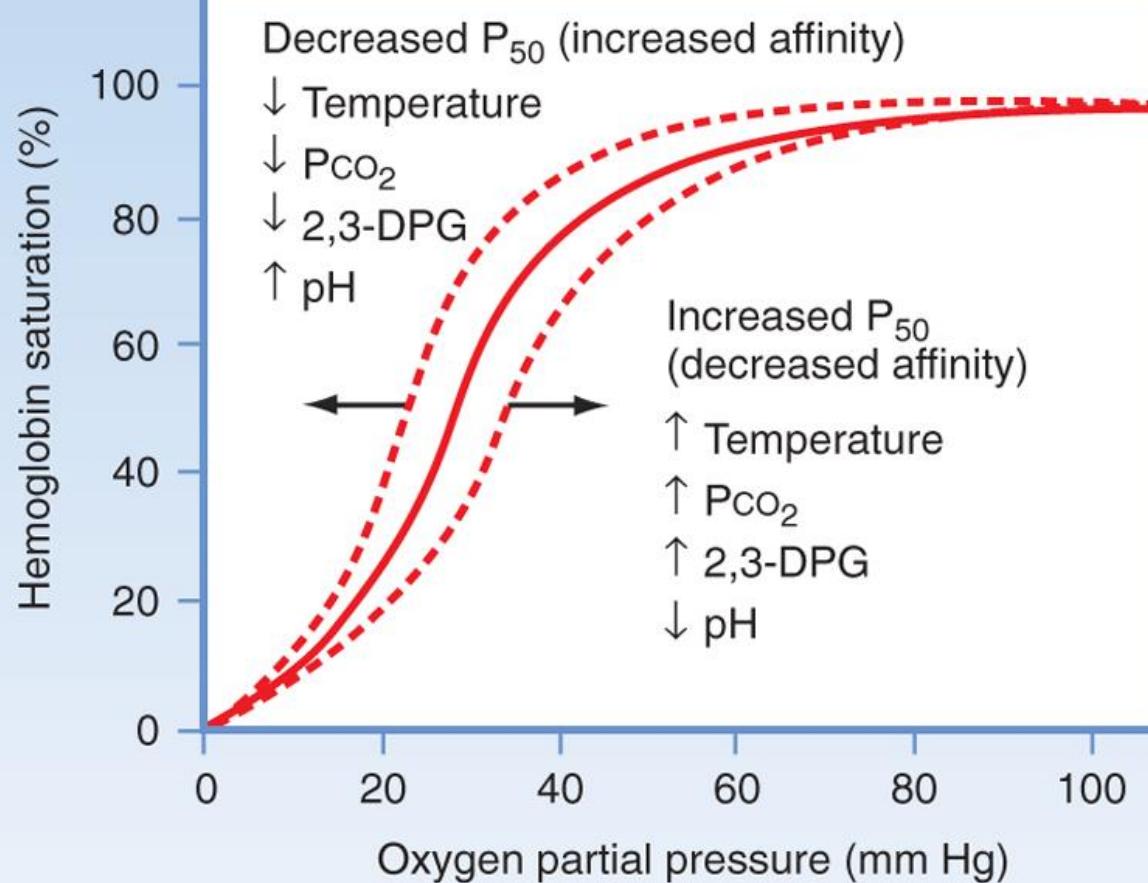


Figure 7-14

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Recap

- Morphology (physical structures)
- Sensitivity
- Genetic



Deep Sea Diving Humans

Problems Associated with Diving



What factors will diving mammals/humans need to account for?



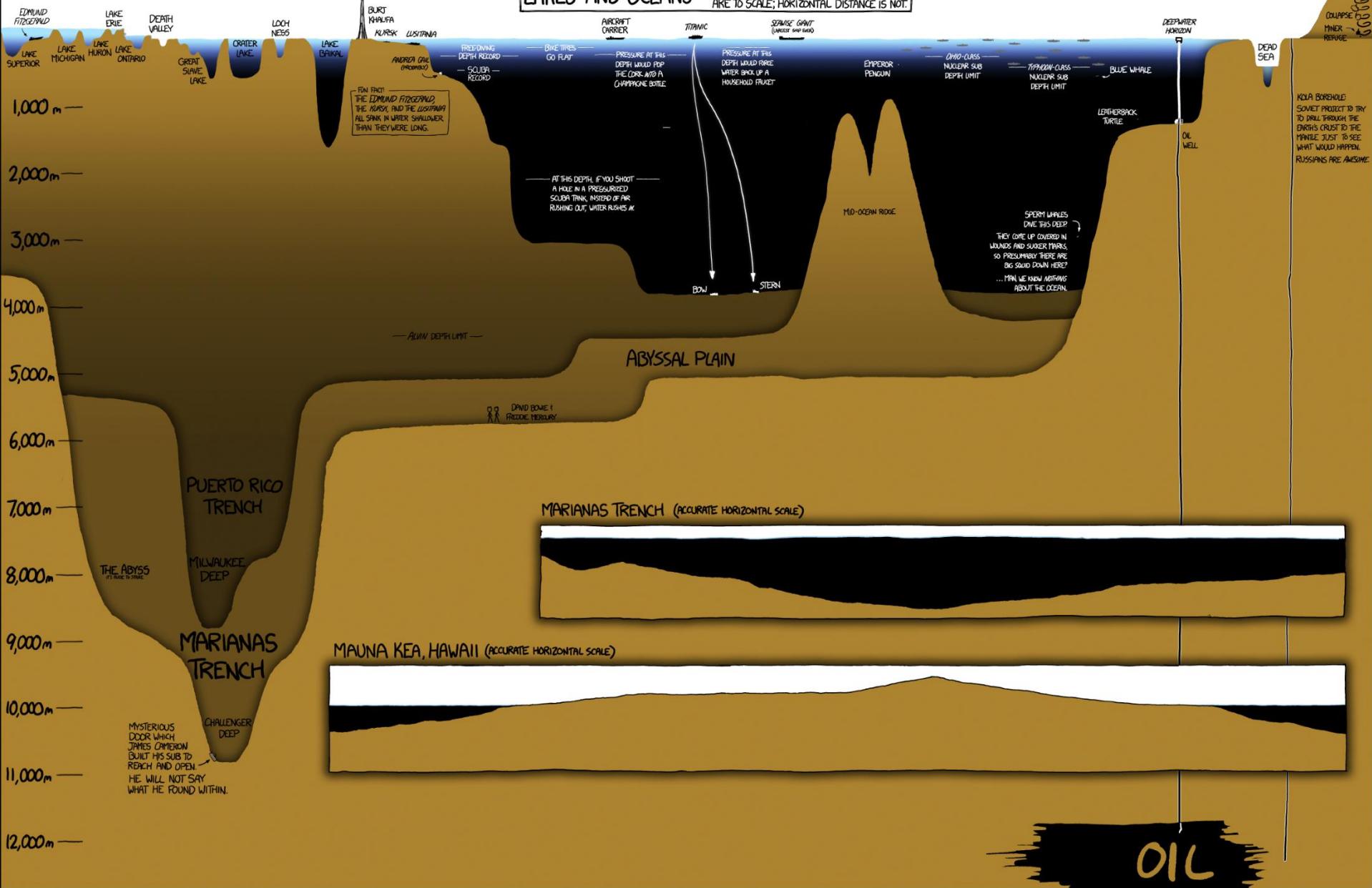
Factors

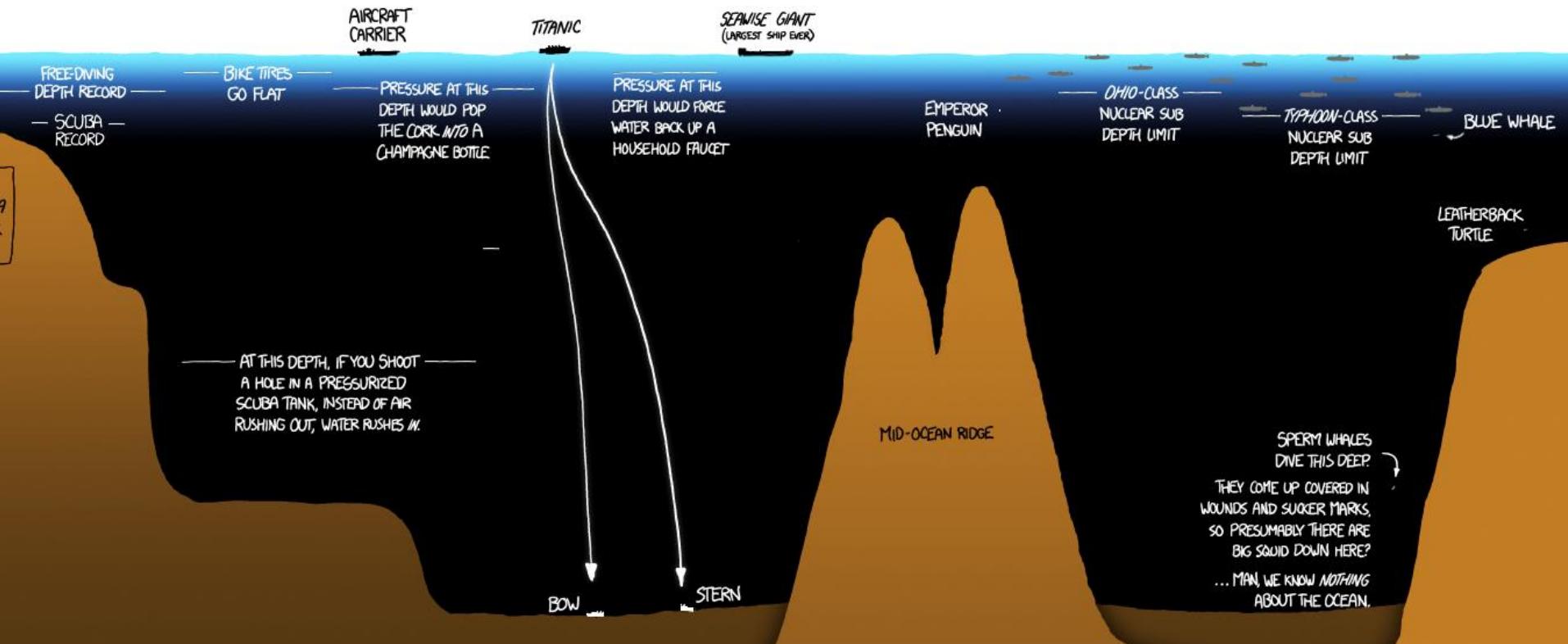
- Hypoxic Environment
- Increased Pressure
- Lower Temperatures
- Collapse of Airway
- Gas Release



LAKES AND OCEANS

DEPTHS AND ANIMAL/SHIP/BOAT LENGTHS
ARE TO SCALE; HORIZONTAL DISTANCE IS NOT.



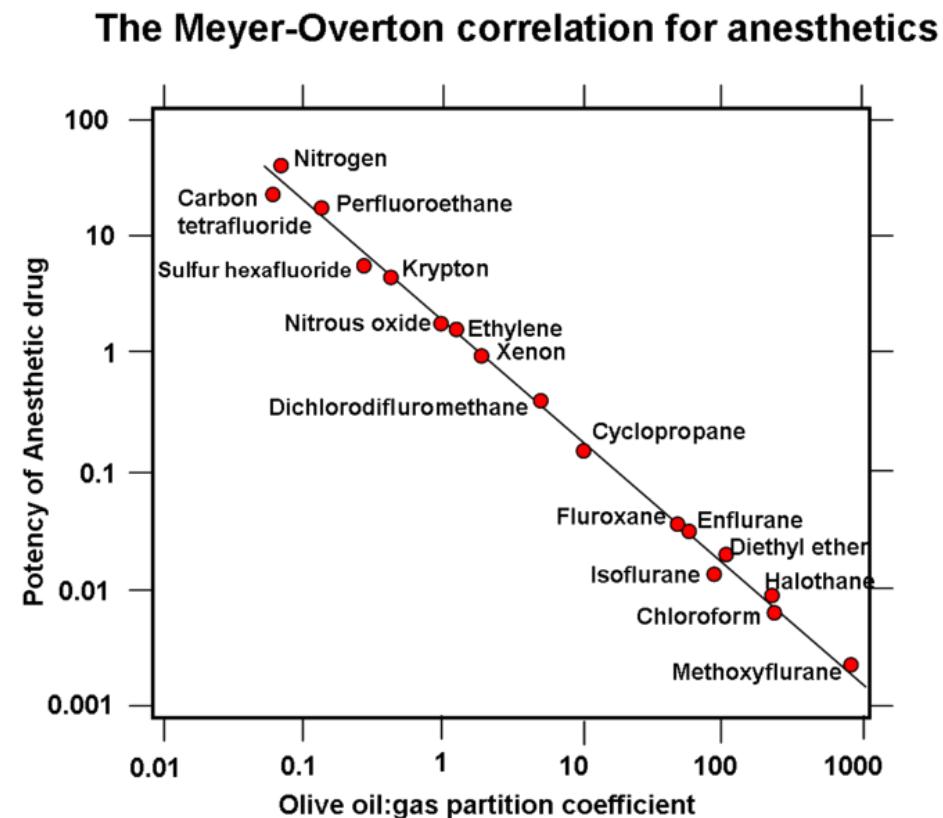


Total Air Pressure

Depth (ft)	Pressure (psia:atm)	Pound-force per square foot area
- 53,900 ft	1.47 psia : 0.1 atm	211
- 38,400 ft	2.54 psia : 0.2 atm	365
- 18,000 ft	7.35 psia : 0.5 atm	1,058
0 ft - sea level	14.7 psia : 1.0 atm	2,117
33 ft	29.4 psia : 2.0 atm	4,234
66 ft	44.1 psia : 3.0 atm	6,350
99 ft	58.8 psia : 4.0 atm	8,467
132 ft	73.5 psia : 5.0 atm	10,584
165 ft	88.2 psia : 6.0 atm	12,701

Inert Gas Narcosis

- Symptoms: confusion, impaired judgment, delayed response to stimuli, memory loss, anxiety, euphoria, hallucinations, & unconsciousness
- Symptoms appear at 30m (100ft) and increase in intensity
 - Led to deaths in several divers attempting to go below 120m (400ft)
- Gases dissolve into neuron membranes & interfere with synaptic transmission
 - May specifically antagonize certain receptors or interfere with ion permeability



Why?

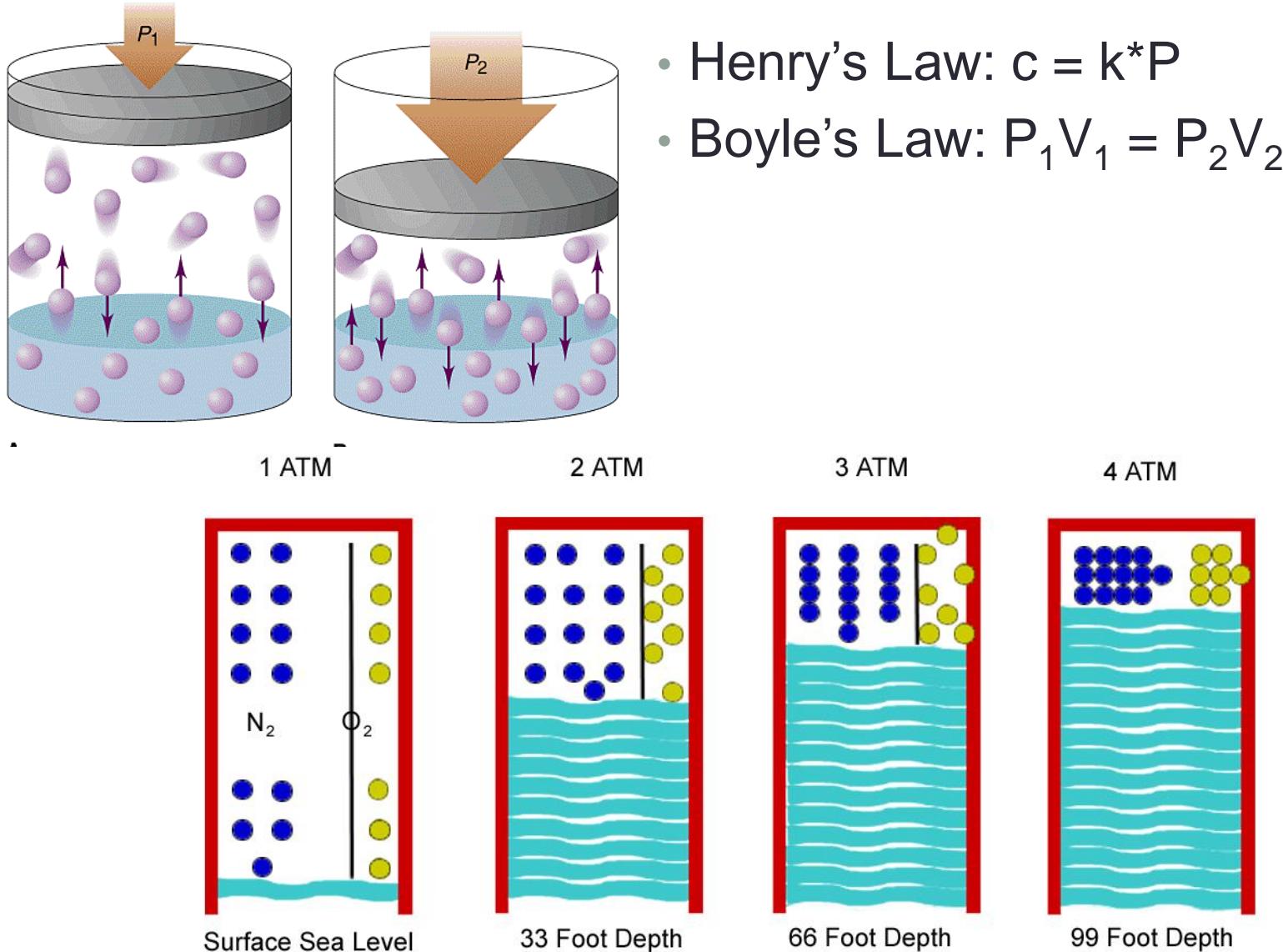
Decompression Sickness

- Symptoms appear in 48 hours following a scuba dive
 - Joint pain ("the bends"), skin itch & rash, dizziness, vertigo, muscle weakness/paralysis, fatigue, headache, pulmonary distress, hypovolemic shock
 - During ascent, lag occurs before saturated tissues start releasing gases back into the blood
- Arterial gas embolism: gases expand, rupture lung tissue, & release gas bubbles into circulation, which may block arteries
 - NS symptoms: dizziness, blurred vision, muscle weakness/paralysis, unconsciousness, seizures
- Can reduce risk with saturation diving or 100% O₂ prebreathing



Why?

Blood Gases



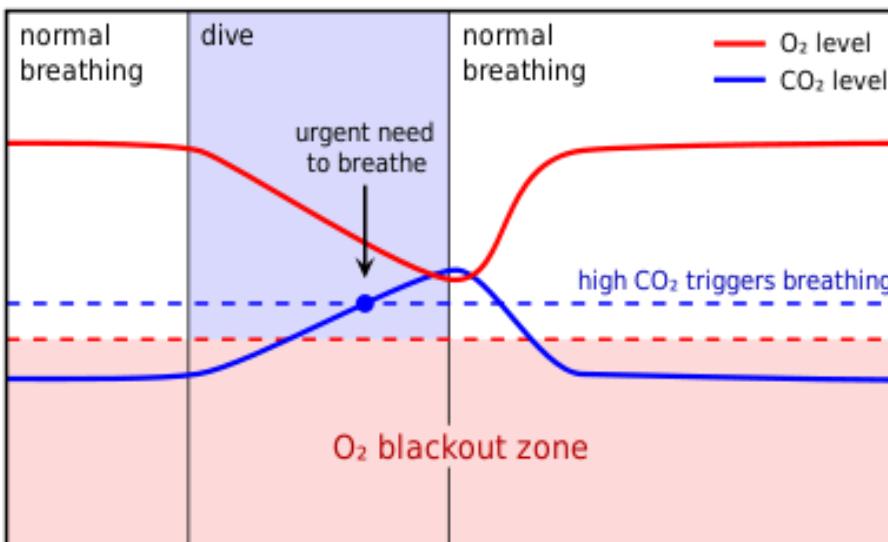
Shallow Water Blackout



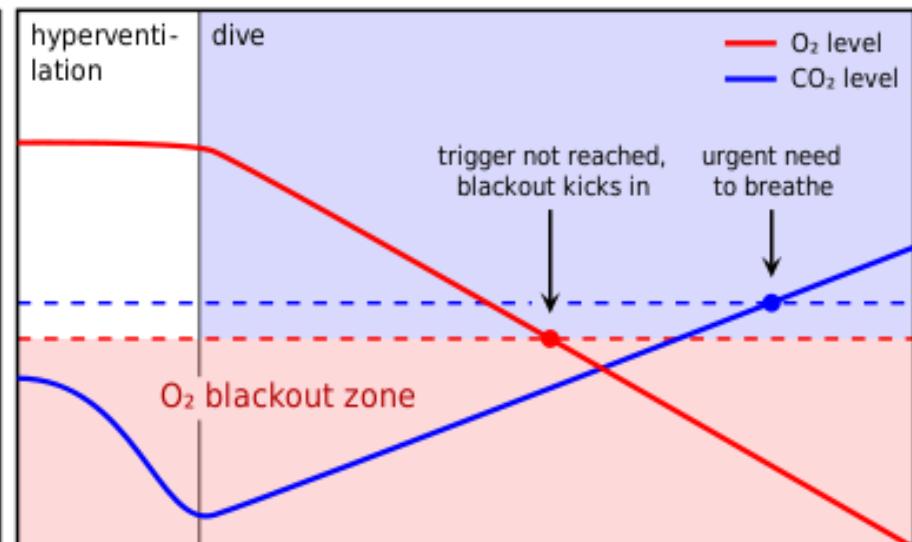
Why?

- Cerebral hypoxia near the end of a breath-hold dive
- Hyperventilation depletes CO₂ saturation (hypocapnia), but does not increase O₂ saturation
- CO₂ increases [H⁺], dropping blood pH and triggering a chemoreceptor response

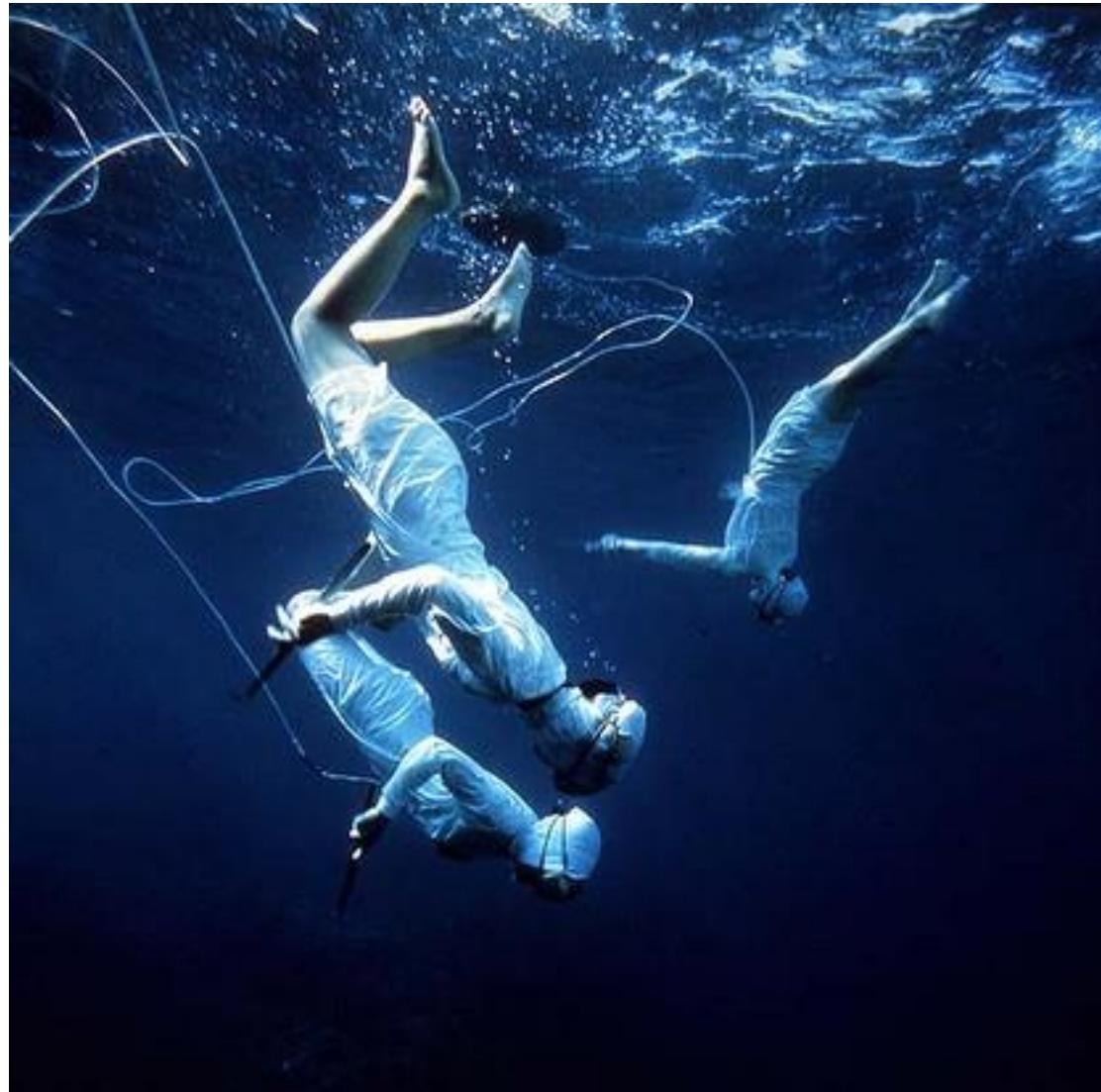
Normal dive



Dive with hypocapnia



Japanese Pearl Divers (Ama)

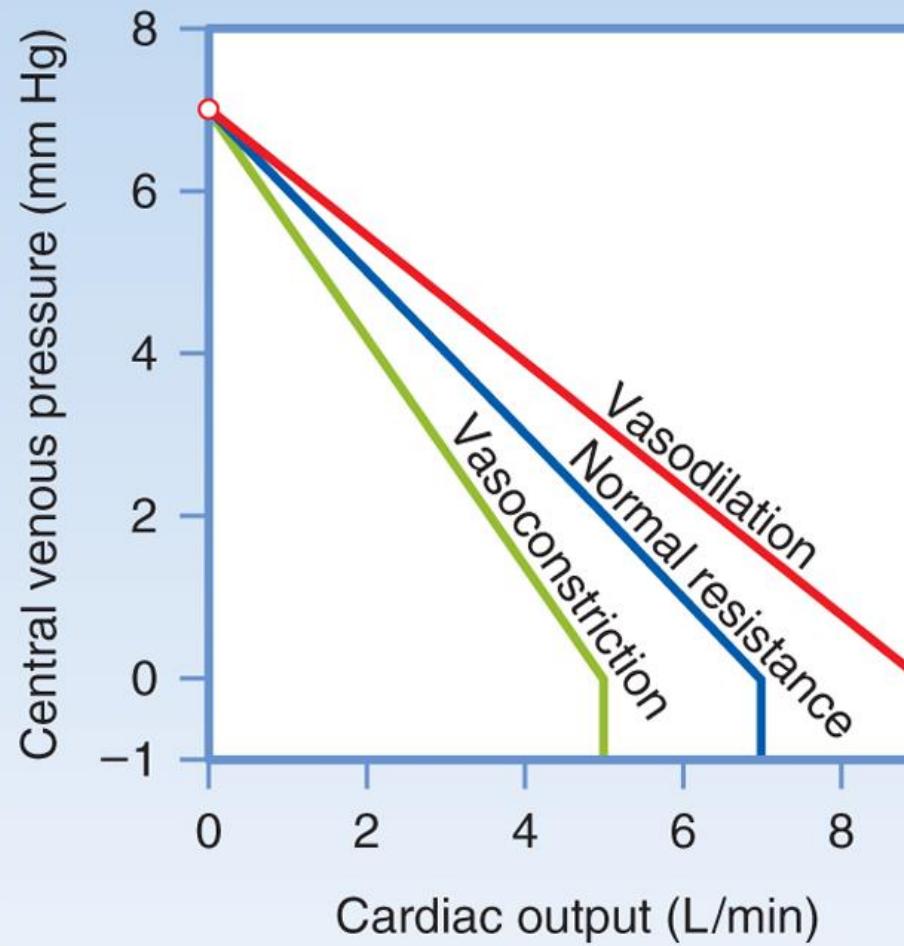


Oxygen Conservation Reflex

- Cardiovascular
 - Bradycardia (trigemino-cardiac reflex) increases CBF via cariovagal motor medullary pathway
 - Peripheral vasoconstriction → ↓ BF to skin, ↓ CO, & ↑ MAP
 - Baroreceptor stimulation further decreases heart rate
 - ↑ Hematocrit
- Metabolism
 - ↓ blood pH
 - Low muscle perfusion → shift to anaerobic metabolism → ↑ organic acids (like lactic acid)



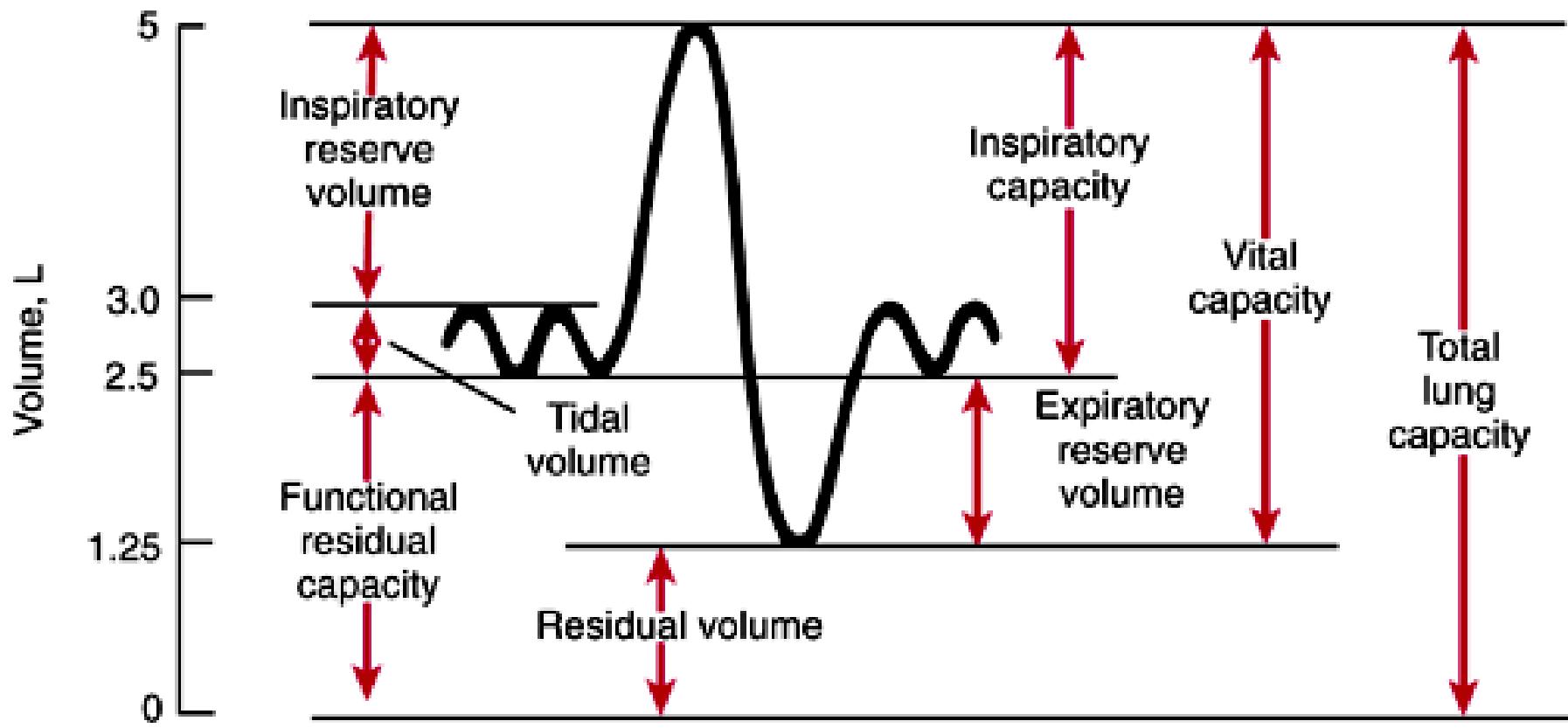
How does this conserve oxygen?



Diving Adaptations

- Thermal regulations
 - Lower critical water temperature
 - Higher metabolic rate
 - Peripheral vasoconstriction
- Blunted ventilation response to hypercapnia
- 15% higher vital capacity than non-diving peers
- Bradycardia as low as 20bpm

Lung Capacity





Deep Sea Animals

Mammalian Diving Reflex

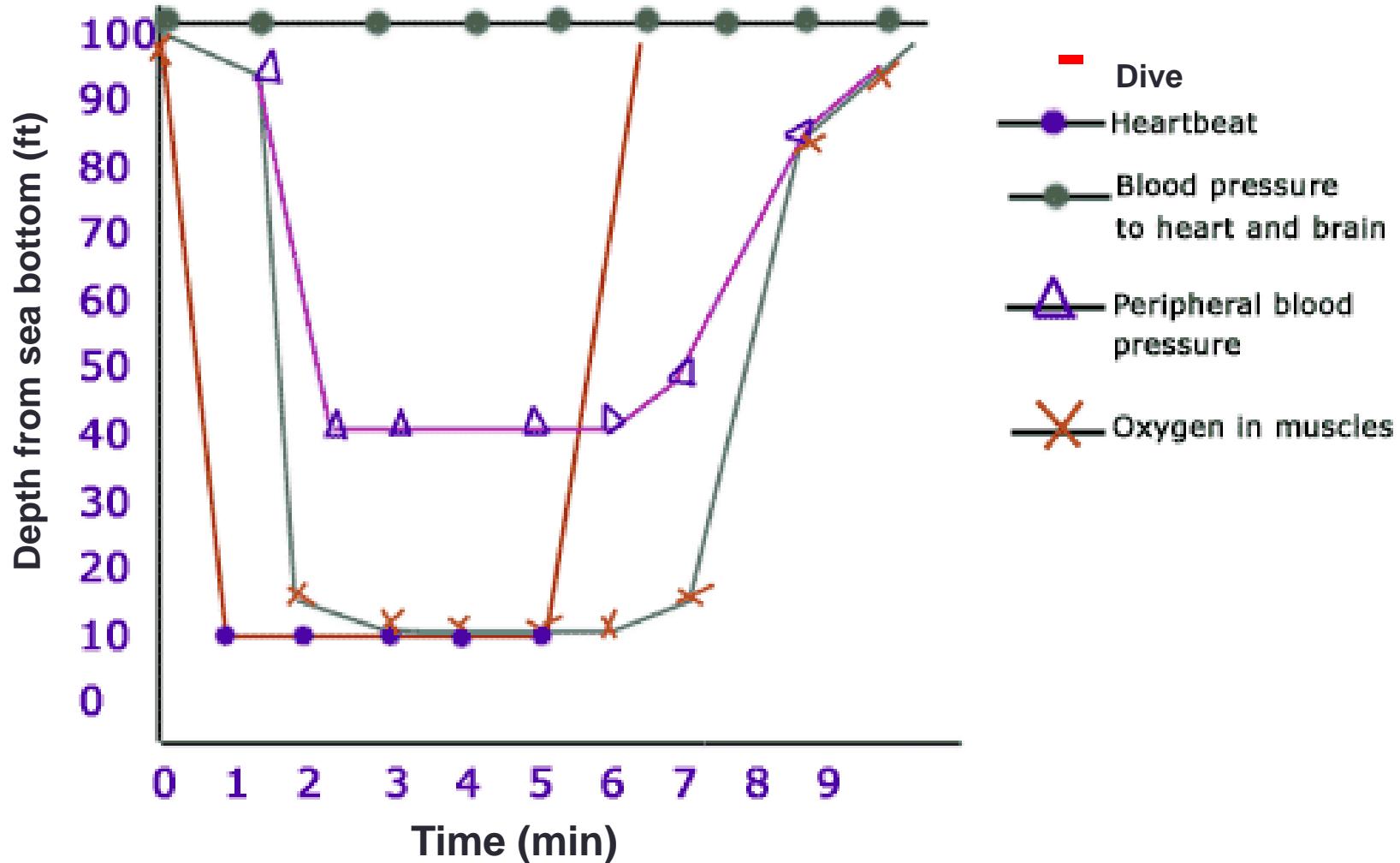
- Three parts:

- Apnea
- Bradycardia
- Peripheral Vasoconstriction



Additional part in marine mammals:

- Blood Shift



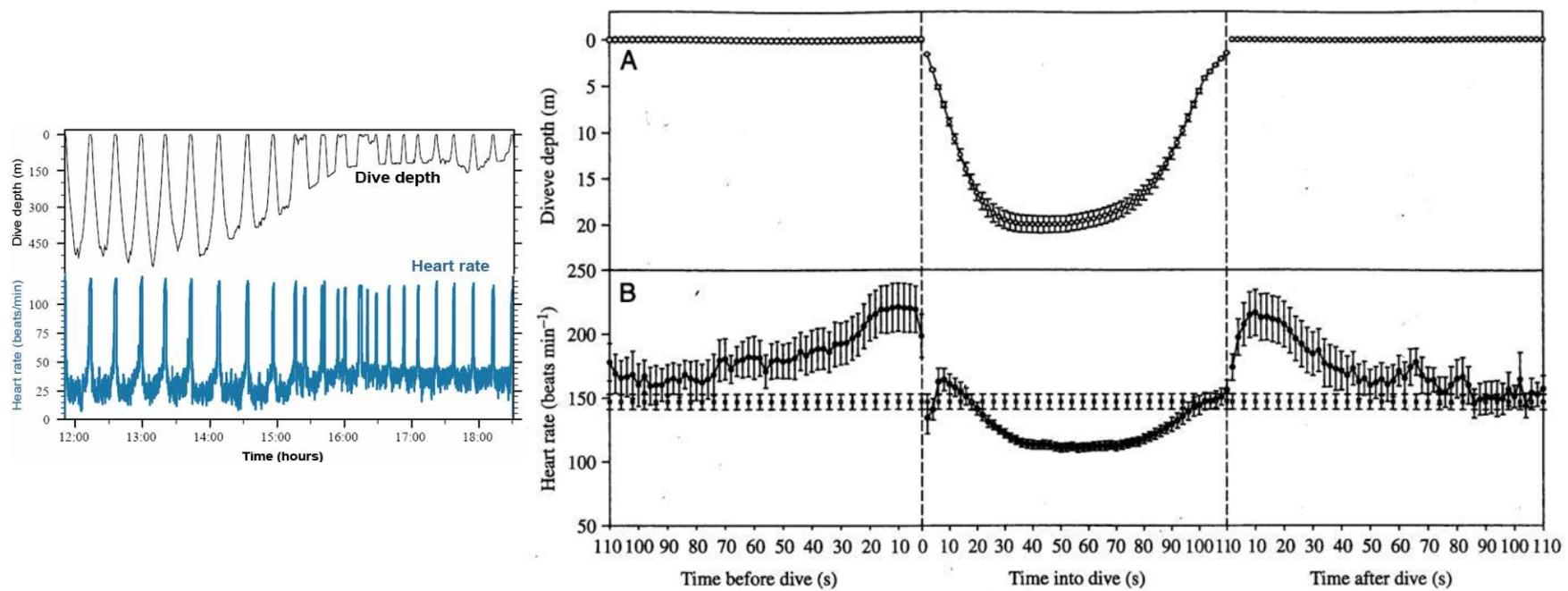
Mammalian Diving Reflex: Apnea

- Apnea: Temporary stop in breathing
- Stimuli: Receptors on face
 - Trigeminal nerve
- Prevents aspiration of water



Mammalian Diving Reflex: Bradycardia

- Heart Rate Slows
 - Humans: 70% Pre-dive HR v. Marine Mammals: 5% Pre-dive HR



Mammalian Diving Reflex: Vasoconstriction

- Arteries constrict to limit blood flow to viscera and muscles
- Lactic Acid is blocked

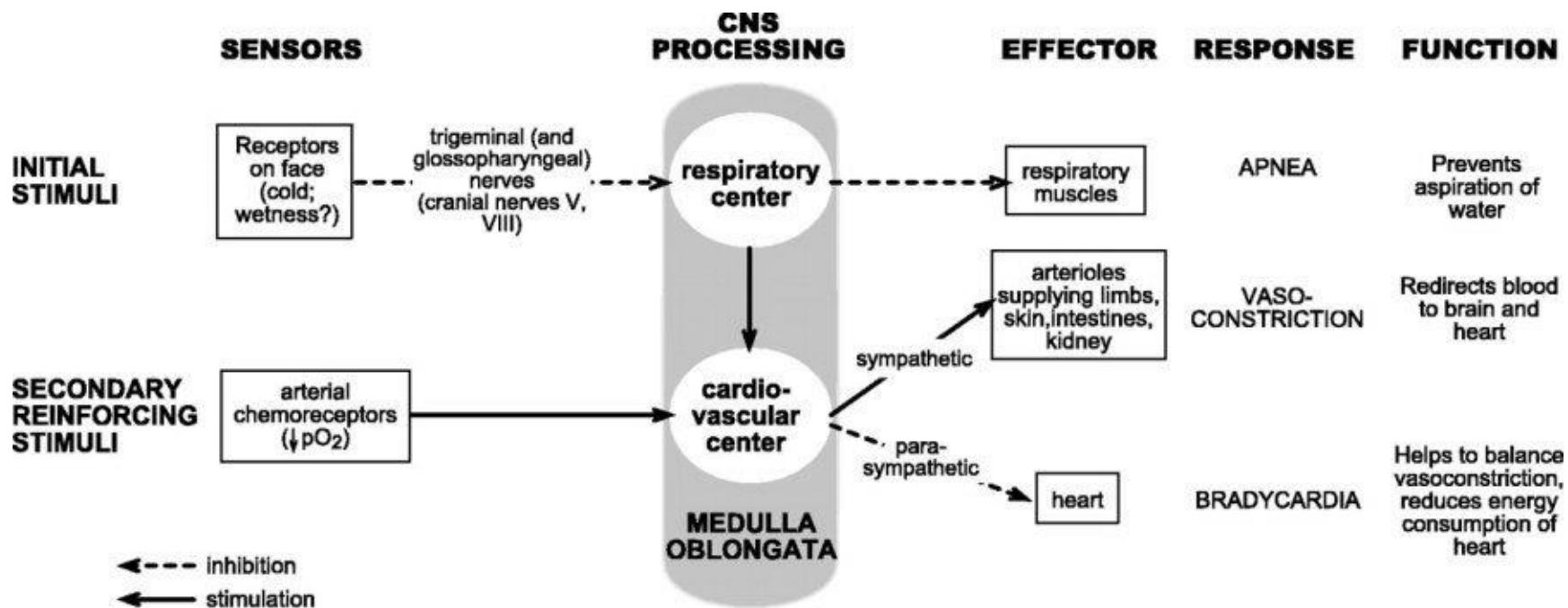


©ADAM

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Why do you want to block lactic acid?

Mammalian Reflex Overview



Specialized Mammalian Diving Response

- Blood Shift
 - Blood vessels in the periphery contract leaving more blood volume in the torso
 - Creates a pressure differential in the lungs → which leads to an influx of venous blood into the lung cavity

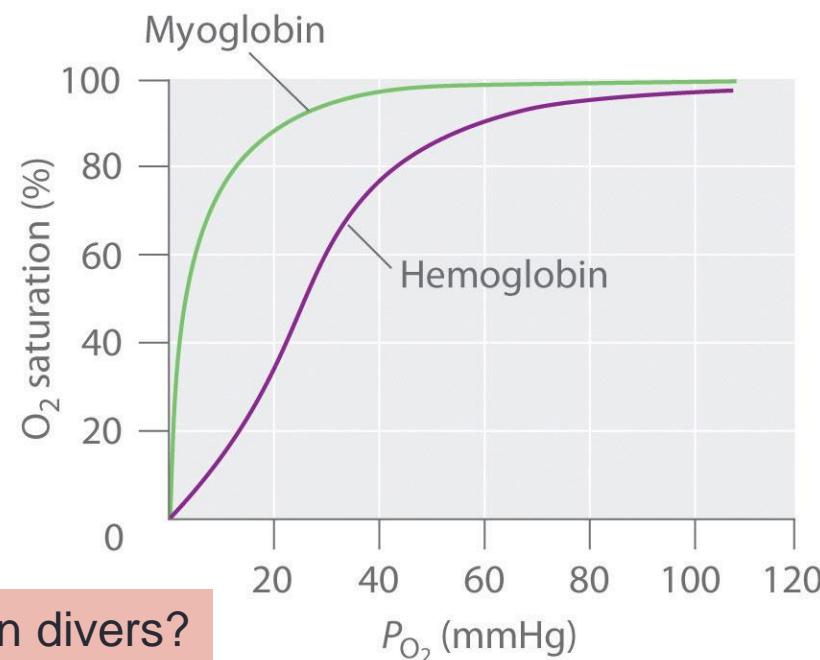
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If blood is directed away from the legs why is this beneficial?
(Hint: Where will they get energy?)

- Prevents “lung squeeze” by filling the capillaries of the alveoli

Hemoglobin and Myoglobin

- Comparison:
 - Terrestrial Mammals:
 - 14-17 g hemoglobin / 100 mL blood
 - 1 g myoglobin / 100 g muscle
 - Marine Mammals:
 - 21-25 g hemoglobin / 100 mL blood
 - 3-7 g myoglobin / 100 g muscle



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Why is Hb elevated in long-duration divers?

Oxygen Stores

- Main oxygen stores are in the blood and muscles
- Determinants of the rate of blood O₂ storage depletion
 - Changes in heart rate
 - Accompanying changes in renal and splanchnic blood flow
 - Degree of muscle perfusion during diving

Species	mL O ₂ kg ⁻¹	Lung %	Blood %	Muscle %
Human	20	24	57	15
Odontocetes	35	22	30	48
Otariids	40	13	54	33
Phocids	60	7	65	28
Sea Otter	55	55	29	16
Manatee	21	33	60	7

Aerobic Diving Limit (ADL)

Amount of time an animal may spend diving before an increase in blood lactate levels occurs

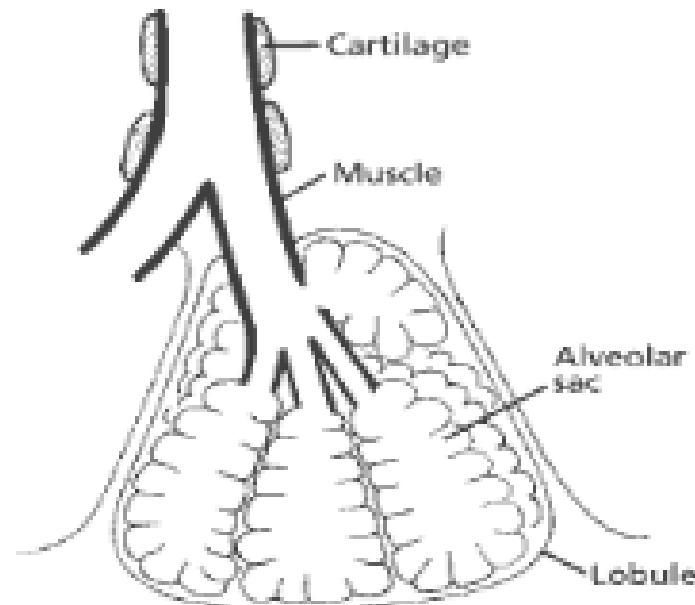
Factors:

- Oxygen Store Depletion Rates
- Lowest Tolerable Level of Blood Oxygen Store

$$cADL = [\text{total blood oxygen stores (in blood/muscle/lung)} / \text{oxygen demand}]$$

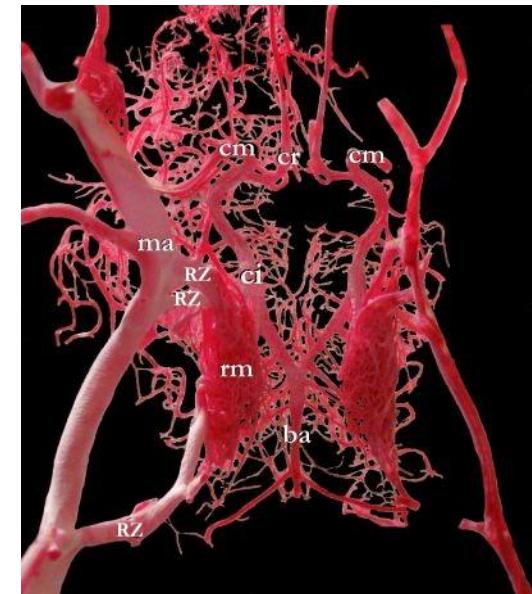
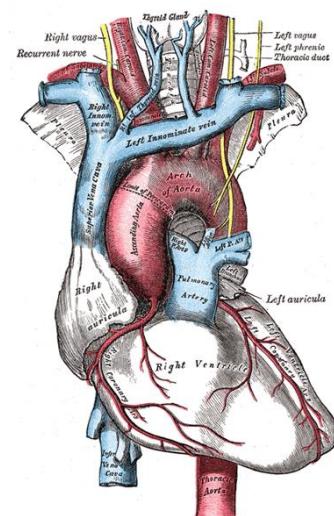
Respiratory Adaptations

- Rigid Airways
- Collapsible Lungs with Flexible Chest Walls
- Vascularized Alveoli
- Sphincter Muscles



Cardiovascular Adaptations

- Changes in Heart Rate and Cardiac Output
- Vasoconstriction
- Aortic Bulb Expansion
- Retia Mirabilia



Increased Blood Volume

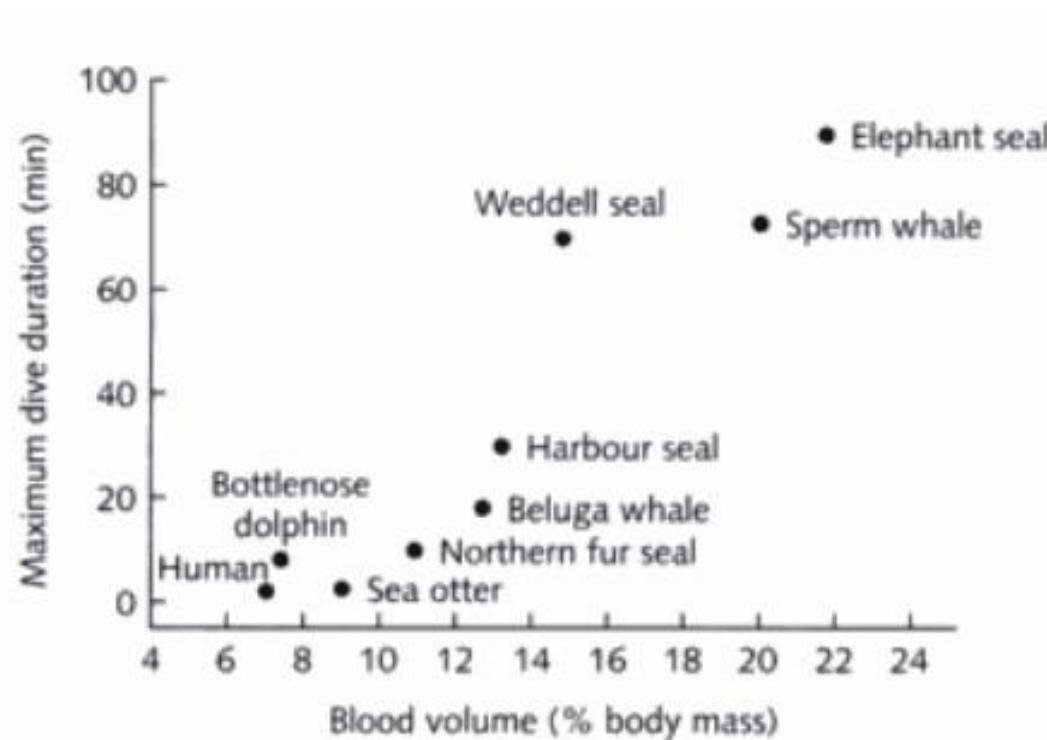
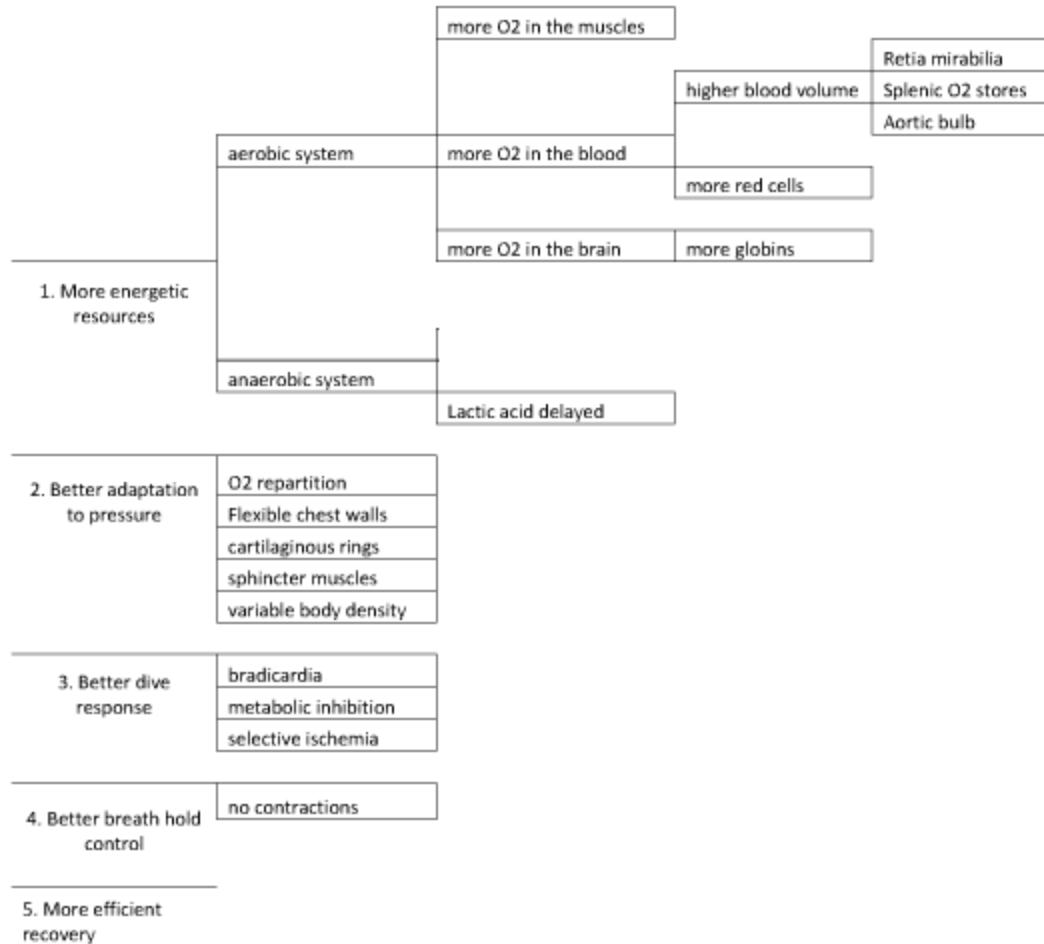


Fig. 3.8 Blood volume of marine mammals as a percentage of body mass in relation to maximum dive duration.
(Data from Kooyman 1989.)

Advantages

- Efficient ventilation
- Enhanced oxygen storage
- Regulated transport and delivery of gases
- Extreme hypoxic tolerance
- Pressure tolerance

Review



Sea Otter

Maximum Depth: 100 m

Maximum Duration of
Breath Hold: 4 min



Otter Adaptations

- Partially calcified trachea rings
- Densest fur of all mammals
- Larger chest volume



Weddell Seal



Maximum Depth: 626 m

Maximum Duration of Breath
Hold: 82 min

Seal Adaptations

- Higher concentration of oxygen is stored in myoglobin
- Efficient O₂ Storage
- Higher Blood Volume
- Spleen Adaptations
- Kidney Adaptations



Consequences for Immature Animals

- Young mammals have difficulty diving beyond very shallow depths.

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What biological phenomena could reduce their ability to dive?

