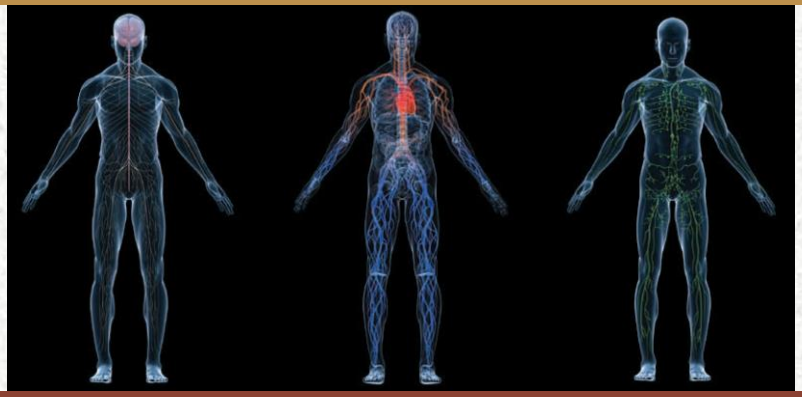
UNIT VII

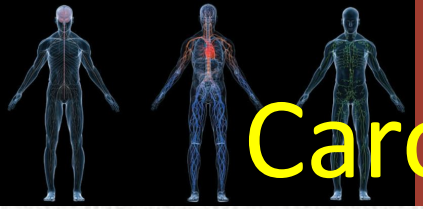
GUYTON AND HALL *Textbook of*
Medical Physiology
TWELFTH EDITION



Chapter 41:

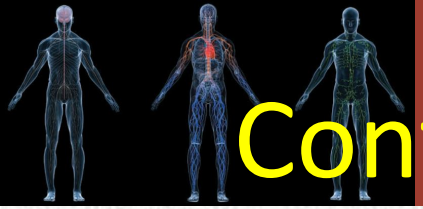
Regulation of Respiration

Slides by Robert L. Hester, PhD



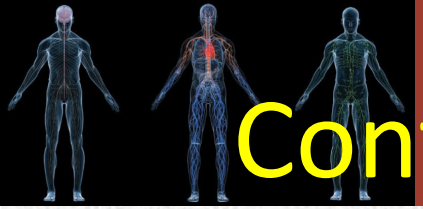
Carotid blood flow (ml/g/min)

Tissue	Blood flow (ml/g/min)	A-V difference (Vol %)	Flow ml/min	O_2 consumption ml/min
Heart	0.8	11	250	27
Brain	0.5	6.2 (25-30% Extraction)	750-900	
Skeletal Muscle	0.03	6	1200	70
Liver	0.6	3.4 Reconditioner organ		
SKIN	0.1			
Kidney	4.2	1.4	1250	18
Carotid bodies	20	0.5	0.6	



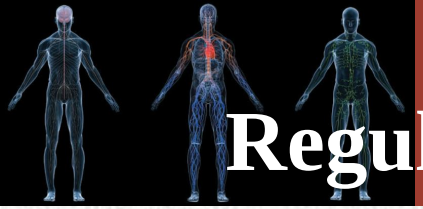
Control of Breathing....Introduction

- Q: What the controller system is going to do?
- A: Homeostasis of O_2, CO_2, H^+…Normal ABGs
- Q: How? What are the tools?
- A: by: ↑ventilation or ↓ventilation
- Q: What is the feedback system…nature of the receptor?
- A: ↓ $PaCO_2$, ↑$PaCO_2$, ↓ PaO_2 (below 60 mmHg), ↓ H+, and finally ↑H+
- **Note: ↑PaO_2 has almost no effect on the controller system**



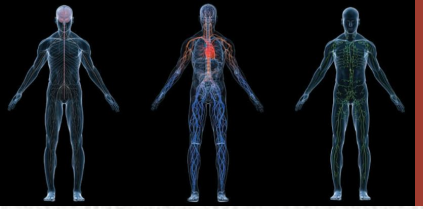
Control Of Breathing ….Introduction

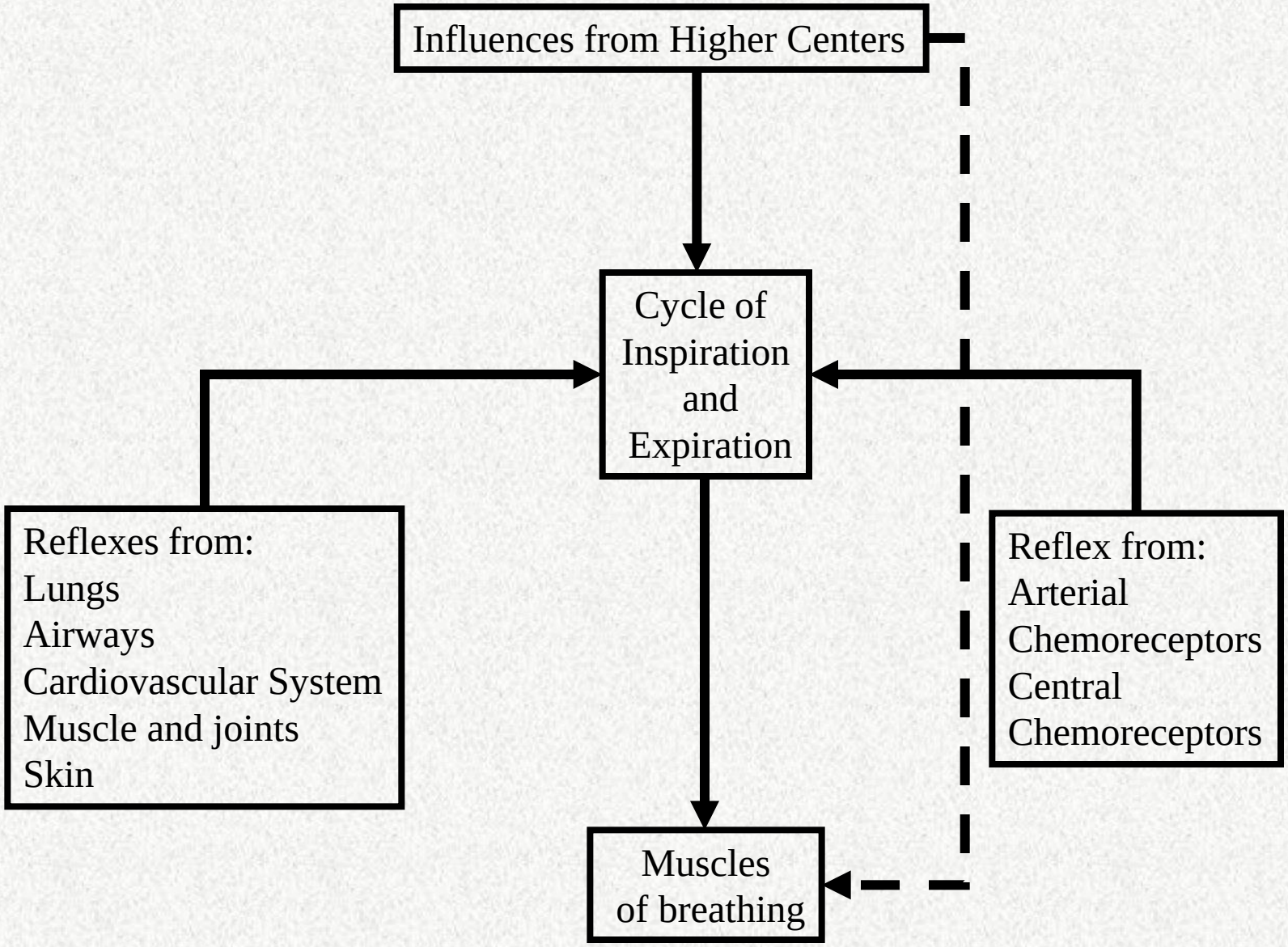
- Again: The main goal of the respiratory system is to maintain normal ABGs: O_2, CO_2, and pH
- The controller center receives feedback response from O_2, CO_2, and pH
- What are the tools: Manipulating ventilation
- Sensor and response: Peripheral and central nervous system



Regulation of Respiration ….Introduction

- Sensors…receptor… afferent pathway
  - gather information regarding CO2, O2, and pH
- Central controller
  - integrate signals…translation…output orders…the efferent pathway.
- Effectors
  - Respiratory muscles…receive the output from the respiratory center and produce a response that change the controlled condition.





How alveolar ventilation V_A affects P_AO_2 and P_ACO_2

P_AO_2 depends on :

1. O_2 delivery to alveoli (Alveolar Ventilation V_A).
2. Rate of O_2 absorption to blood (O_2 Consumption VO_2)

$$P_AO_2 \propto (V_A/VO_2)$$

HYPERVENTILATION is when alveolar ventilation is more than CO_2 production $\rightarrow$ decrease P_aCO_2

HYPOVENTILATION is when alveolar ventilation is LESS than CO_2 production $\rightarrow$ increase P_aCO_2

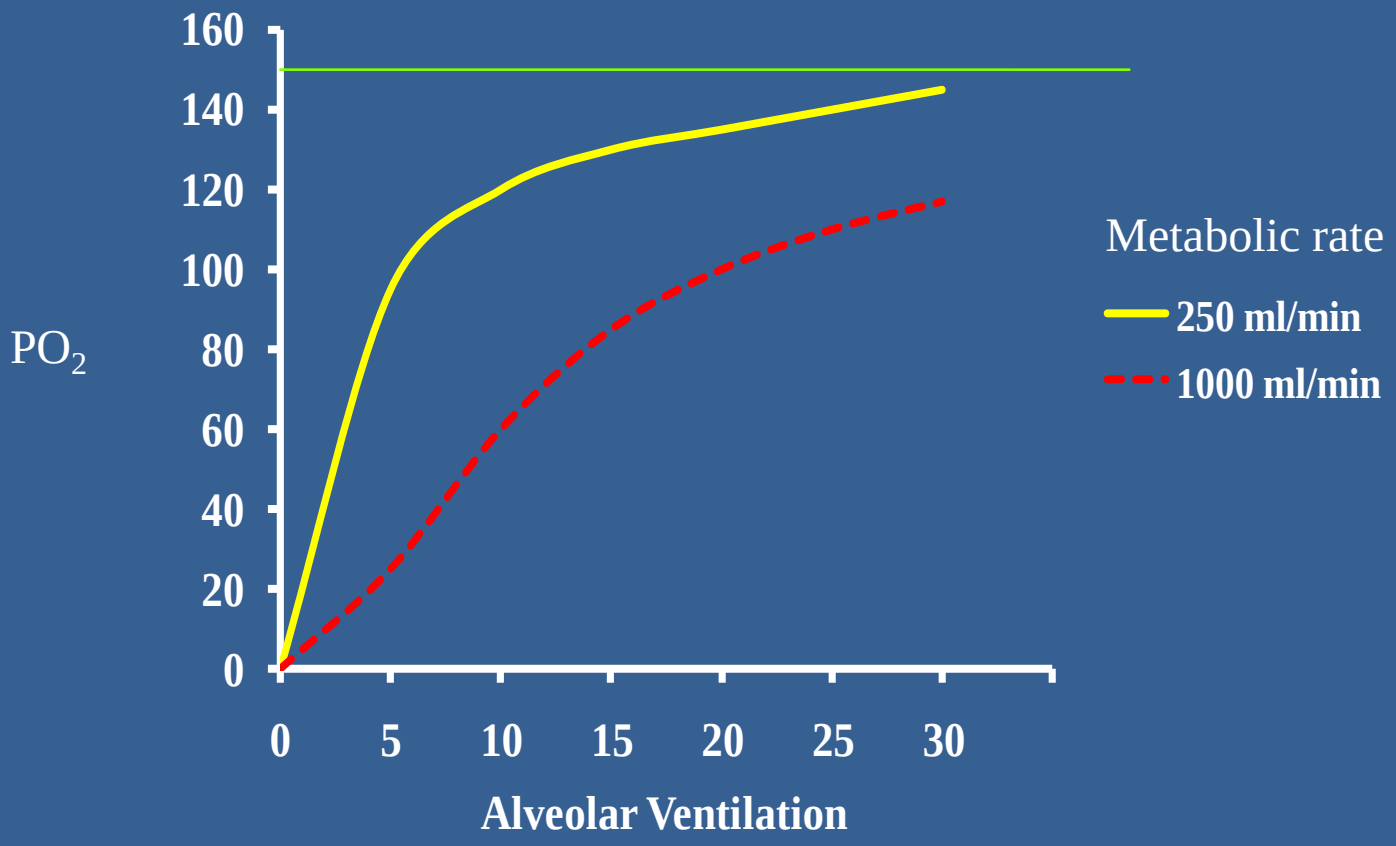
$$P_ACO_2 = (VCO_2/V_A)* K$$

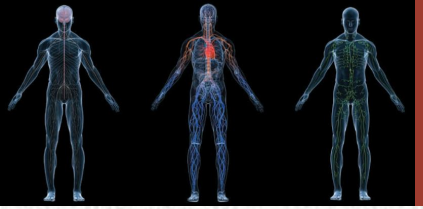
K"= constant (= 0.863 mmHg. lit/ml).

If ventilation is doubled then P_ACO_2 decreases to ½

If ventilation is halved then PCO_2 is doubled…keeping CO_2 production constant.....*See the two graphs in the next two slide.*

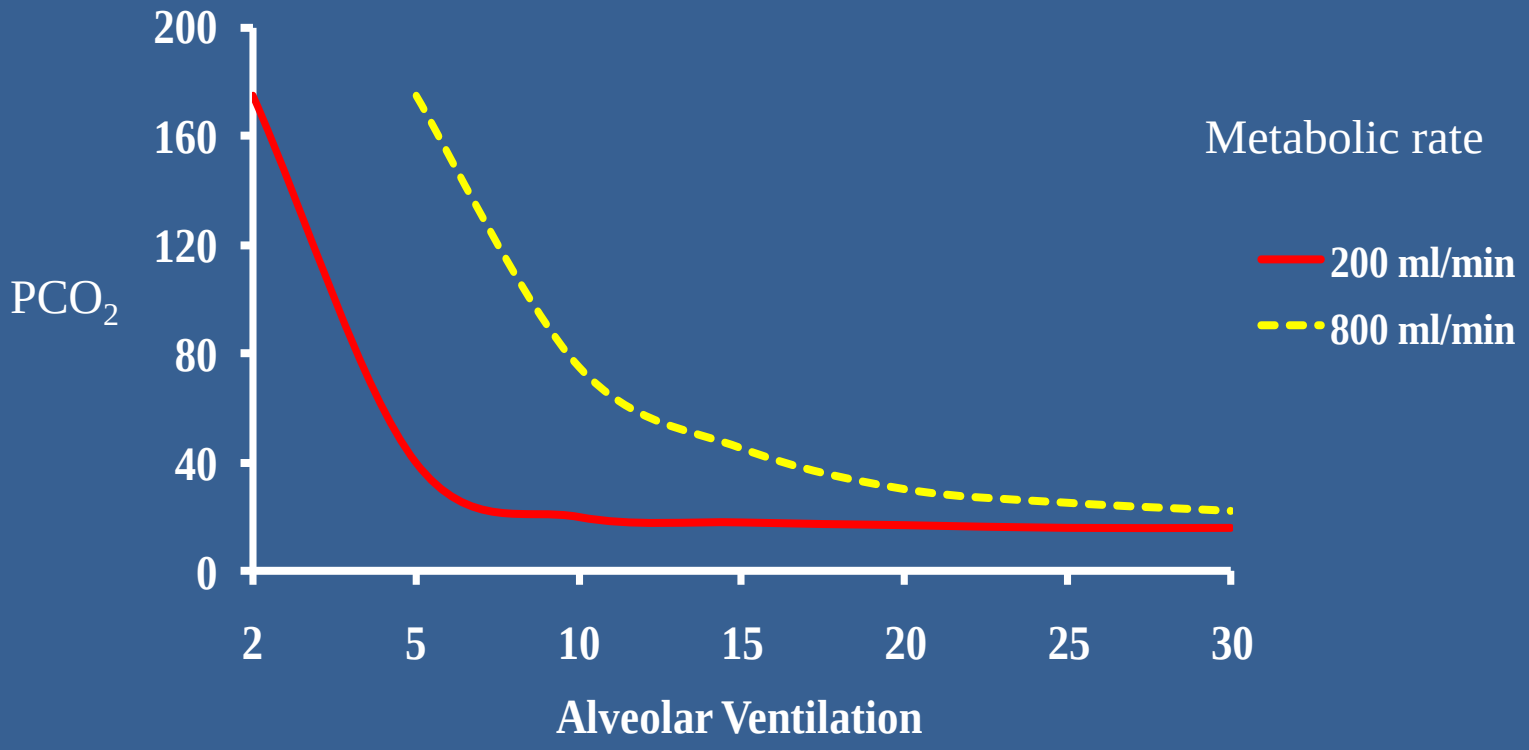
Partial pressure of oxygen in alveoli

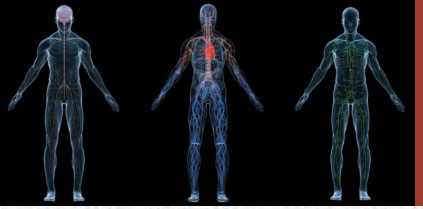




- Assuming perfusion is adequate … hyperventilation makes alveolar air like atmospheric air …. Hypoventilation makes alveolar air like mixed venous blood.

Partial pressure of CO_2 in alveoli





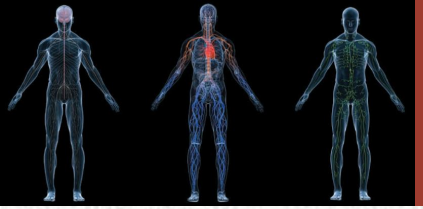
Question

Metabolic rate is doubled but alveolar ventilation is not changed. What happens to systemic arterial PCO_2?

A. Increases

B. Decreases

C. no change



Question

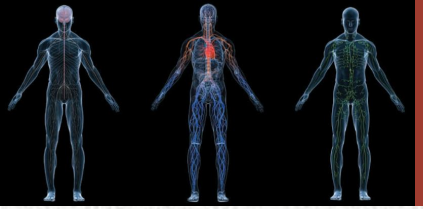
In which of the following conditions is alveolar PO_2 increased and alveolar PCO_2 decreased

A. Breathing air with 19% PO_2

B. Increased alveolar ventilation and unchanged metabolism

C. Decreased alveolar ventilation and unchanged metabolism

D .Increased metabolism and unchanged alveolar ventilation



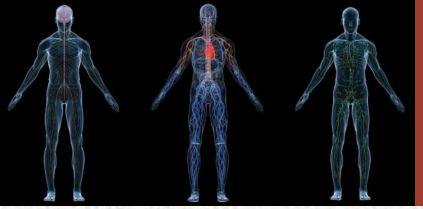
Question

What is the effect of anemia on ventilation?

A. decrease ventilation

B. increase ventilation

C. no change in ventilation.



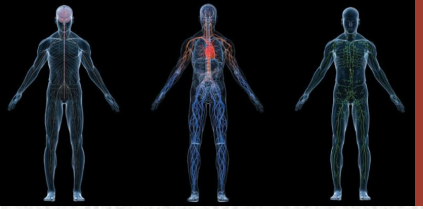
Question

Breathing CO acutely will __?__ respiration?

A. increase

B. decrease

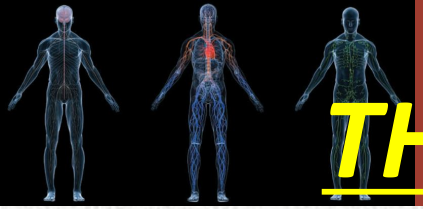
C. not change



Answer

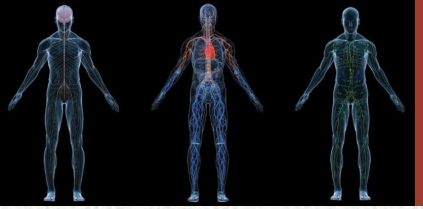
Breathing CO will not change respiration?

Arterial PO_2 does not change, PCO_2 does not change



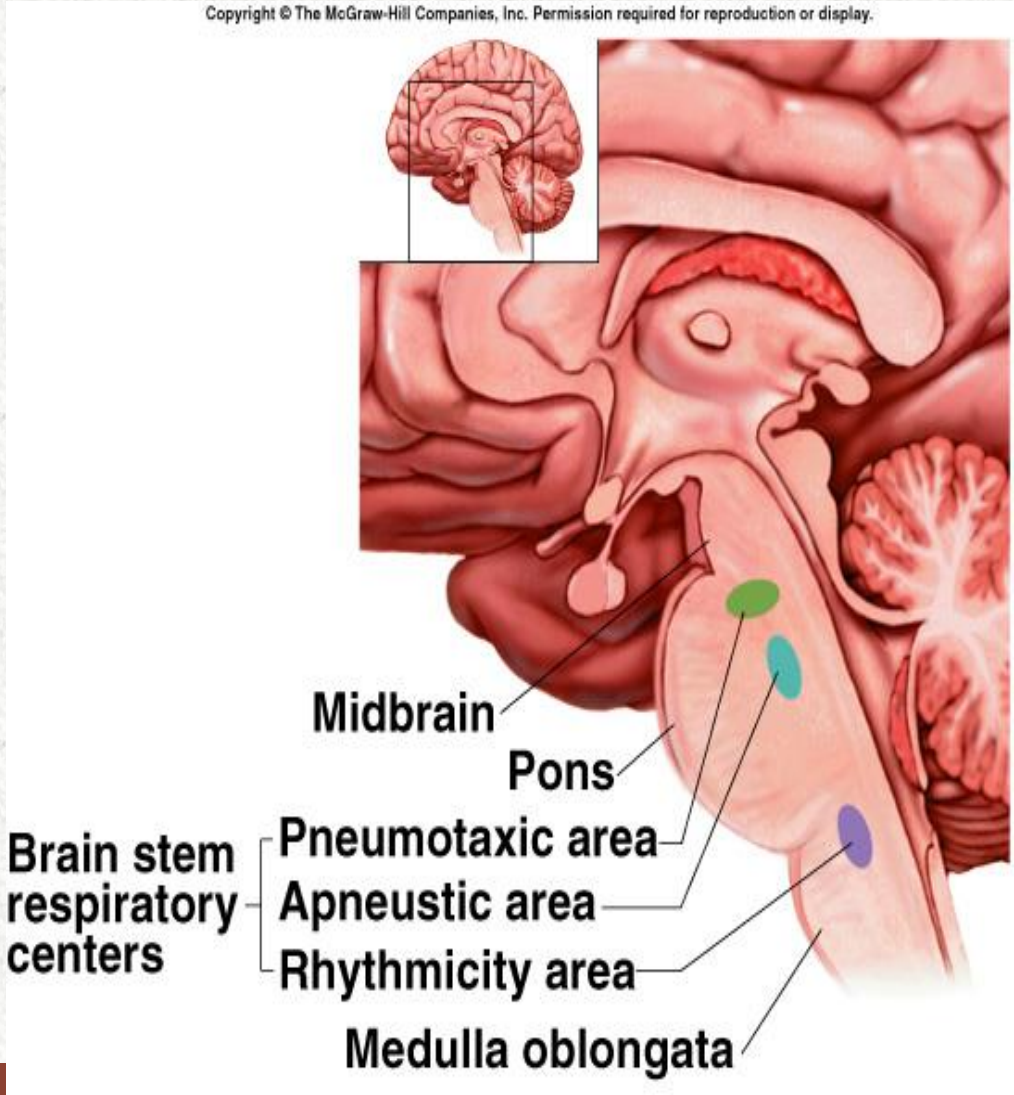
THE RESPIRATORY CENTER

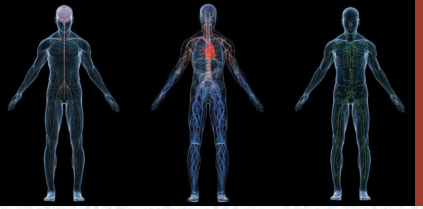
- It is a loose collection of inspiratory and expiratory neurons situated in the medulla oblongata of the brain stem. Is not a discrete identifiable center in the strict anatomical sense. When inspiratory neurons are active, expiratory neurons are inhibited and vise versa.



Brain Stem Respiratory Centers

- Neurons in the reticular formation of the medulla oblongata form the rhythmicity center:
  - Controls automatic breathing.
  - Consists of interacting neurons that fire either during inspiration (I neurons) or expiration (E neurons).





Respiratory Center

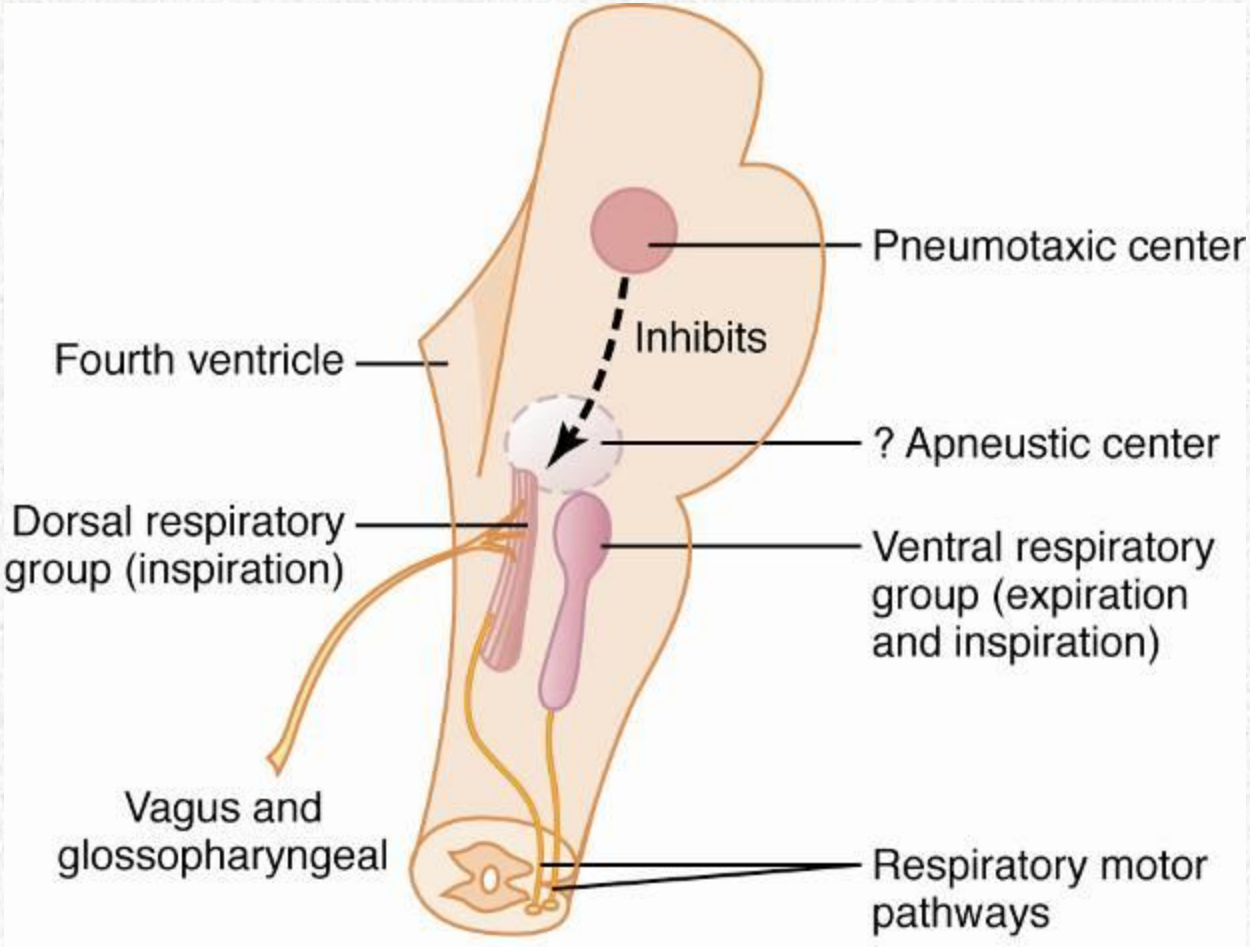
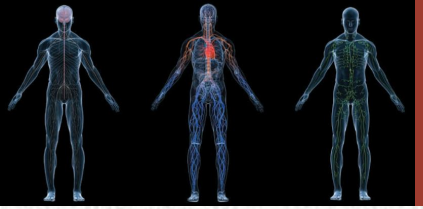


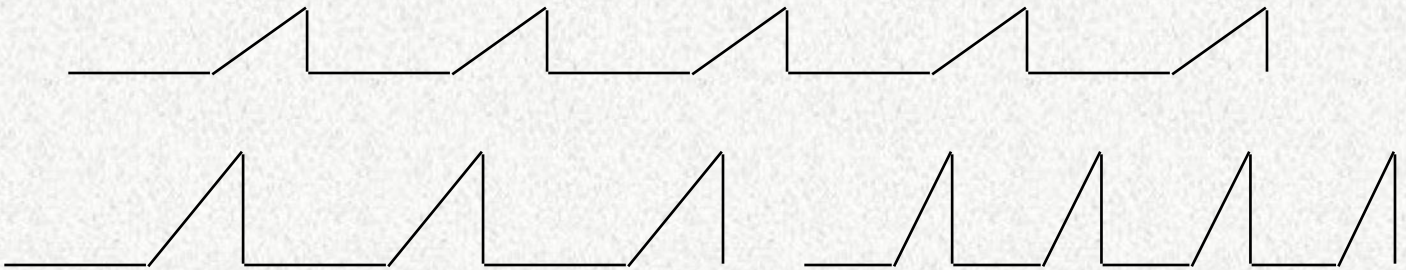
Figure 41-1

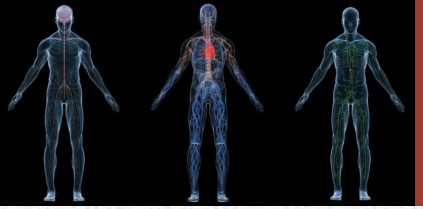


Medullary Respiratory Center

Dorsal respiratory group

- inspiration, intrinsic nerve activity



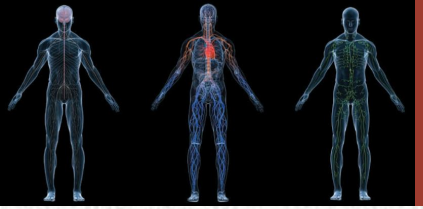


Respiratory Center

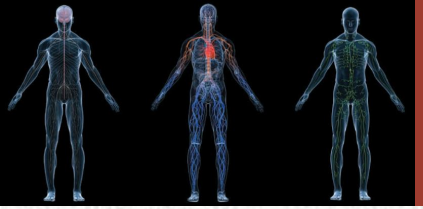
- Ventral Respiratory Group
  - Inactive during quiet respiration
  - Active respiration
  - Projections from the Dorsal Respiratory Group

Brain Stem Respiratory Centers (continued)

- "I" neurons project to, and stimulate spinal motor neurons that innervate respiratory muscles.
- Expiration is a passive process that occurs when the I neurons are inhibited.
- Activity varies in a reciprocal way.

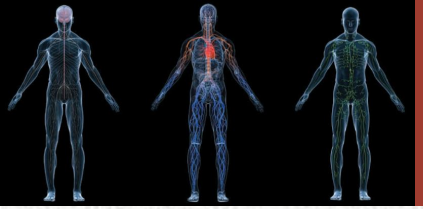


- **Inspiratory Neurons**:
- Easily excited and connected to one another by connexons that serve to synchronize their excitation to inspiratory muscles.
- **Expiratory Neurons:**
- Less numerous, less easily excited, but are linked too.
- Inspiratory **RAMP** signals, where inspiratory groups discharge slowly, then increase steadily but not suddenly, to make inspiration gradual and not gasping in nature. After 2 sec it ceases for the coming 3 sec. Actually, some inspiratory impulses even continue during early expiration to make the transition between inspiration and expiration smooth. If the rate of the ramp is increased then this will increase filling of lungs during exercise. Any thing control the limiting point of the ramp will increase RR.



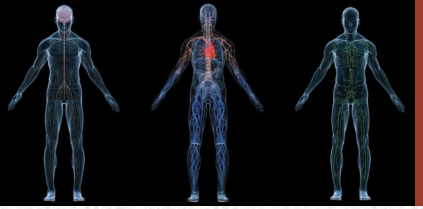
Rhythmicity Center

- "I" neurons located primarily in dorsal respiratory group (DRG):
  - Regulate activity of phrenic nerve.
    - Project to and stimulate spinal interneurons that innervate respiratory muscles.
- "E" neurons located in ventral respiratory group (VRG):
  - Passive process.
    - Controls motor neurons to the internal intercostal muscles.
- Activity of E neurons inhibit I neurons.
  - Rhythmicity of I and E neurons may be due to pacemaker neurons located in the upper part of the VRG.



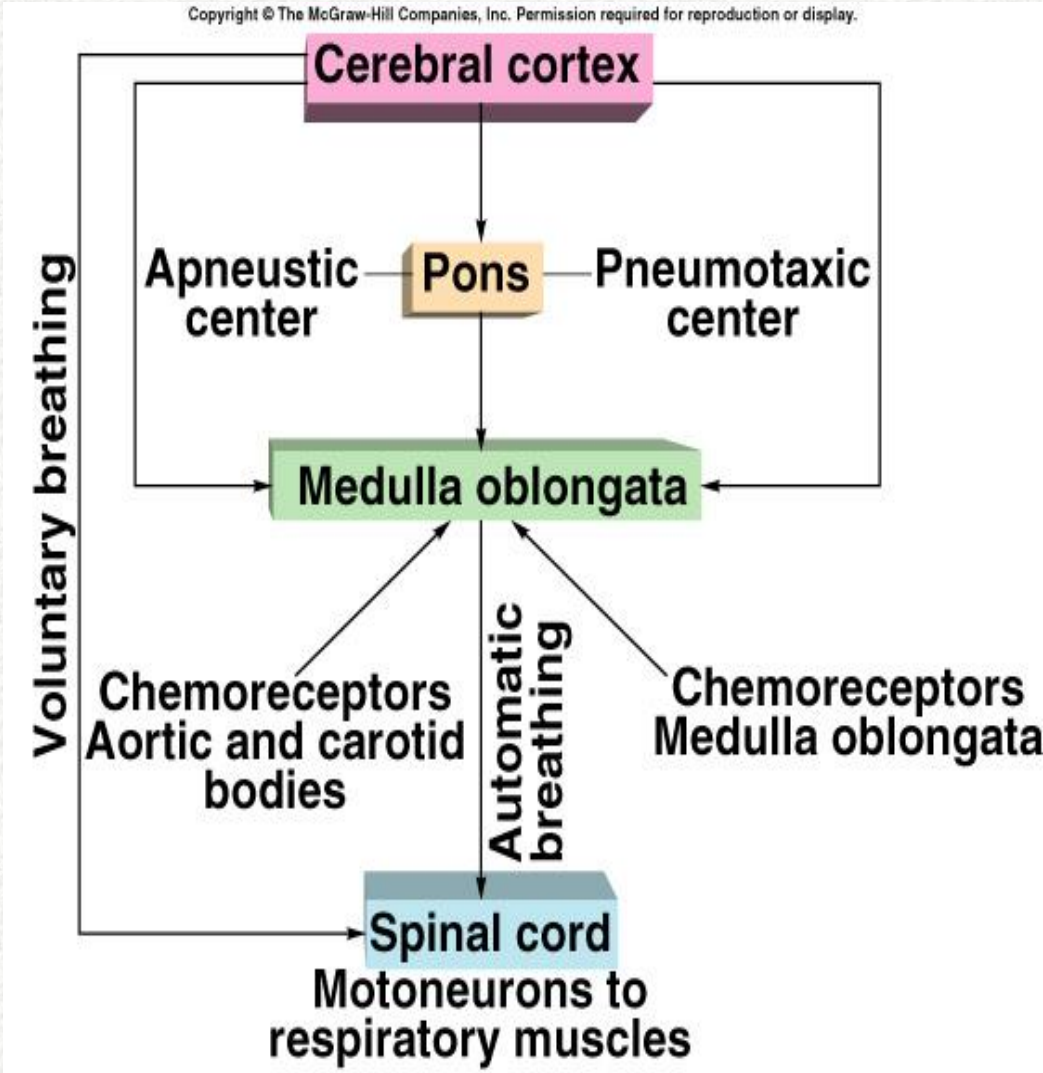
Pons Respiratory Centers

- Activities of medullary rhythmicity center is influenced by pons.
- Apneustic center:
  - Promotes inspiration by stimulating the I neurons in the medulla.
- Pneumotaxic center:
  - Antagonizes the apneustic center.
  - Inhibits inspiration and thus increase RR.
- **It is the Switch of** inspiration and modulate respiratory system



Chemoreceptors

- 2 groups of chemo-receptors that monitor changes in blood PCO_2, PO_2, and pH.
- Central:
  - Medulla…chemosensitive area…sensitive to H+
- Peripheral:
  - Carotid and aortic bodies.
    - Control breathing indirectly via sensory nerve fibers to the medulla (X, IX). Sensitive to O2

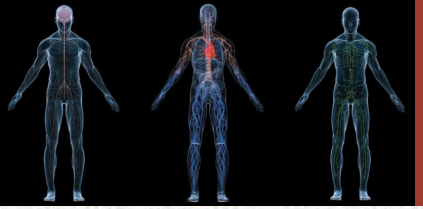


Effects of Blood P_{C0_2} and pH on Ventilation

- Chemoreceptor input modifies the rate and depth of breathing.
  - Oxygen content of blood decreases more slowly because of the large "reservoir" of oxygen attached to hemoglobin. HbO_2 dissociation curve is sigmoidal
  - Central Chemoreceptors are more sensitive to changes in PCO_2 through the H+

- $H_20 + C0_2 \longleftrightarrow H_2C0_3 \longleftrightarrow H^+ + HC0_3^-$

- Rate and depth of ventilation adjusted to maintain arterial PCO_2 equals to 40 mm Hg.



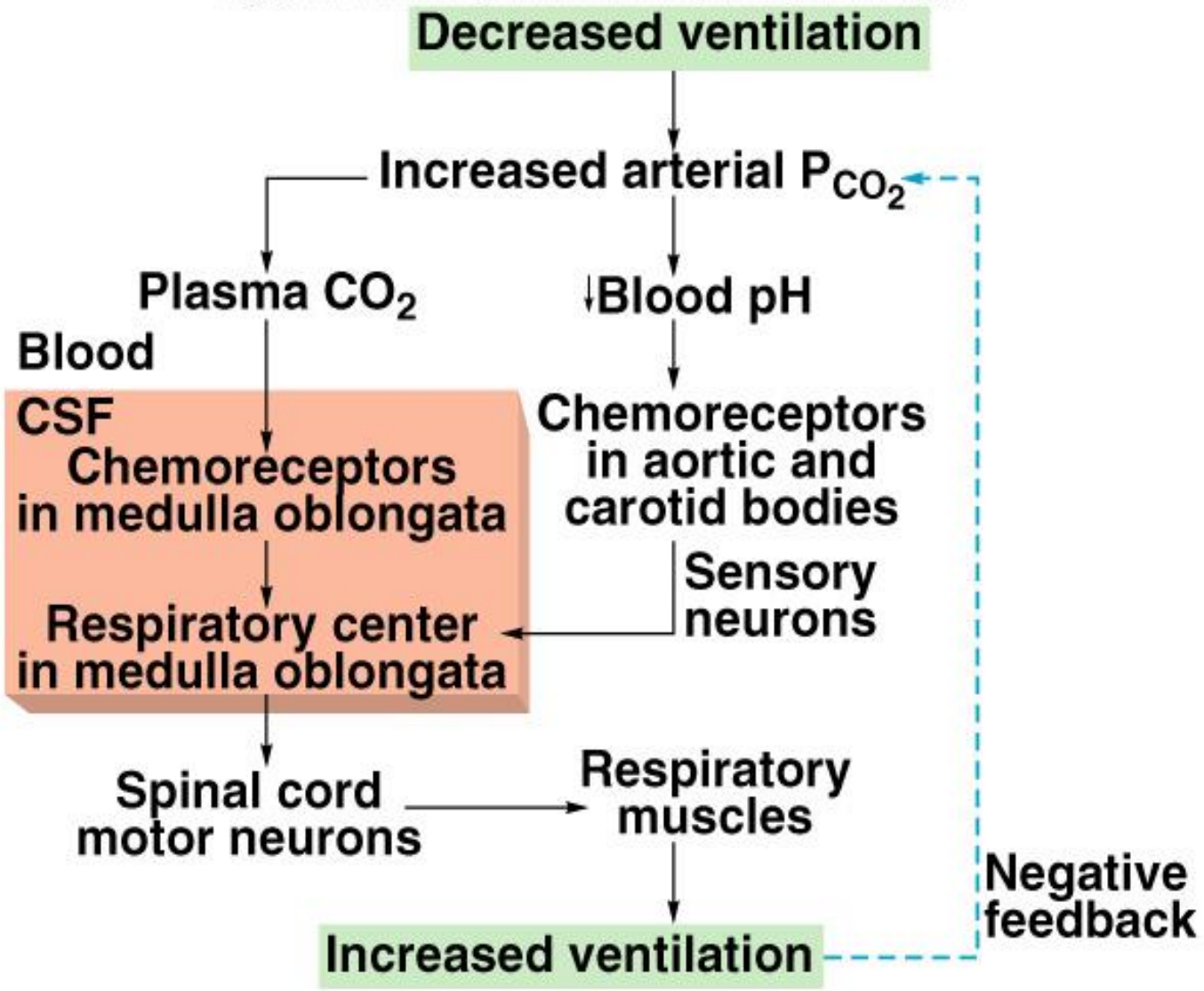
Chemoreceptor Control

- Central chemoreceptors:

  More sensitive to changes in arterial $PC0_2$ through H+

- $\mathbf{H_20 + CO_2} \longrightarrow \mathbf{H_2C0_3} \longrightarrow \mathbf{H^+}$
- H^+ cannot cross the blood brain barrier.
- CO_2 can cross the blood brain barrier and will form H_2CO_3.
  - H^+ lowers pH of CSF fasters than it lowers blood pH…no enough buffers in CSF
    - Directly stimulates central chemoreceptors.

Chemoreceptor Control of Breathing

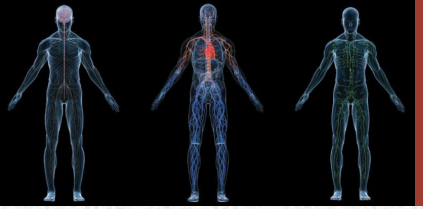


Effects of Blood PO_2 and PCO2 on Ventilation

- **O_2 and CO_2 potentiation effect**
  - Low PO_2 Influences chemoreceptor sensitivity to changes in POC_2….potentiation
  - High PCO_2 enhances sensitivity of carotid bodies to fall in PO_2…..potentiation
- Hypoxic drive:
  - Emphysema blunts the chemoreceptor response to PCO_2…because kidneys correct pH in chronic situation. By making more $HC0_3^-$ which buffers the fall in CSF pH. Therefore, giving the COPD patient pure O_2 to breath will suppress ventilation…since the low PO_2 is the one which drives ventilation in this patient…don't remove the drive!

Effects of Pulmonary Receptors on Ventilation

- Lungs contain receptors that influence the brain stem respiratory control centers via sensory fibers in vagus.
  - Unmyelinated C fibers can be stimulated by:
    - Histamine and bradykinin:
      - Released in response to noxious agents.
  - Irritant receptors are rapidly adaptive receptors.



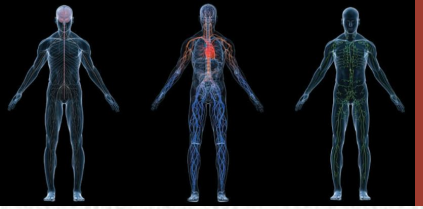
Lung receptors

- **Pulmonary Stretch Receptors**

- Located in smooth muscle of large and small airway and minimize work of breathing by inhibiting large tidal volumes

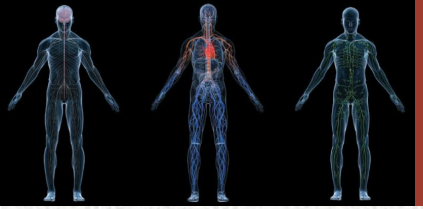
- **Hering-Breuer reflex**" are Pulmonary stretch receptors activated during inspiration.
- Inhibits respiratory centers to prevent undue tension on lungs.
- Hering Breuer inflation reflex can be easily manifested in dogs & cats but not in man (unless $V_T \geq 1.5$ liters). So its function in man is uncertain. However, in newborn where V_T is small, it may be important.

- Irritant receptors
  - Nasal mucosa, upper airways, possibly alveoli
  - Bronchoconstriction which lead to cough and sneeze
- J receptors
  - Located in the capillary wall, interstitium
  - Lung disease and edema (pulmonary congestion)
  - Rapid shallow breathing (tachypnea)



Other Reflexes

- Arterial Baroreceptors
  - Stimulation by elevated blood pressure results in brief apnea and bronchodilation
- Muscles and Tendons
  - Muscles of respiration as well as skeletal muscles, joints and tendons
  - Adjust ventilation to elevated workloads



Chemical Control of Respiration

- Carbon Dioxide works centrally through H^+
- Oxygen works peripherally at the carotid and aortic bodies.

Chemosensitive Area of Respiratory Center

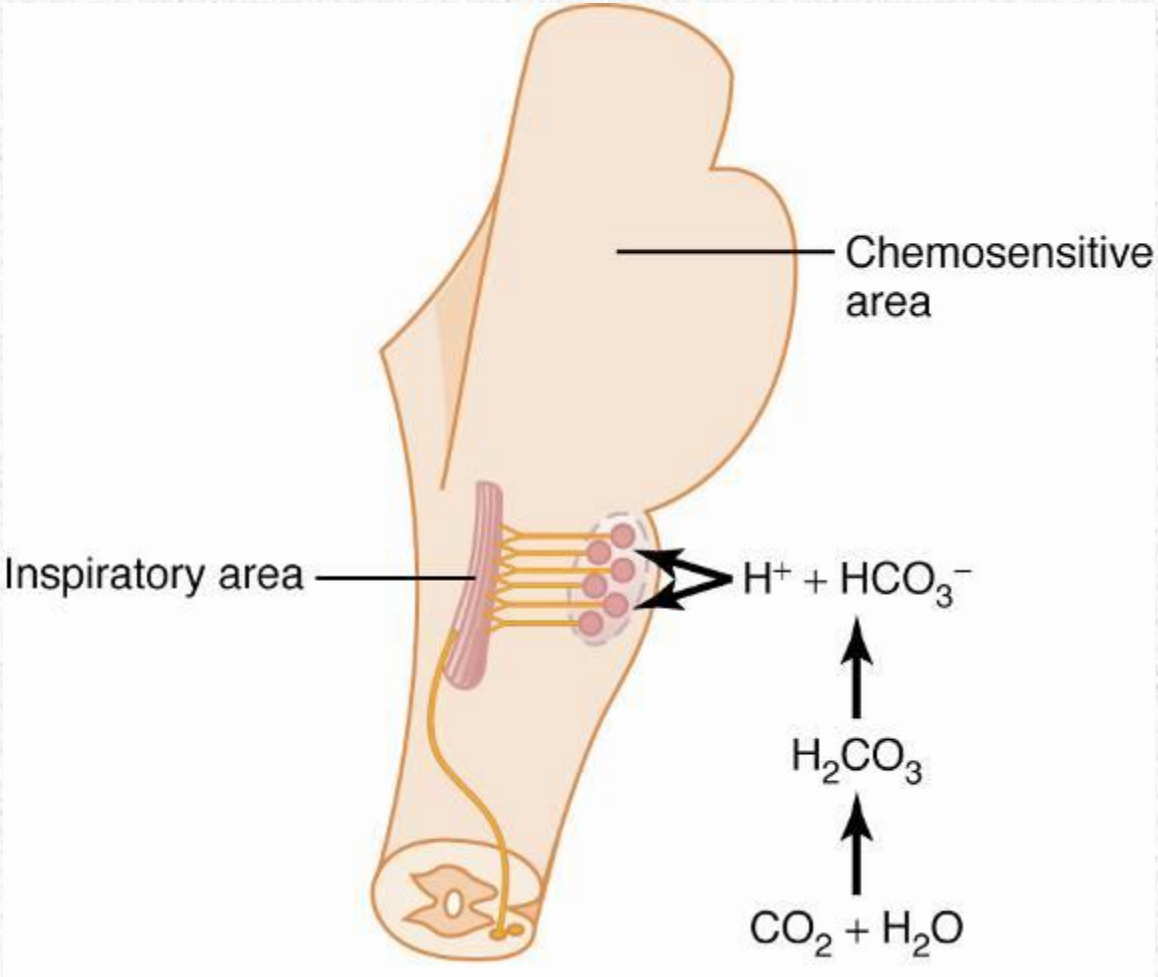
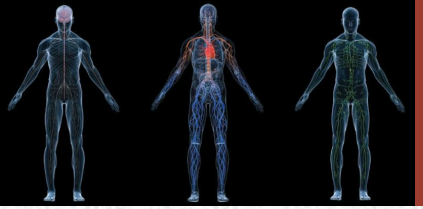


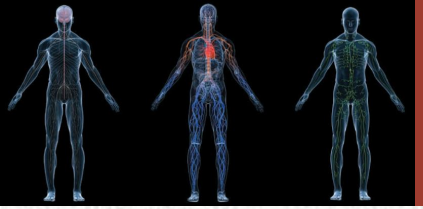
Figure 41-2



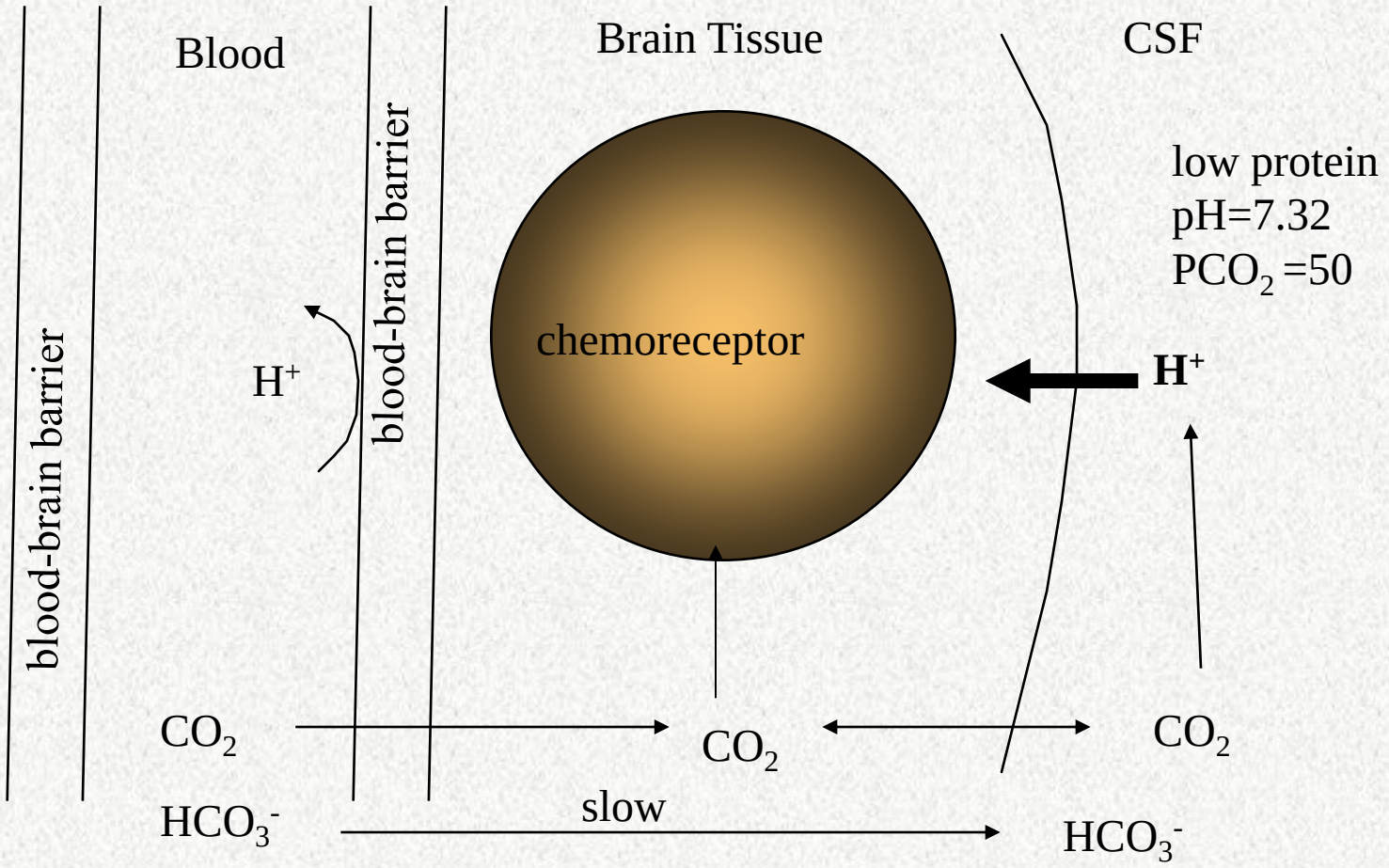
Chemosensitive Area:

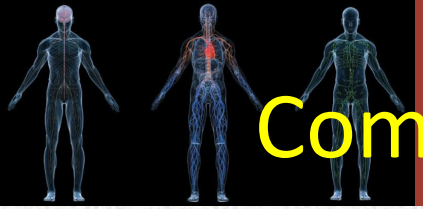
Located bilaterally 1 mm beneath the ventral surface of the medulla in the area between 9th & 10th nerves. It is a distinct from respiratory center. It is sensitive to H^+ even though H+ cannot cross BBB or CSF-barrier easily. pH of CSF is (7.32…slightly acidic). Any change in blood PCO_2 will alter pH of CSF faster than blood (blood has more buffers…CSF has very little buffering capacity). But CSF is restored to normal faster than the blood (24-48 hrs)…. blood takes several days. In COPD PCO_2 is increased while CSF pH is normal and ventilation is not increased.

CO_2 has strong acute effect (hrs) but weak chronic effect (days) because it is compensated by the kidney….it replaces the CSF pH back to normal….as in ascending to high altitude



Chemosensitive Area of Respiratory Center





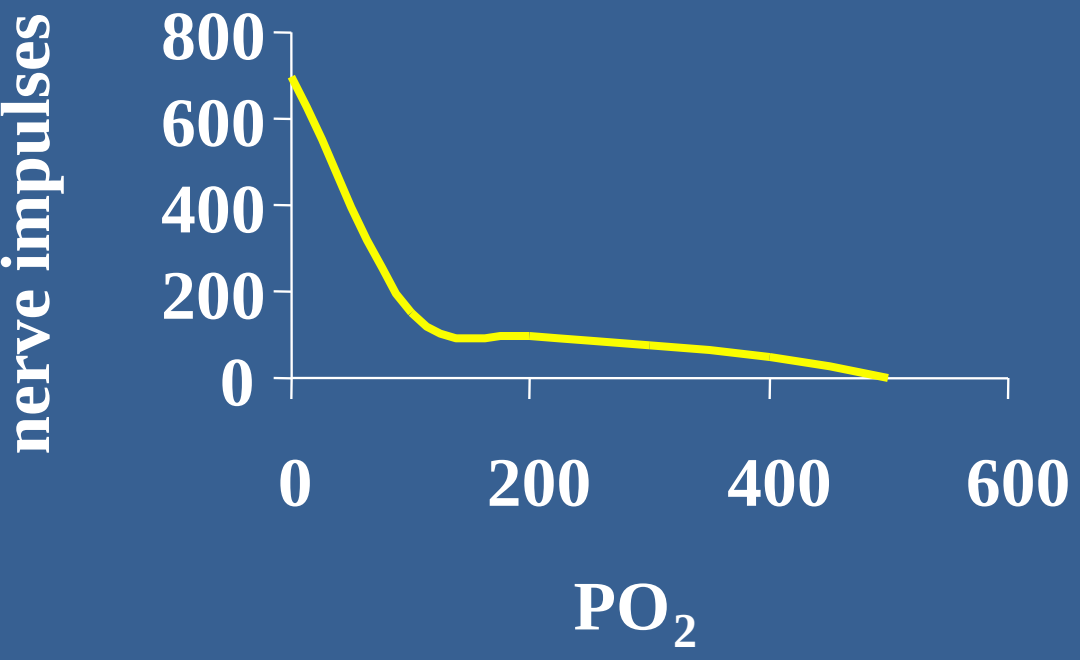
Comparison between Blood and CSF

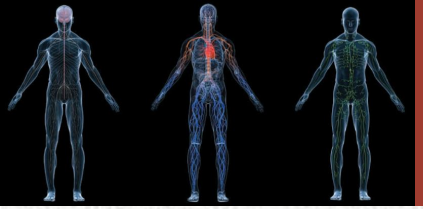
	CSF	***BLOOD***
HCO_3^-	24	28
protein	<45 mg%	6-8 g%
pH	7.32	7.4

CSF have less buffering capacity…and thus pH is shifted faster

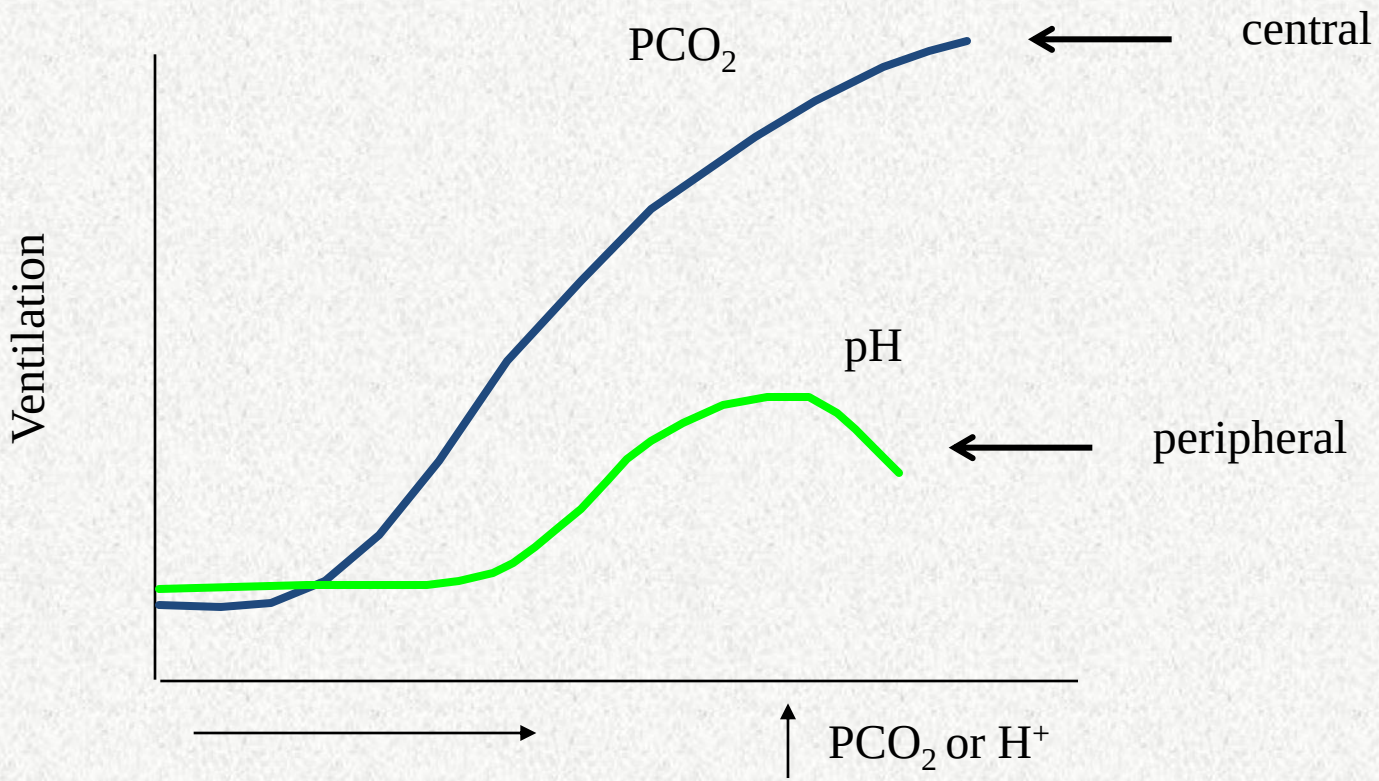
Peripheral Chemoreceptors

- Carotid bodies at the bifurcation of the common carotid artery.
  - –responds mainly (not only) to oxygen (PO_2<60 mmHg)
  - –-responds to carbon dioxide and hydrogen ion…one seventh of the central response but 5 times faster

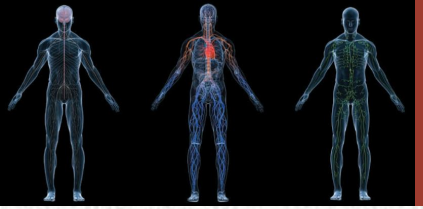




Control of Respiration

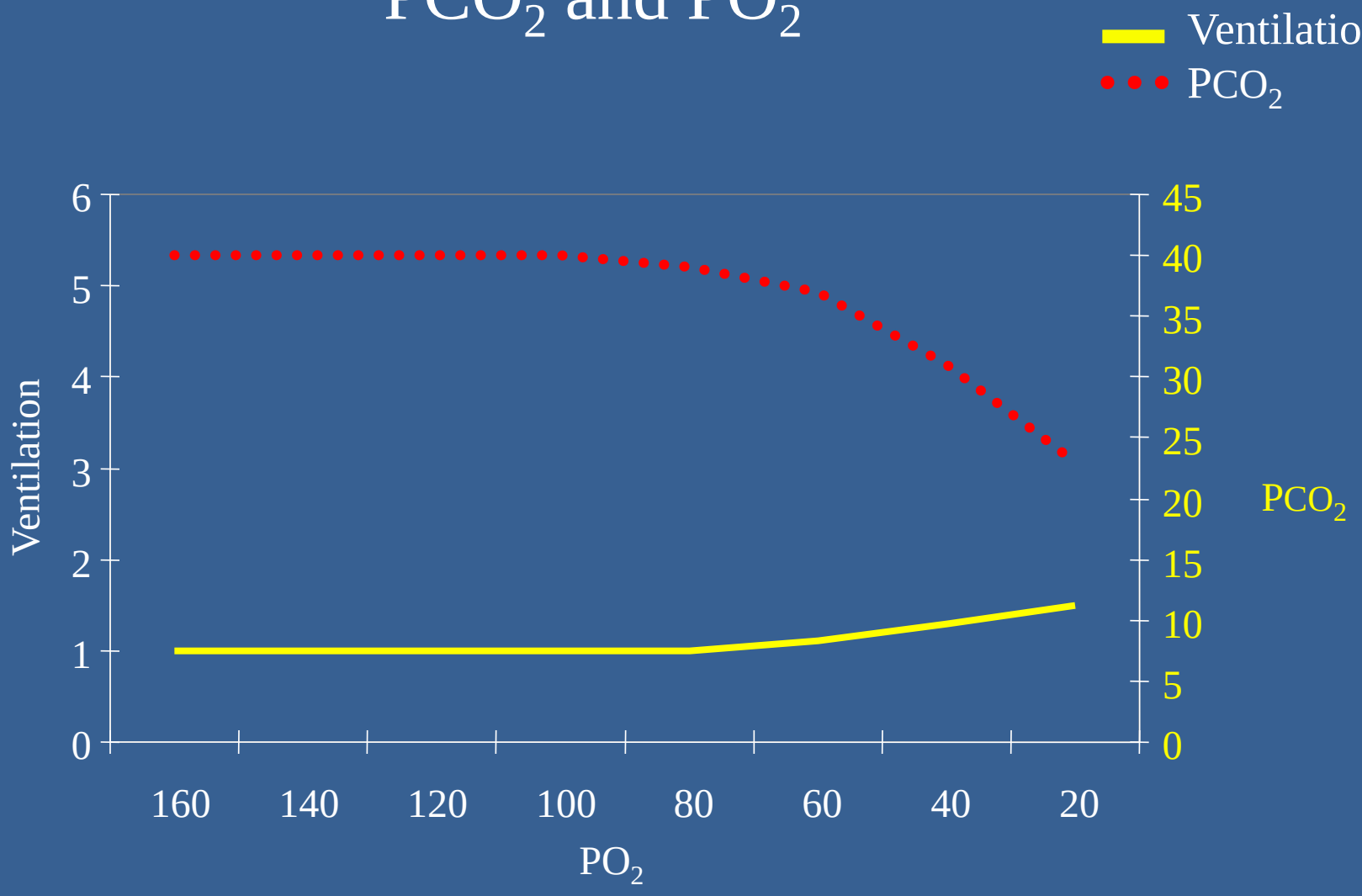


Changes in arterial PCO_2 have greater effect than changes in arterial pH

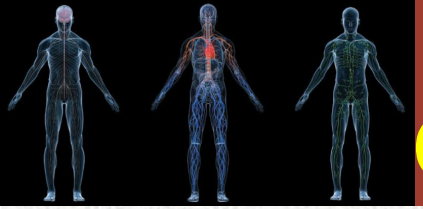


- CO_2 in CSF is more effective than in medullary interstitial fluid because CSF has less protein (acid-base buffers).
- CO_2 has strong acute effect (hrs) but weak chronic effect (days) because it is compensated by the kidney.
- If ↑ $PaCO_2$ while peripheral chemoreceptors are denervated, ventilation will still ↑ to almost the same extent (80-90%), indicating the importance of the central chemosensitive area.

PCO_2 and PO_2

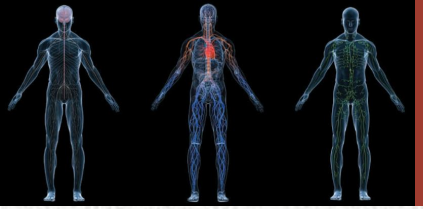


Hypoxic increase in ventilation inhibited by fall in PCO_2



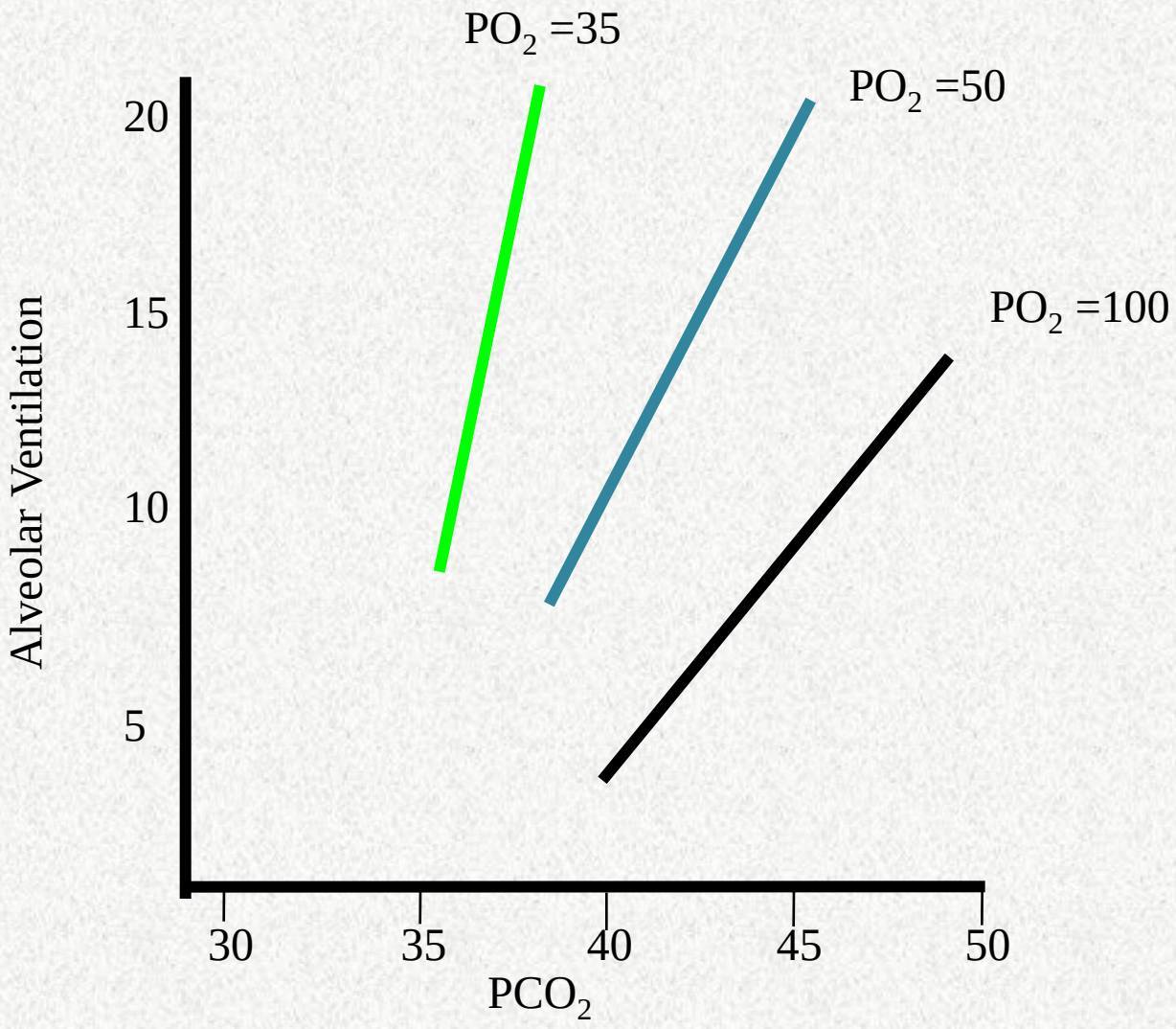
Chemoreceptor Control (continued)

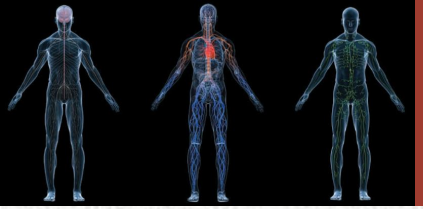
- Peripheral chemoreceptors mainly stimulated by $\downarrow PO_2$
- $\mathbf{H_2O + CO_2 \longrightarrow H_2CO_3 \longrightarrow H^+}$
- Stimulated by rise in $[H^+]$ of arterial blood.
  - Increased $[H^+]$ stimulates peripheral chemoreceptors.



- Peripheral chemoreceptors (the carotid and the aortic bodies): They respond mainly to a decrease in P_aO_2 (between 60-30 mm Hg.), and to a lesser extent to H^+ & PCO_2 . These bodies are exposed to arterial blood all the time (large blood supply).
- CO_2 & H^+ also excite the peripheral chemoreceptors (1/7 of the central response) but 5 times faster.

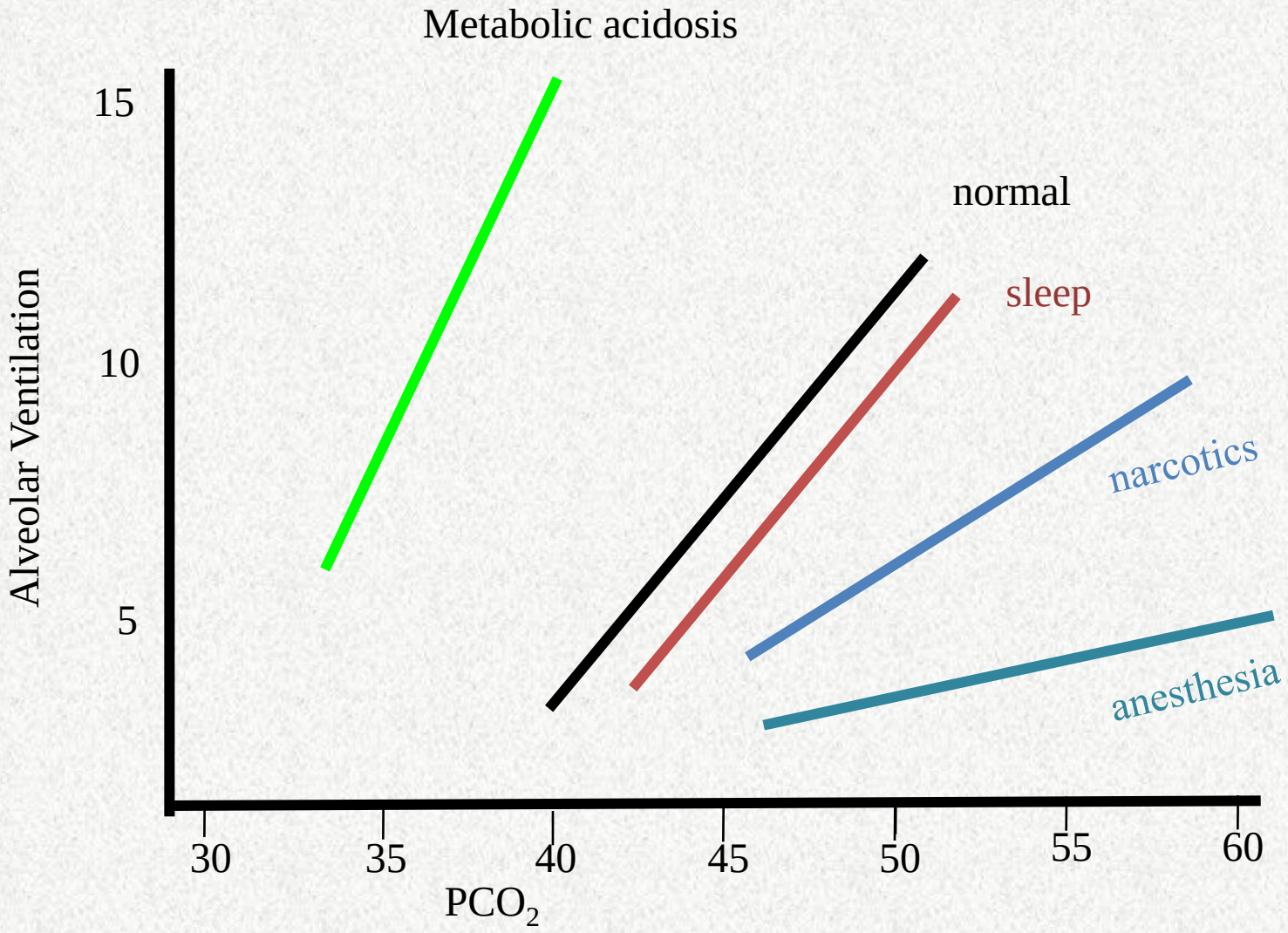
Carbon dioxide response curve at different O2 levels

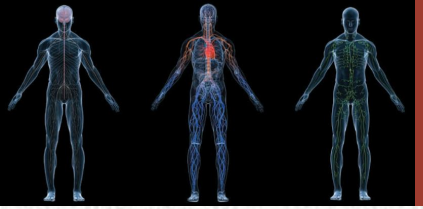




- **<u>Effect of arterial PO_2 on ventilation.</u>**
- The effects of acidosis on either hypercapnea or hypoxemia is purely additive (no potentiation). However, hypercapnea poteniates hypoxemia and hypoxemia poteniates hypercapnea. Hypoxia increases the sensitivity of the peripheral chemoreceptors to respiratory acidosis (increase CO_2). The slop of the curve increases as PO_2 decreases. The same principle applies when changing PO2 at different PCO2.

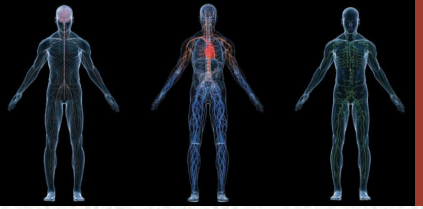
Carbon dioxide response curve under different conditions





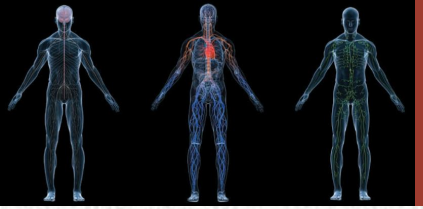
Summary

- Carbon dioxide is major stimulus for increased respiration
- Acts on chemosensitive area through H^+
- Peripheral chemoreceptors are mainly affected by low PO2
- If P_{CO_2} is constant low oxygen can be important
- Questions?
  - Why is oxygen's effect on respiration blunted?
  - Explain ventilatory drive during severe lung disease…see next slide for answer.

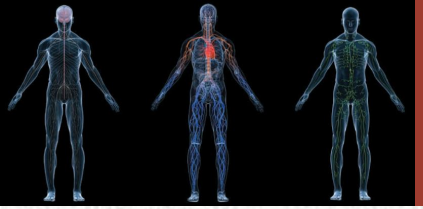


CO_2 Retention

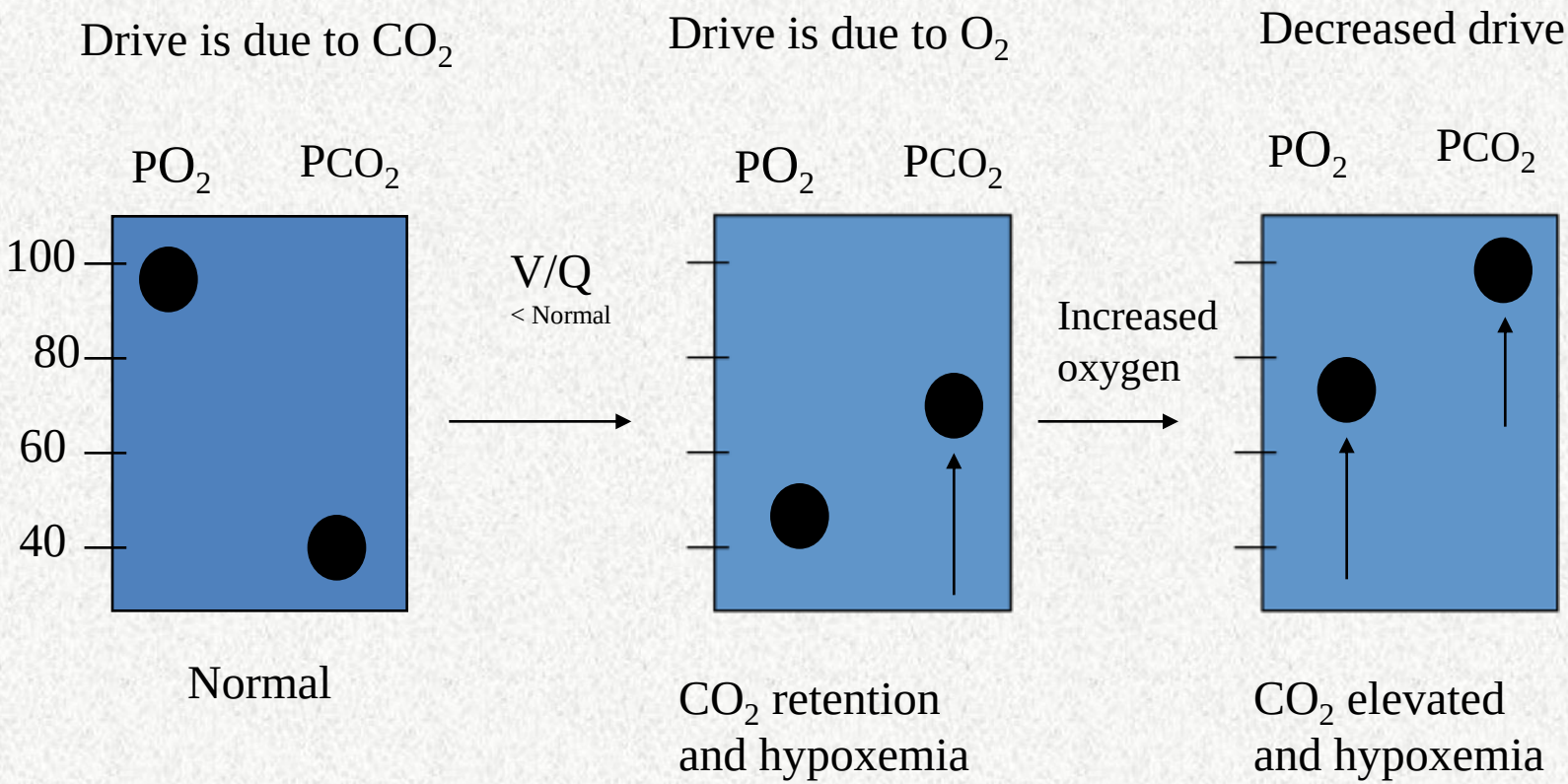
- Severe lung disease, COPD
- Develop hypoxemia and hypercapnia
- Respiratory drive is due to low PO2
- Renal control of acid-base balance
- Treat with hight % oxygen inhibits respiratory drive
- High levels of PCO_2
- Minimal levels of oxygen, monitor blood gases

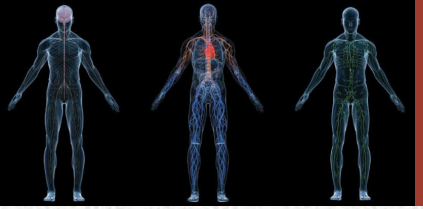


- In pneumonia and emphysema, PO_2 is low but PCO_2 is high. Kidney brings H^+ to normal (normal pH). In this scenario, it is the low PO_2 which drives the ventilation. In these patients if they are given pure O_2 to breath (PO_2 760 mmHg) it will suppress their ventilation ---> death because of increase in H^+ & CO_2 in blood. PCO_2 can reach a value of 100 mmHg. This level is narcotic and can suppress ventilation totally.
- Hence too much O_2 can kill the patient: "too much of a good thing can kill you"



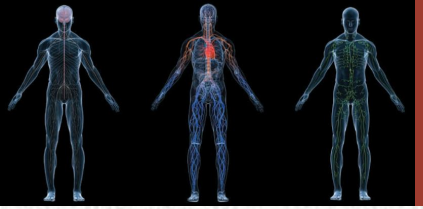
CO_2 Retention



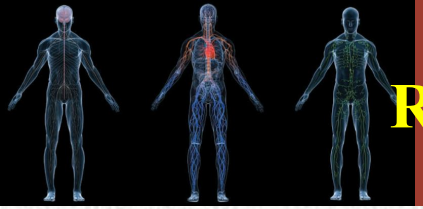


Respiration During Exercise

- Linear increase in ventilation with increasing oxygen consumption. Ventilation increase linearly until it reaches VO_{2max}.
- O_2 consumption at rest is 250 ml/min. In exercise it increases 20 folds (5,000 ml/min).
- arterial P_{O_2}, P_{CO_2} and pH **do not change** during exercise
- In the contrary, P_aCO_2 may decrease slightly…
- Q: What drives ventilation during Exercise?

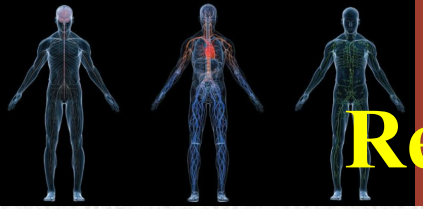


- Actually, near VO_{2max} ventilation is ↑ more O_2 consumption because of the accumulation of metabolic acids (lactate ...etc). This is called hyperventilation bcs PaCO2 decreases



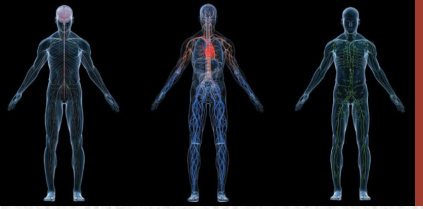
Respiration During Exercise…..Time wise

- Ventilation ↑ immediately (instantaneously) with the onset of exercise, then it gradually ↑ to final value which is determined by the severity of the exercise. The more strenuous the exercise the greater the initial rise at the onset & the higher the final level of ventilation. Following exercise there is an immediate decrease in ventilation followed by a more gradual return to the resting level.
- Because of the initial ↑ in ventilation (before muscle movement) the P_aCO_2 would decrease slightly. And then exercising muscles would produce CO_2 which then returns to normal level which stays at that level until the end of exercise. When muscles stop exercising (end of exercise) ventilation decrease instantly which cause ↑ P_aCO_2, again stimulates the respiratory center which ↑ ventilation slightly and then again decreasing slightly but remains high because of the oxygen debt.



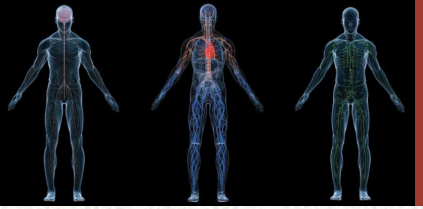
Respiration During Exercise…Drive

- Overflow of signals from cortex
- Body movements
- Increased body temperature
- Designed to control P_{CO_2}
- Learned response
- Conclusion: we are not sure regarding the exact mechanism responsible for increased ventilation during exercise.

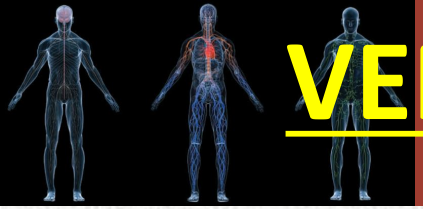


Other Factors to Influence Respiration

- Voluntary control
- Activity from vasomotor center
- Body temperature
  - increased production of carbon dioxide
  - direct effect on respiratory center
- Irritants
- Anesthesia



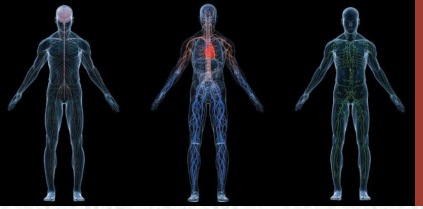
- **The Voluntary Control:**
- The spinal cord is the final integration of respiratory impulses.
- The voluntary impulses from cortex run through corticospinal tract to the respiratory motor neurons in the spinal cord. The phrenic motor neurons located in the ventral horns from **C3 to C5** and the external intercostal motor neurons in the ventral horns throughout the thoracic cord (**T1-T12**). We are lucky, because if somebody had an accident in his thoracic vertebral column, still he can breath because his diaphragm (phrenic C3-C5) is intact. The fibers concern with expiration converges in the internal intercostal motor neurons in the thoracic cord. There is reciprocal inhibition between them.
- Voluntary holding of breath can increase P_aCO_2 to 50 mmHg.
- -If P_aCO_2 ↑ to 75 → deleterious effects (confusion and coma = CO_2 poisoning). In the past this gas was used for anesthesia
- -If P_aCO_2 ↑ to 100 mm Hg then ventilation is depressed



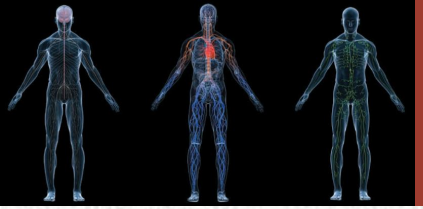
VENTILATION AT HIGH ALTITUDE

		Breathing Air			Breathing Pure O_2	
Height (feet)	Air	Inspired PO_2	P_AO_2	P_ACO_2	P_AO_2	P_ACO_2
0	760	160	100	40		
10,000	523	110	67(77)	36(23)		
20,000	350	73	40(53)	24(10)	262	40
29,029 (8848 m) Mount Everest	226	47	18(30)	24(7)	139	40

**In parenthesis are acclimatized values



- Half of the mass of the earth atmosphere is contained in the first 5500 m. The next quarter is in the next 5500 m. This means the P falls by half for each 5500 m above sea level (falling exponentially).
- **The highest village permanently inhabited by people are in the Andes (5486 m) Their women descend to lower altitudes during late pregnancy.** If one of us is brought suddenly to this height he/she will quickly dies.
- - There is no change in ventilation up to an altitude of 8500 ft (2600 m). .
- - Zone of danger starts between 14,000 and 20,000 ft (4,000-6,000 m). Symptoms and signs resemble alcohol intoxication
- At 65,000 ft (20 km) the barometric pressure is only 47 mmHg (the same as PH_2O, and our body fluids will boil at such a height
- - Commercial jetliners travel at about 33,000 ft (10,000 m) and of course in pressurized cabins.



PO_2 Responses to High Altitude

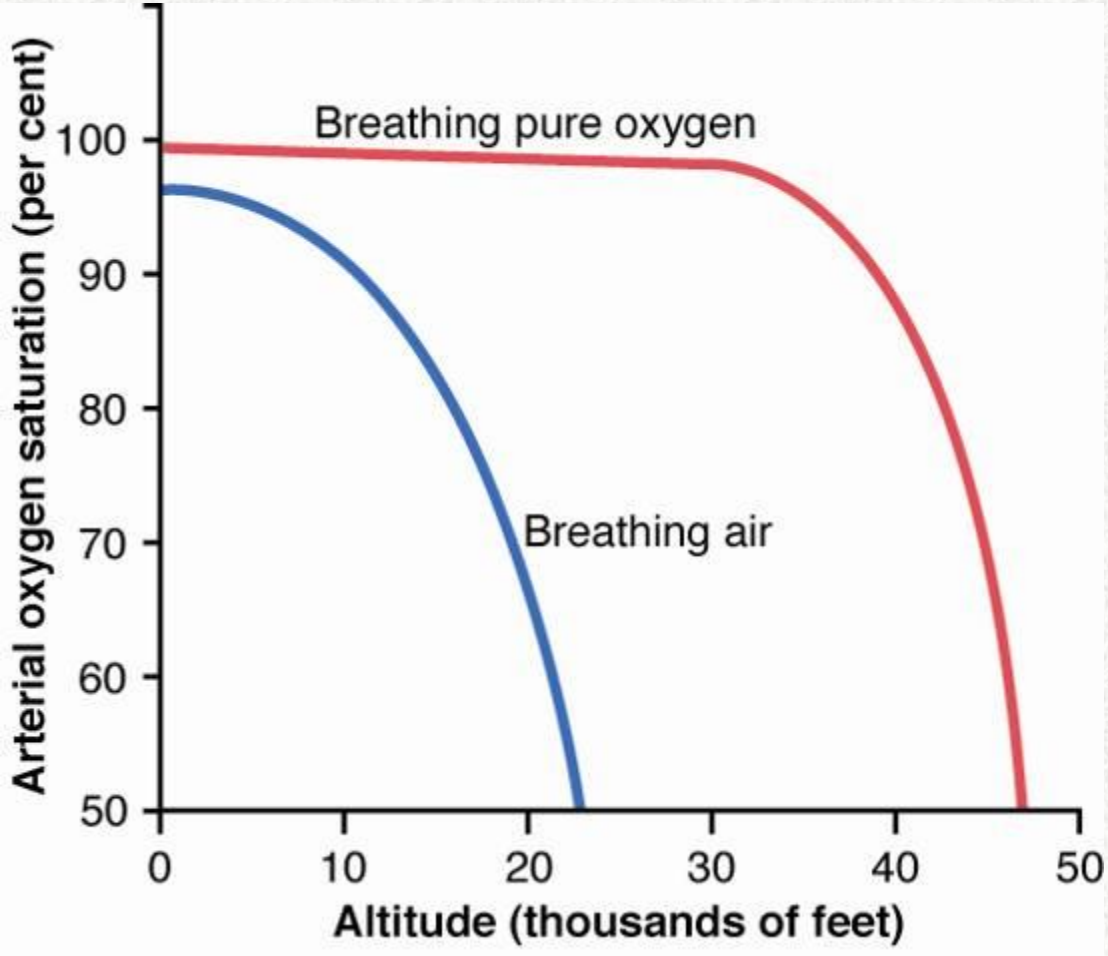
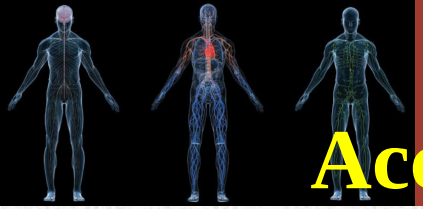
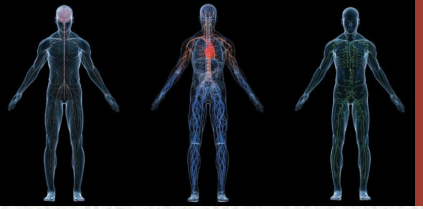


Figure 43-1



Acclimatization….continue

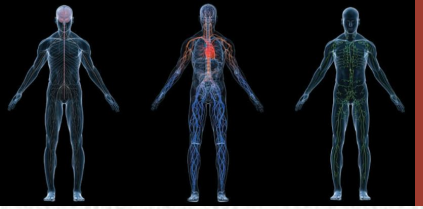
- Increased ventilation
  - due to decreased P_{O_2}
  - increase slowed by decreased P_{CO_2}
  - It increases 70% in the first day and 400-500% in the coming few days.
- Increased hematocrit (content)
- Increased diffusing capacity
- Increased capillarity



- **Respiratory Adjustments:**
- Increased sensitivity of carotid bodies regardless of P_aO_2. Mechanism is not known
- - The kidney takes several days before it can correct the pH of the CSF (14 days). The HCO_3^- is transported out the CSF leaving normal pH. The pH of the plasma comes down very slowly when compared to CSF pH…..we have more buffers in plasma.
- - increased sensitivity to central chemoreceptors.

- increased diffusion capacity (ΔPO_2 here is only 2 mmHg while at sea level is about 11 mmHg)
- Much better V/Q matching in the lung.

- - The disadvantage is the increased in work of breathing.
- - Increased Q slightly.
- - **Generalized vasoconstriction (except heart, brain, and skin), results in increased systemic and pulmonary arterial BP (pulmoary arterial blood pressure rises from 14 to 30 mmHg…pulmonary hypertension and the risk for corpulmonale).**
- - Increased vascularity of the tissue.
- - Haemopoitic Responses:
- - After 4-6 wks Hb rises to 20 gm/dl blood. PCV 60%... blood volume increases 10-15%...more liable to thrombotic and embolic phenomena.
- - 2,3 BGP: is also increased to compensate for the decrease in PCO2 (they cancel each other).



Hematocrit Responses during Acclimatization

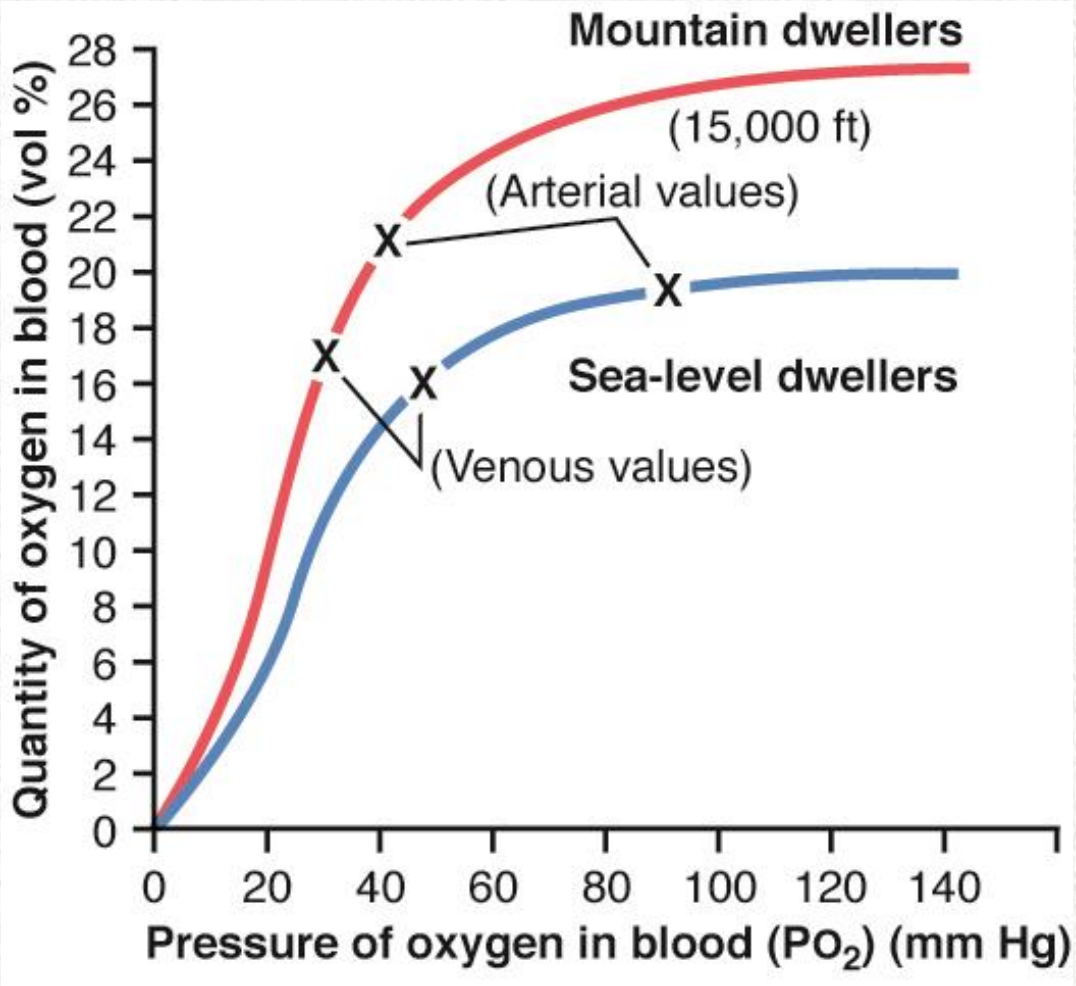
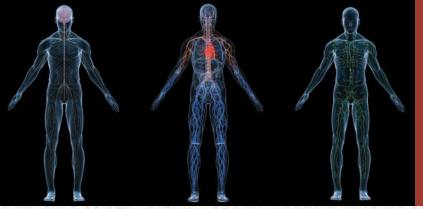
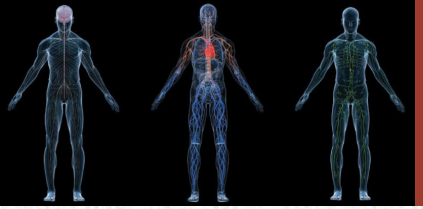


Figure 43-2

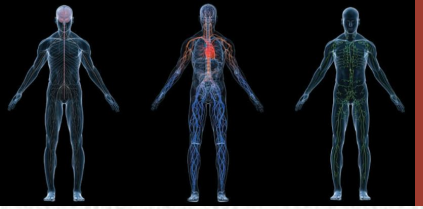


Mountain Sickness

- Chronic mountain sickness
  - increase in red cell mass
  - increase in pulmonary arterial pressure
  - enlargement of right heart
- Acute mountain sickness
  - acute cerebral edema
  - acute pulmonary edema



- **COR PULMONALE**: Is a condition in which right heart dilate and hypertrophy ± heart failure due to lung disease. At high altitude, **hypoxia can lead to pulmonary arterial vasoconstriction which lead to pulmonary hypertension**.



Question

What is atmospheric PO_2 at 10,000 ft (barometric pressure = 508 mmHg)?

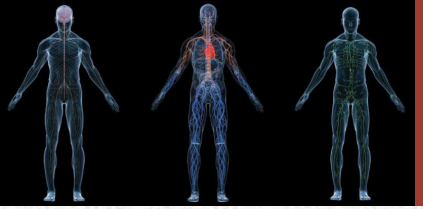
Person has normal alveolar ventilation

A. 95 mmHg

B. 106

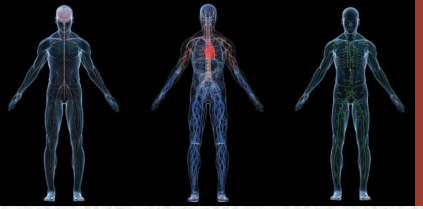
C. 149

D. 159



Answer

508*0.21=106



- See you again next semester in renal Physiology…
  - GOOD LUCK