The Respiratory System Physiology

Part Two

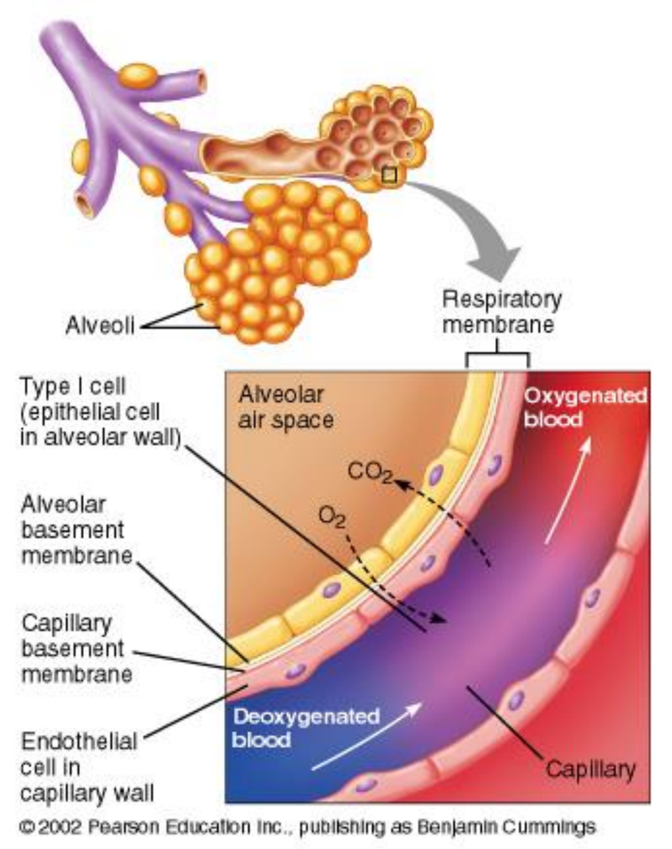
Dr. A. K.Goudarzi, D.V.M. Ph.D
Department of Basic Sciences
School of Veterinary Medicine
I.A. University, Karaj Branch

GAS EXCHANGE

Diffusion of Gases

Partial Pressure of Gases (P_{gas})

- Concentration of gases in a mixture (air)
- Gases move from areas of high partial pressure to areas of low partial pressure
- Movement of gases also occurs between cells and the blood in the capillaries
- Movement of gases occurs between blood in the pulmonary capillaries and the air within the alveoli
  - Movement of gasses is by diffusion across the respiratory membrane of the alveoli



Dalton's Law of Partial Pressure

- Each gas in a mixture (air) tends to diffuse independently of all other gases
  - Oxygen does not interfere with carbon dioxide diffusion or vice versa
- Each gas diffuses at a rate proportional to its partial pressure gradient until it reaches equilibrium
  - This allows for two-way traffic of gases in the lungs and in the body tissues
- The total pressure exerted by a mixture of gases is the same as the sum of the pressure exerted by each individual gas in the mixture
  - $P_{air} = P_{N2} + P_{O2} + P_{H2O}$

Partial Pressure: Atmospheric Air

- The partial pressure of a gas is the pressure exerted by each gas in a mixture and is directly proportional to its percentage in the total gas mixture
- Example: Atmospheric Air
- At sea level, atmospheric pressure is 760 mmHg
  - Air is ~78% Nitrogen
    - The partial pressure of nitrogen (P_{N2}) is:
      - 0.78 x 760 mmHg = P_{N2} = 593 mmHg
  - Air is ~ 21% Oxygen
    - The partial pressure of oxygen (P_{O2}) is:
      - 0.21 x 760 mmHg = P_{O2} = 160 mmHg
  - Air is ~ 0.04% carbon dioxide
    - The partial pressure of carbon dioxide (P_{CO2}) is:
      - 0.0004 x 760 mmHg = P_{CO2} = 0.3 mmHg.

- Composition of the partial pressures of oxygen and carbon dioxide in the pulmonary capillaries and alveolar air:
  - Pulmonary arterial capillary blood
    - P_{CO2} of pulmonary capillary blood is 45 mmHg
    - P_{O2} of pulmonary capillary blood is 40 mmHg
  - Alveolar air:
    - P_{CO2} of alveolar air is 40 mmHg
    - P_{O2} of alveolar air is 104 mmHg

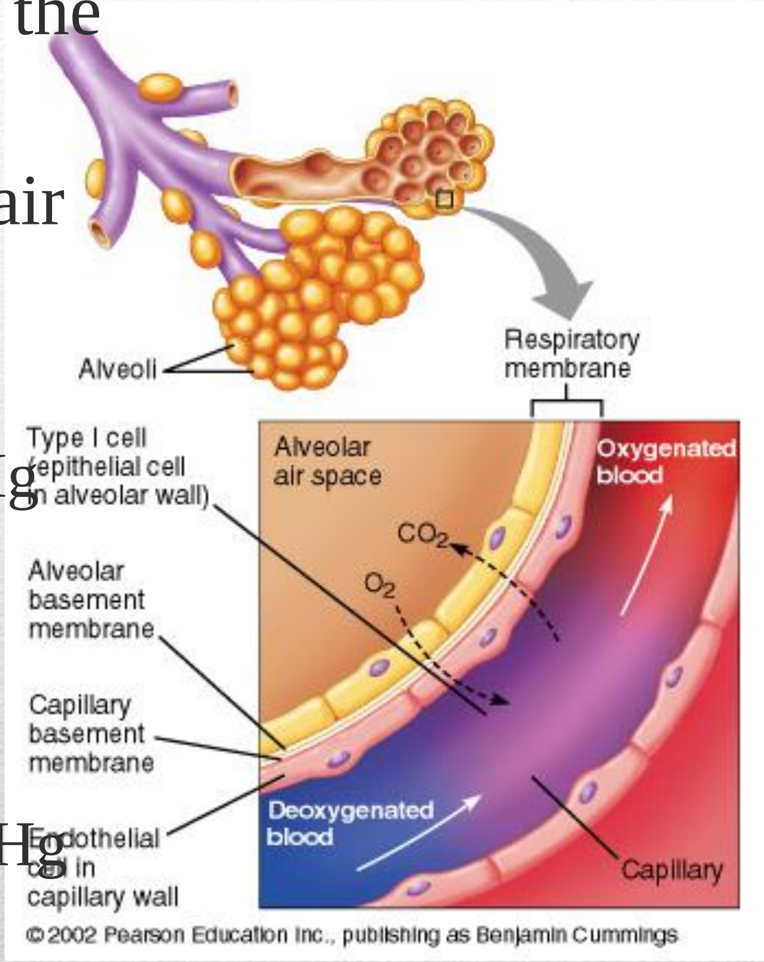
Partial Pressure: Alveolar Air

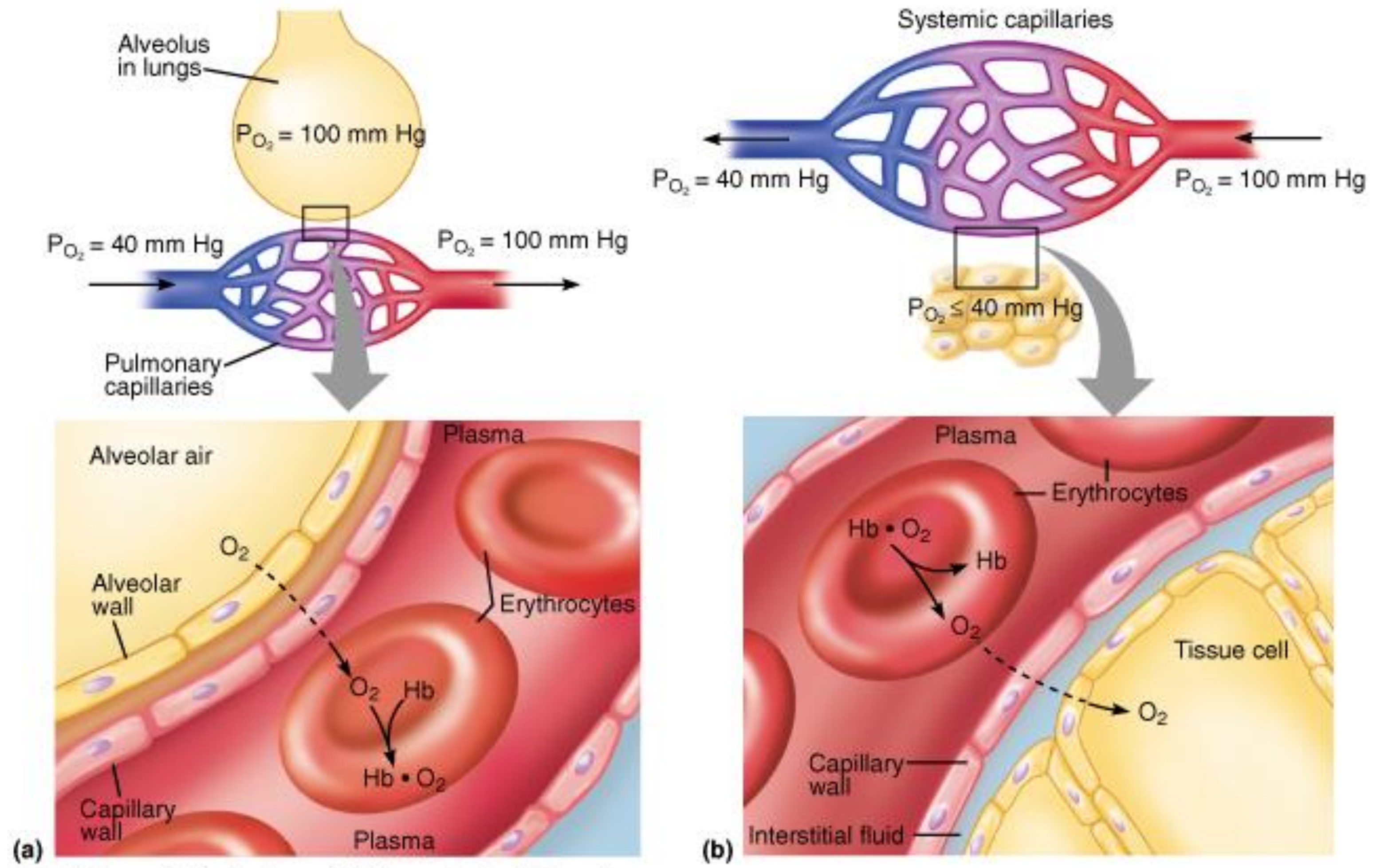
- The ability of a gas to dissolve in water
- Important because O_2 and CO_2 are exchanged between air in the alveoli and blood (which is mostly water)
- Even when dissolved in water, gases exert a partial pressure
- Gases diffuse from regions of higher partial pressure toward regions of lower partial pressure

Solubility of Gases in a Liquid

Gas Exchange in the Lungs

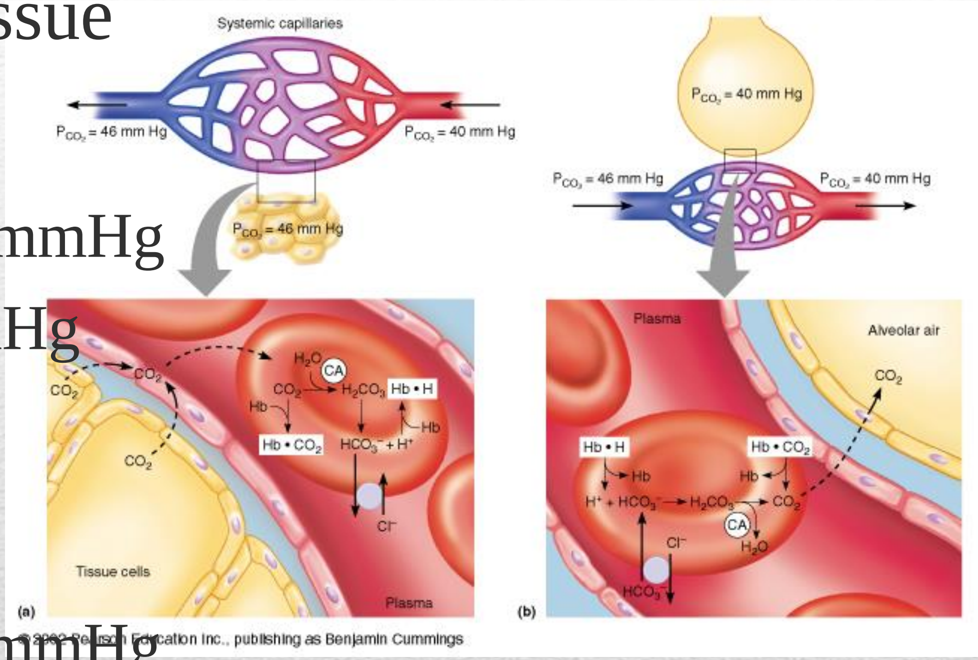
- Gas exchange occurs by diffusion across the respiratory membrane in the alveoli
- Oxygen diffuses from the alveolar air into the blood
  - Alveolar air P_{O2} = 104 mmHg
  - Pulmonary capillaries P_{O2} = 40 mmHg
- Carbon dioxide diffuses from the pulmonary capillary blood into the alveolar air
  - Pulmonary capillaries P_{CO2} = 46 mmHg
  - Alveolar air P_{CO2} = 40 mmHg

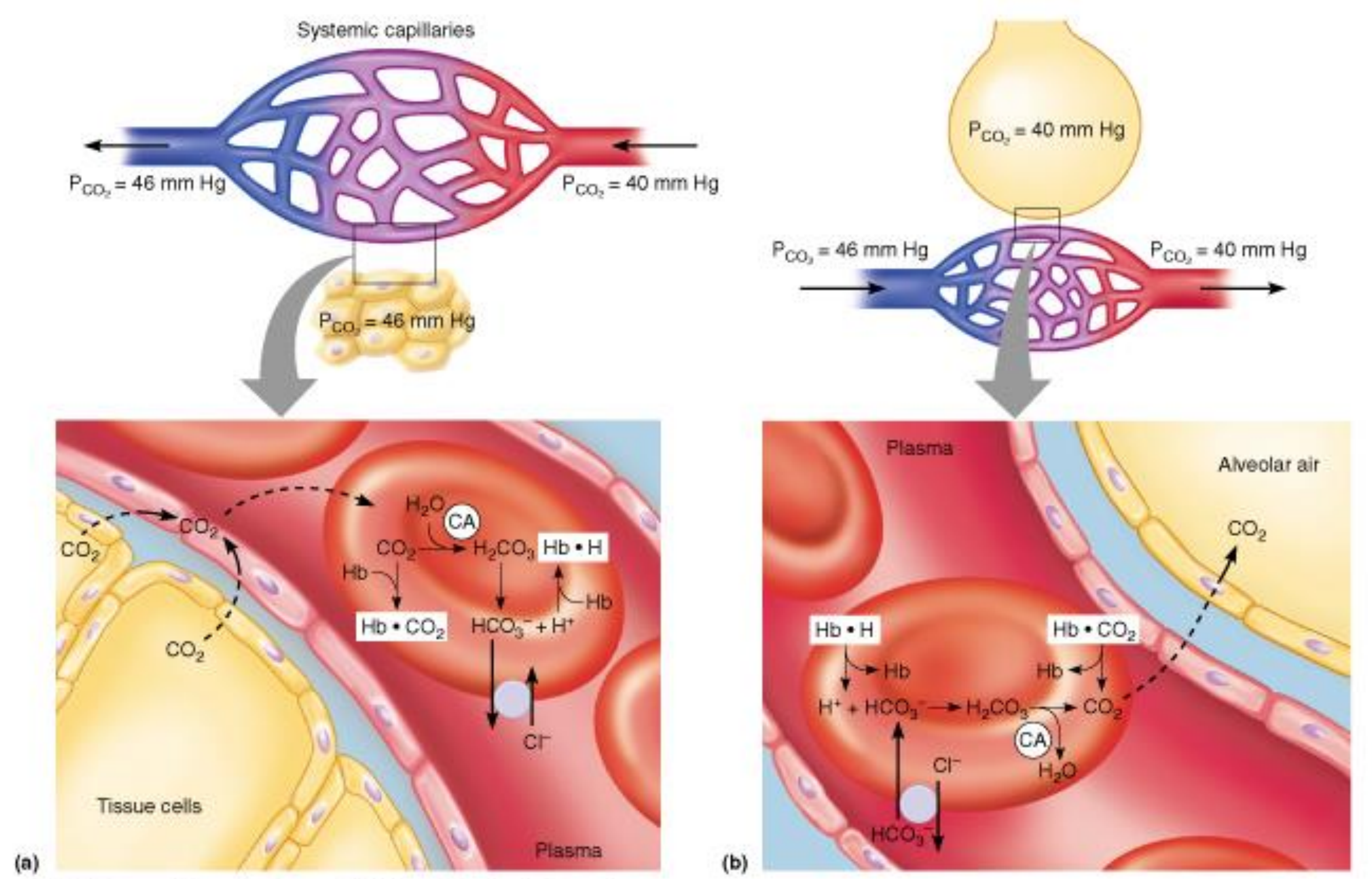



Alveolus in lungs
P_{O_2} = 100 mm Hg
P_{O_2} = 40 mm Hg
P_{O_2} = 100 mm Hg
Pulmonary capillaries
Alveolar air
Plasma
O_2
Alveolar wall
Erythrocytes
O_2 Hb
Hb • O_2
Capillary wall
Plasma
(a)
Systemic capillaries
P_{O_2} = 40 mm Hg
P_{O_2} = 100 mm Hg
P_{O_2} ≤ 40 mm Hg
Plasma
Erythrocytes
Hb • O_2
Hb
O_2
Tissue cell
O_2
Capillary wall
Interstitial fluid
(b)

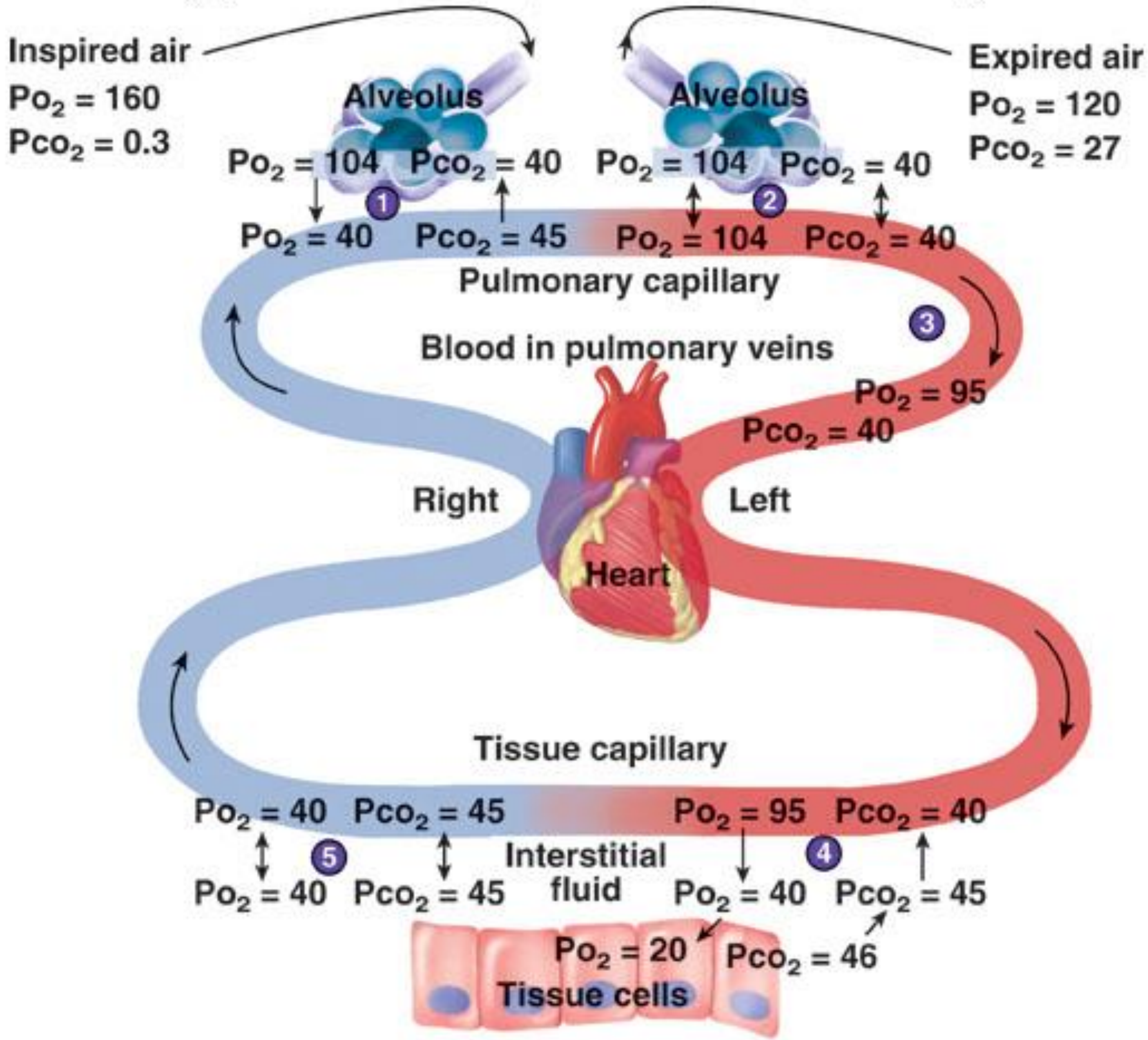
Gas Exchange in Respiring Tissue

- Gas partial pressures in systemic capillaries depends on the metabolic activity of the tissue
- Oxygen concentrations
  - Systemic arteries P_{O2} = 100 mmHg
  - Systemic veins P_{O2} = 40 mmHg
- Carbon dioxide concentrations
  - Systemic arteries P_{CO2} = 40 mmHg
  - Systemic veins P_{CO2} = 46 mmHg





Systemic capillaries
P_{CO_2} = 46 mm Hg
P_{CO_2} = 40 mm Hg
P_{CO_2} = 46 mm Hg
CO_2
CO_2
CO_2
H_2O
CA
CO_2
H_2CO_3
Hb • H
Hb
Hb
Hb • CO_2
HCO_3^- + H^+
Cl^-
Tissue cells
Plasma
(a)
P_{CO_2} = 40 mm Hg
P_{CO_2} = 46 mm Hg
P_{CO_2} = 40 mm Hg
Plasma
Alveolar air
CO_2
Hb • H
Hb • CO_2
Hb
Hb
H^+ + HCO_3^-
H_2CO_3
CO_2
CA
H_2O
Cl^-
HCO_3^-
(b)


Inspired air
$Po_2 = 160$
$Pco_2 = 0.3$
Alveolus
$Po_2 = 104$ $Pco_2 = 40$
1
$Po_2 = 40$ $Pco_2 = 45$
Alveolus
$Po_2 = 104$ $Pco_2 = 40$
2
$Po_2 = 104$ $Pco_2 = 40$
Expired air
$Po_2 = 120$
$Pco_2 = 27$
Pulmonary capillary
3
Blood in pulmonary veins
$Po_2 = 95$
$Pco_2 = 40$
Right
Left
Heart
Tissue capillary
$Po_2 = 40$ $Pco_2 = 45$
5
$Po_2 = 40$ $Pco_2 = 45$
Interstitial fluid
$Po_2 = 95$ $Pco_2 = 40$
4
$Po_2 = 40$ $Pco_2 = 45$
$Po_2 = 20$ $Pco_2 = 46$
Tissue cells

- 98% of O_2 is transported in combination

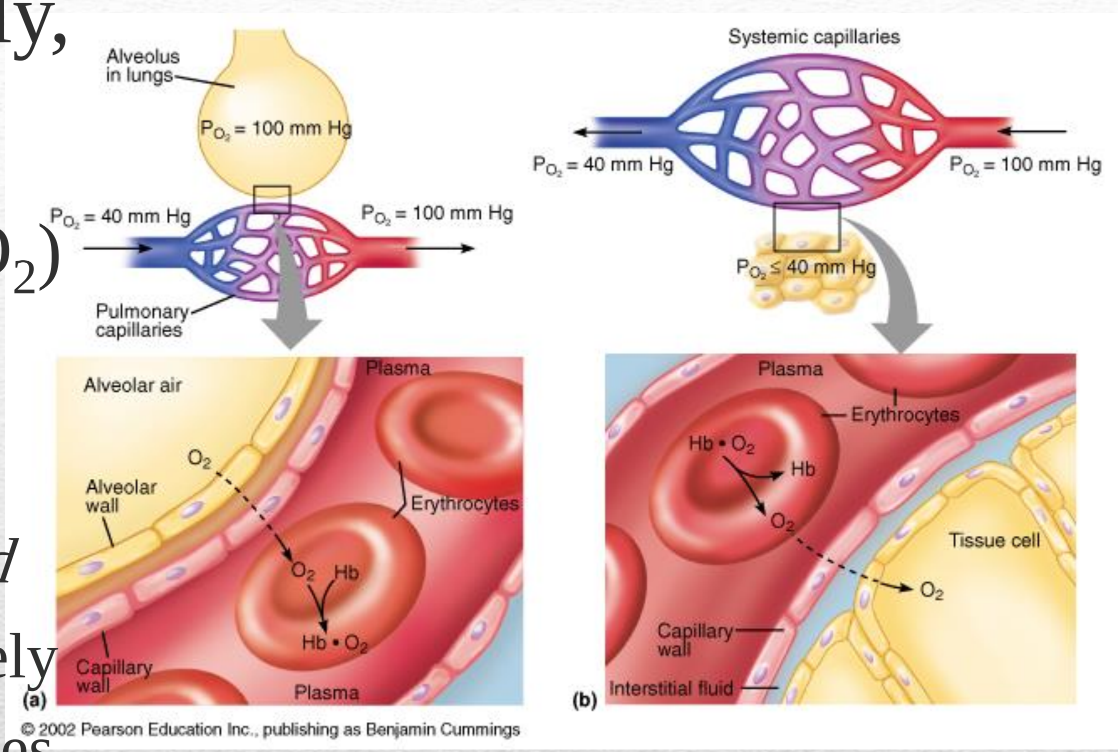
with hemoglobin molecules (98%)

  - 2% of O_2 is dissolved and transported in the plasma
- Hemoglobin (Hb)
  - A protein found in RBCs
  - O_2 binds loosely to Hb due to its molecular structure
- Hemoglobin consists of four polypeptide chains
  - Consists of 4 globin molecules, each of which is bound to a heme group
  - The heme group contains an iron molecule, which is the site of O_2 binding
- Each Hb molecule is able to carry 4 molecules of O_2

Transport of Gases in the Blood: O_2

Transport of Gases in the Blood: O_2

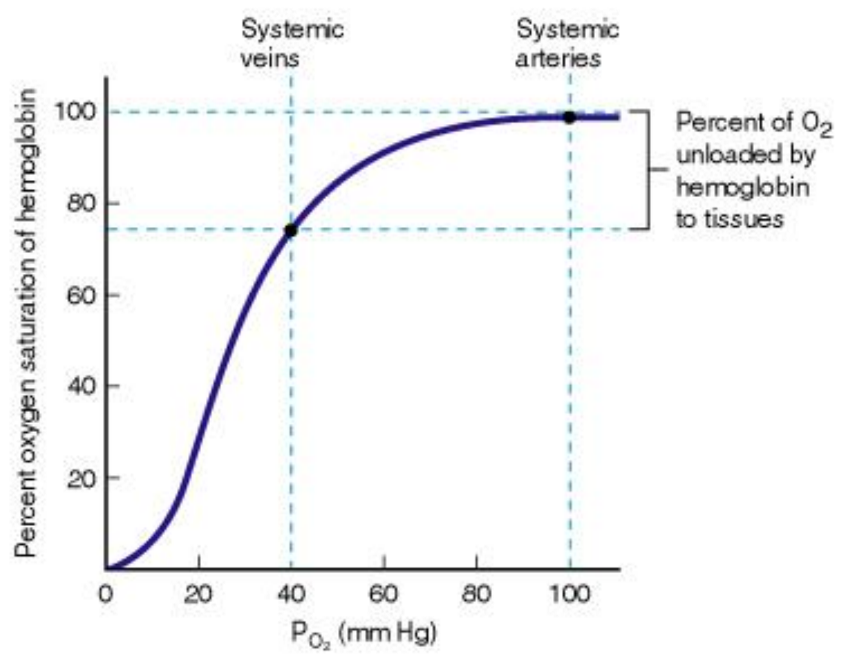
- O_2 binds temporarily, or reversibly, to Hb
- Oxyhemoglobin (HbO_2)
  - $Hb + O_2 = HbO_2$
  - Hb attached to four O_2 molecules is *saturated*
  - Saturated Hb is relatively unstable and easily releases O_2 in regions where the P_{O2} is low
- Deoxyhemoglobin (HHb)
  - $HHb = Hb + O_2$



The Hemoglobin-Oxygen Dissociation Curve

- Describes the relationship between the aterial P_{O2} and Hb saturation

- The Hb- O_2 Dissociation Curve plots the percent saturation of Hb as a function of the P_{O2}

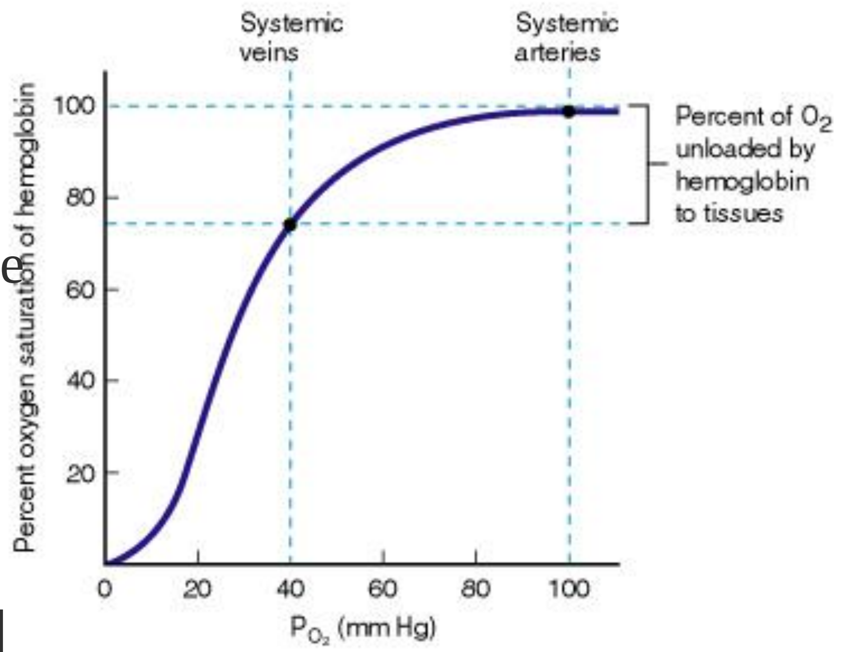


	P_{O_2} (mm Hg)	Percent hemoglobin saturation
Systemic arteries	100	98%
Systemic veins	40	75%

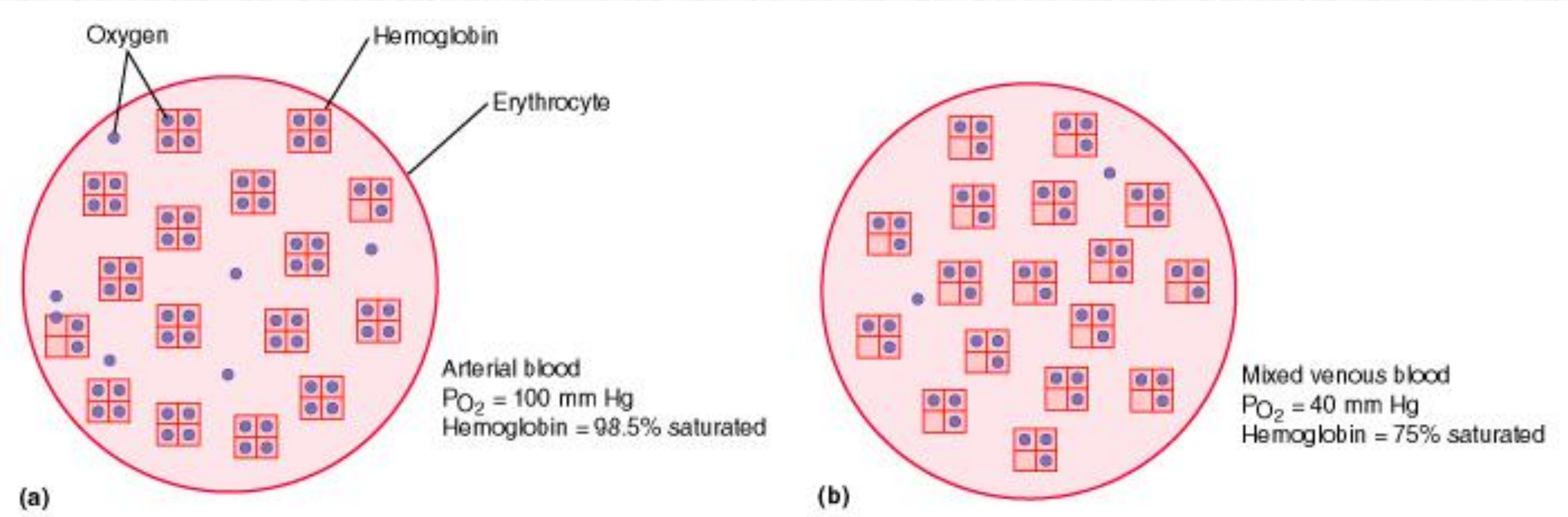
The Hemoglobin-Oxygen Dissociation Curve

Hb Saturation

- Full saturation
  - All four heme groups of the Hb molecule in the blood are bound to O_2
- Partial saturation
  - Not all of the heme groups are bound to O_2
- Hb saturation is largely determined by the P_{O2} in the blood
- At normal alveolar P_{O2} (104 mm Hg), Hb is 97.5 - 98% saturated



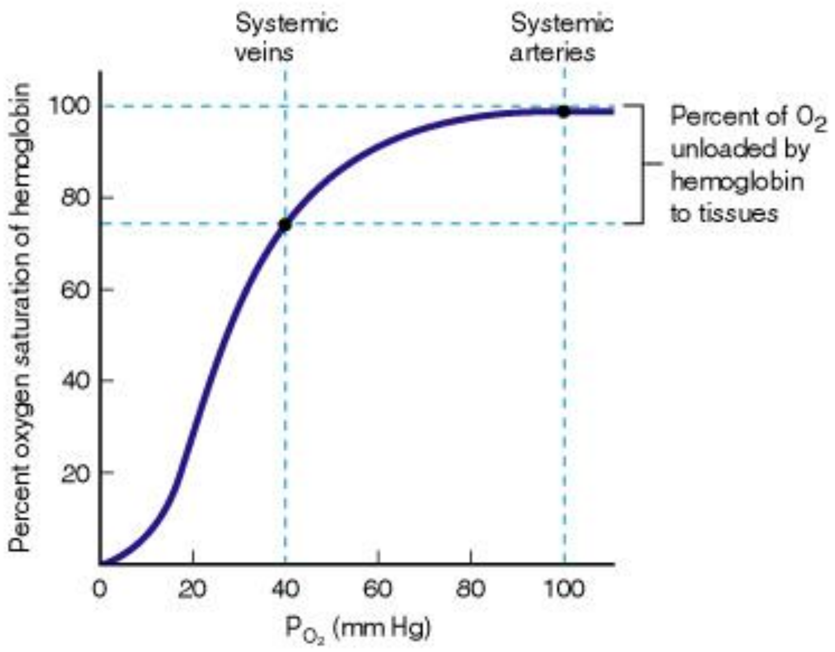
	P_{O_2} (mm Hg)	Percent hemoglobin saturation
Systemic arteries	100	98%
Systemic veins	40	75%


Oxygen
Hemoglobin
Erythrocyte
Arterial blood
P_{O_2} = 100 mm Hg
Hemoglobin = 98.5% saturated
(a)
Mixed venous blood
P_{O_2} = 40 mm Hg
Hemoglobin = 75% saturated
(b)

The Hemoglobin-Oxygen Dissociation Curve

Hb Unloading of O_2

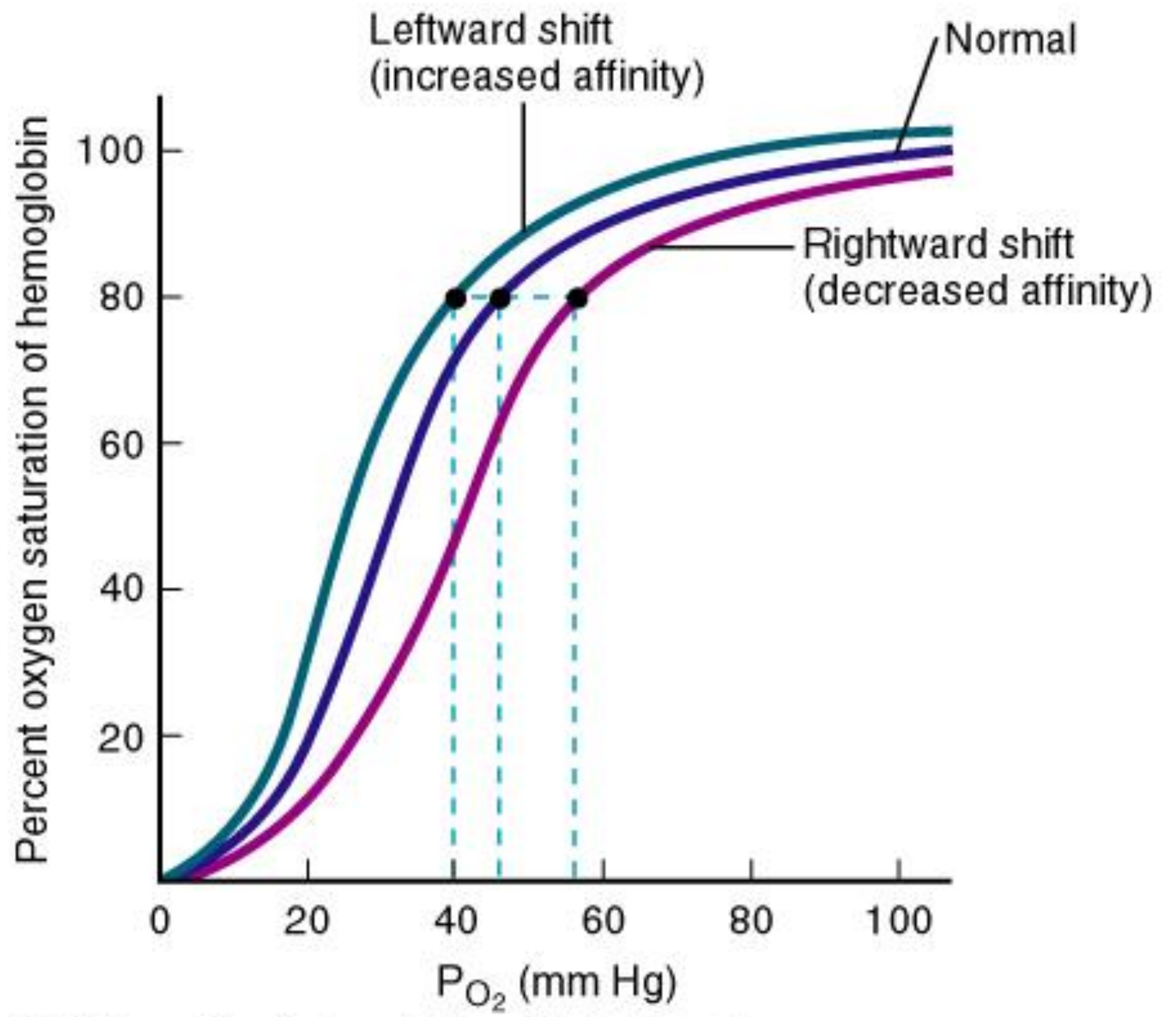
- Factors that increase O_2 unloading from hemoglobin at the tissues:
  - Increased body temperature
    - Decreases Hb affinity for O_2
  - Decreased blood pH (the Bohr effect)
    - H^+ ions bind to Hb
  - Increased arterial P_{CO2} (the Carbamino effect)



	P_{O_2} (mm Hg)	Percent hemoglobin saturation
Systemic arteries	100	98%
Systemic veins	40	75%

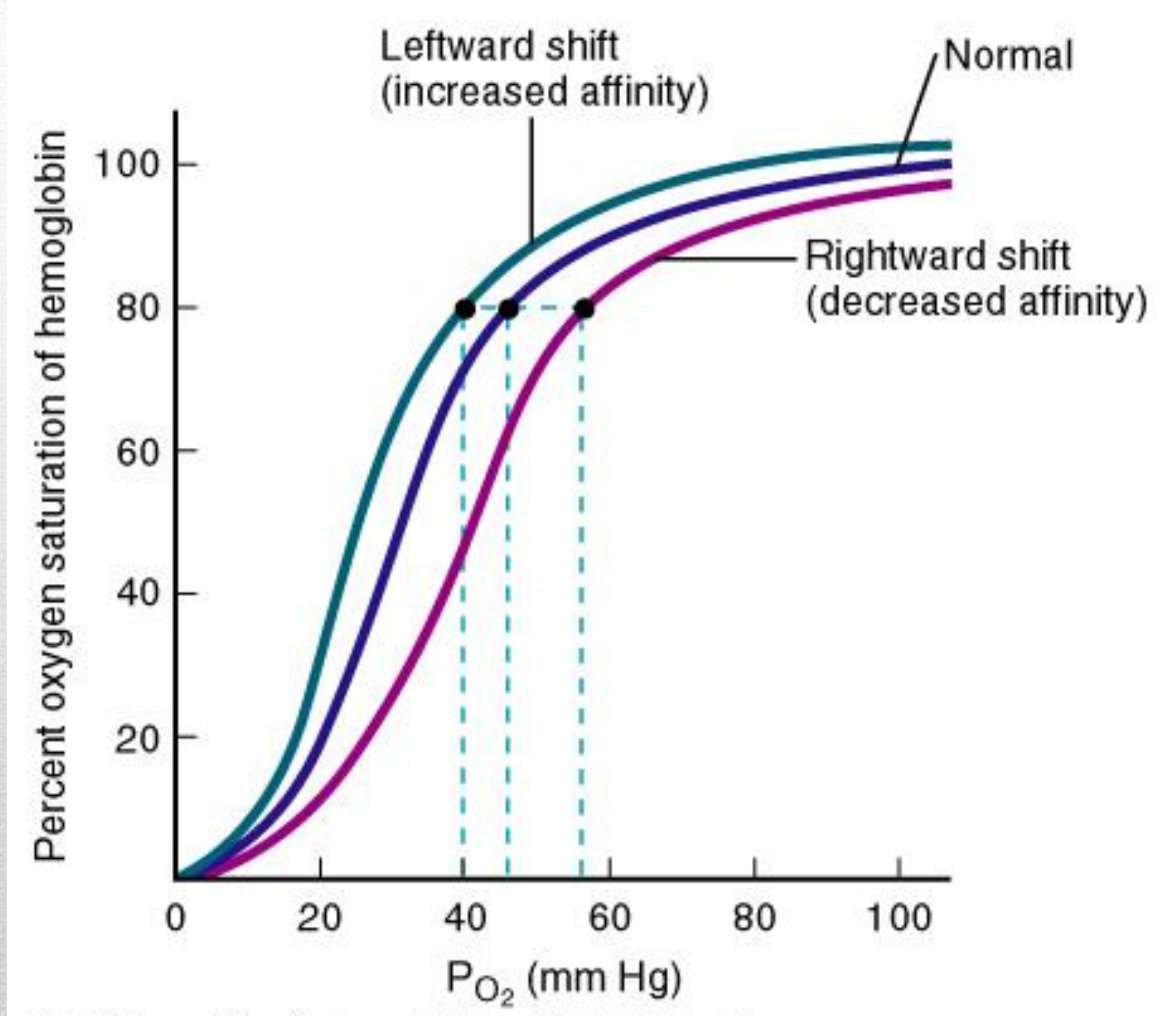
- Based on the fact that when O_2 binds to Hb, certain amino acids in the Hb molecule release H^+ ions
  - $Hb + O_2 \leftrightarrow HbO_2 + H^+$
  - An increase in H^+ (a decrease in pH) pushes the reaction to the left, causing O_2 to dissociate from Hb
- Hb affinity for O_2 is decreased when H^+ ions bind to Hb, therefore O_2 is unloaded from Hb
- H^+ concentration increases in active tissues, which facilitates O_2 unloading from Hb so that it may be utilized by the active tissues

The Bohr Effect


Leftward shift
(increased affinity)
Normal
Rightward shift
(decreased affinity)
Percent oxygen saturation of hemoglobin
100
80
60
40
20
0
20
40
60
80
100
P_{O_2} (mm Hg)

- Based on the fact that CO_2 may bind to Hb
  - $Hb + CO_2 \leftrightarrow HbCO_2$
  - An increase in P_{CO2} pushes the reaction to the right, forming carbaminohemoglobin ($HbCO_2$)
- $HbCO_2$ decreases Hb affinity for O_2
  - This decreases O_2 transport in the blood
- The carbamino effect is one method of transporting CO_2 in the blood

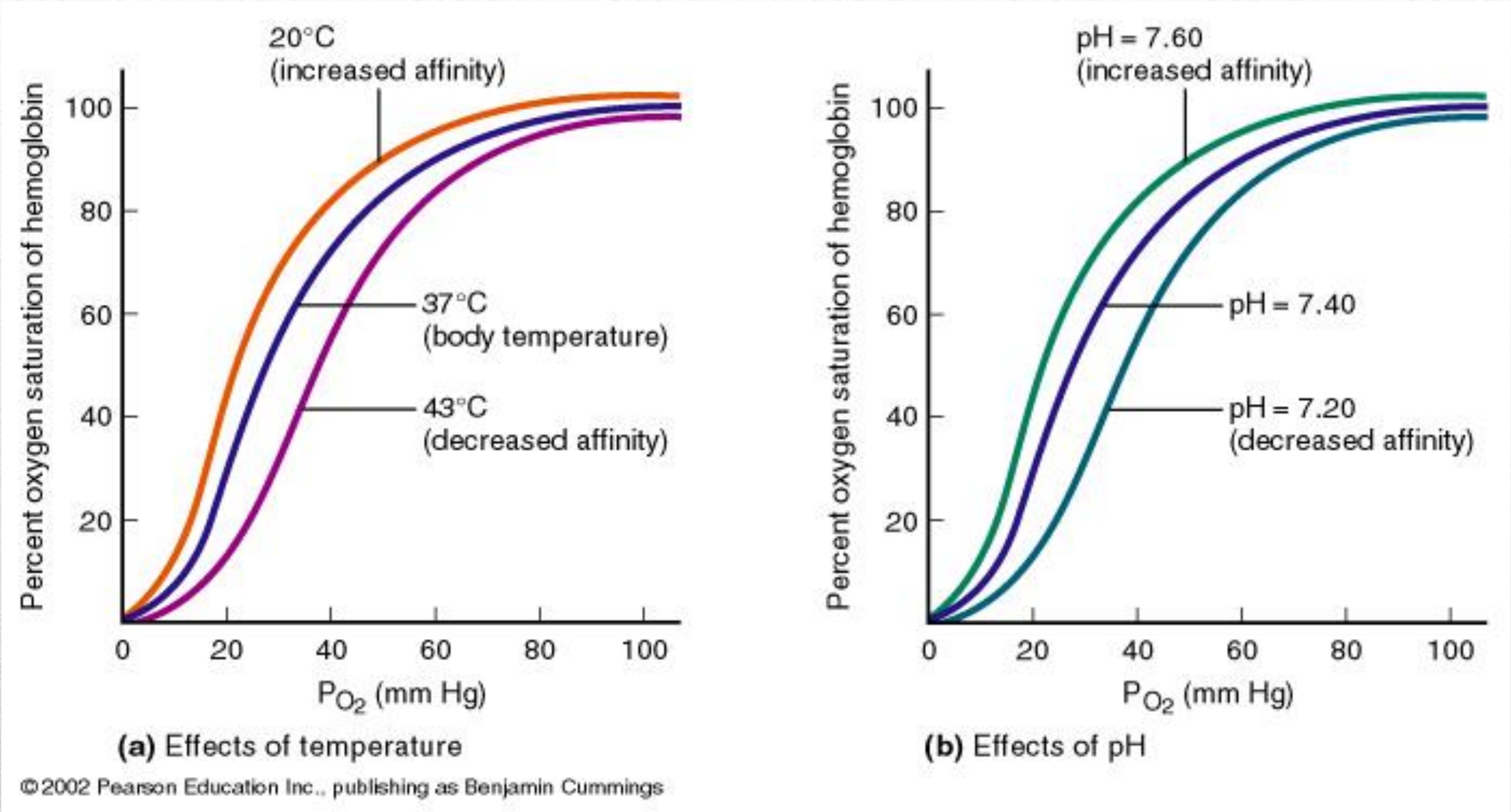
The Carbamino Effect


Leftward shift
(increased affinity)
Normal
Rightward shift
(decreased affinity)
Percent oxygen saturation of hemoglobin
100
80
60
40
20
0
20
40
60
80
100
P_{O_2} (mm Hg)

- These factors are all present during exercise and enable Hb to release more O_2 to meet the metabolic demands of working tissues

  - ↑ body temperature = ↓ Hb affinity for O_2
  - ↑ H^+ ions (↓ pH) = ↓ Hb affinity for O_2
  - ↑ arterial P_{CO2} = ↓ Hb affinity for O_2

The Hemoglobin-Oxygen Dissociation Curve



20°C
(increased affinity)
37°C
(body temperature)
43°C
(decreased affinity)
Percent oxygen saturation of hemoglobin
100
80
60
40
20
0
20
40
60
80
100
P_{O_2} (mm Hg)
(a) Effects of temperature
pH = 7.60
(increased affinity)
pH = 7.40
pH = 7.20
(decreased affinity)
Percent oxygen saturation of hemoglobin
P_{O_2} (mm Hg)
(b) Effects of pH
©2002 Pearson Education Inc., publishing as Benjamin Cummings

CO_2 may be transported in the blood by…

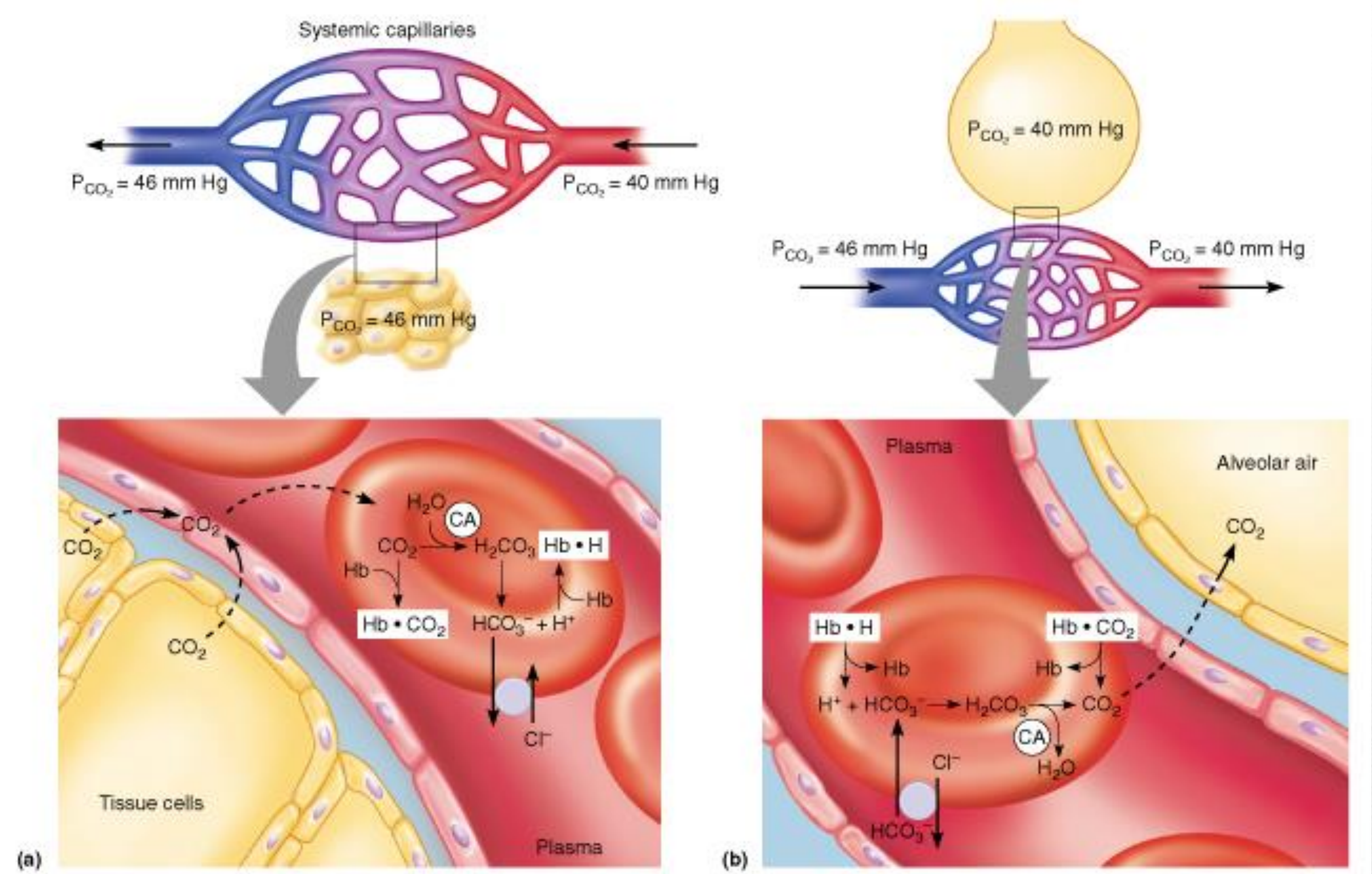
- Dissolving in the plasma
- Dissolving as bicarbonate
- Binding to Hb (carbaminohemoglobin)

Transport of Gases in the Blood: CO_2

CO_2 Dissolved in Plasma

- CO_2 is very soluble in water
- ~ 5 - 6% of CO_2 in the blood is dissolved in plasma
- The partial pressure gradient between the tissues and blood allows CO_2 to easily diffuse from the tissues into the plasma
- The amount of CO_2 dissolved in the plasma is proportional to the partial pressure of CO_2

Transport of Gases in the Blood: CO_2

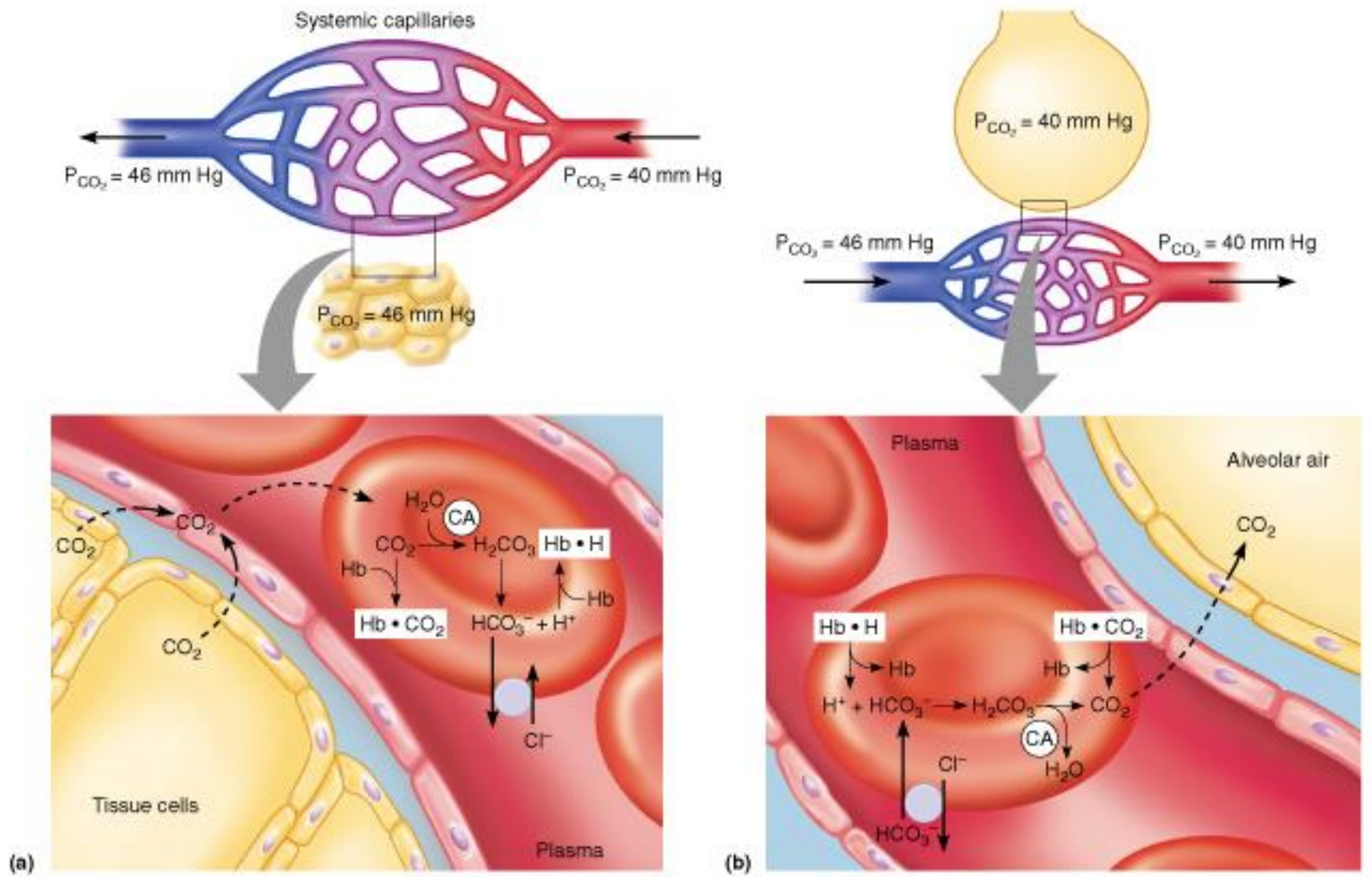


Systemic capillaries
P_{CO_2} = 46 mm Hg
P_{CO_2} = 40 mm Hg
P_{CO_2} = 46 mm Hg
CO_2
CO_2
CO_2
H_2O
CA
CO_2
H_2CO_3
Hb • H
Hb
Hb
Hb • CO_2
HCO_3^- + H^+
Cl^-
Tissue cells
Plasma
(a)
P_{CO_2} = 40 mm Hg
P_{CO_2} = 46 mm Hg
P_{CO_2} = 40 mm Hg
Plasma
Alveolar air
CO_2
Hb • H
Hb • CO_2
Hb
Hb
H^+ + HCO_3^-
H_2CO_3
CO_2
CA
H_2O
Cl^-
HCO_3^-
(b)

CO_2 as Bicarbonate (H_2CO_3)

- ~ 86 – 90% of CO_2 in the blood is transported in the form of bicarbonate ions
- In water, carbonic acid dissociates to release H^+ ions and bicarbonate ions
  - $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3$-
  - Catalyzed by carbonic anhydrase
- This chemical reaction occurs slowly in both plasma and in red blood cells
- The blood becomes more acidic due to the accumulation of CO_2

Transport of Gases in the Blood: CO_2



Systemic capillaries
P_{CO_2} = 46 mm Hg
P_{CO_2} = 40 mm Hg
P_{CO_2} = 46 mm Hg
P_{CO_2} = 40 mm Hg
P_{CO_2} = 46 mm Hg
P_{CO_2} = 40 mm Hg
CO_2
CO_2
CO_2
H_2O
CA
CO_2
H_2CO_3
Hb • H
Hb
Hb
Hb • CO_2
HCO_3^- + H^+
Cl^-
Tissue cells
Plasma
(a)
Plasma
Alveolar air
CO_2
Hb • H
Hb • CO_2
Hb
Hb
H^+ + HCO_3^-
H_2CO_3
CO_2
CA
H_2O
Cl^-
HCO_3^-
(b)

CO_2 bound to Hb (carbaminohemoglobin)

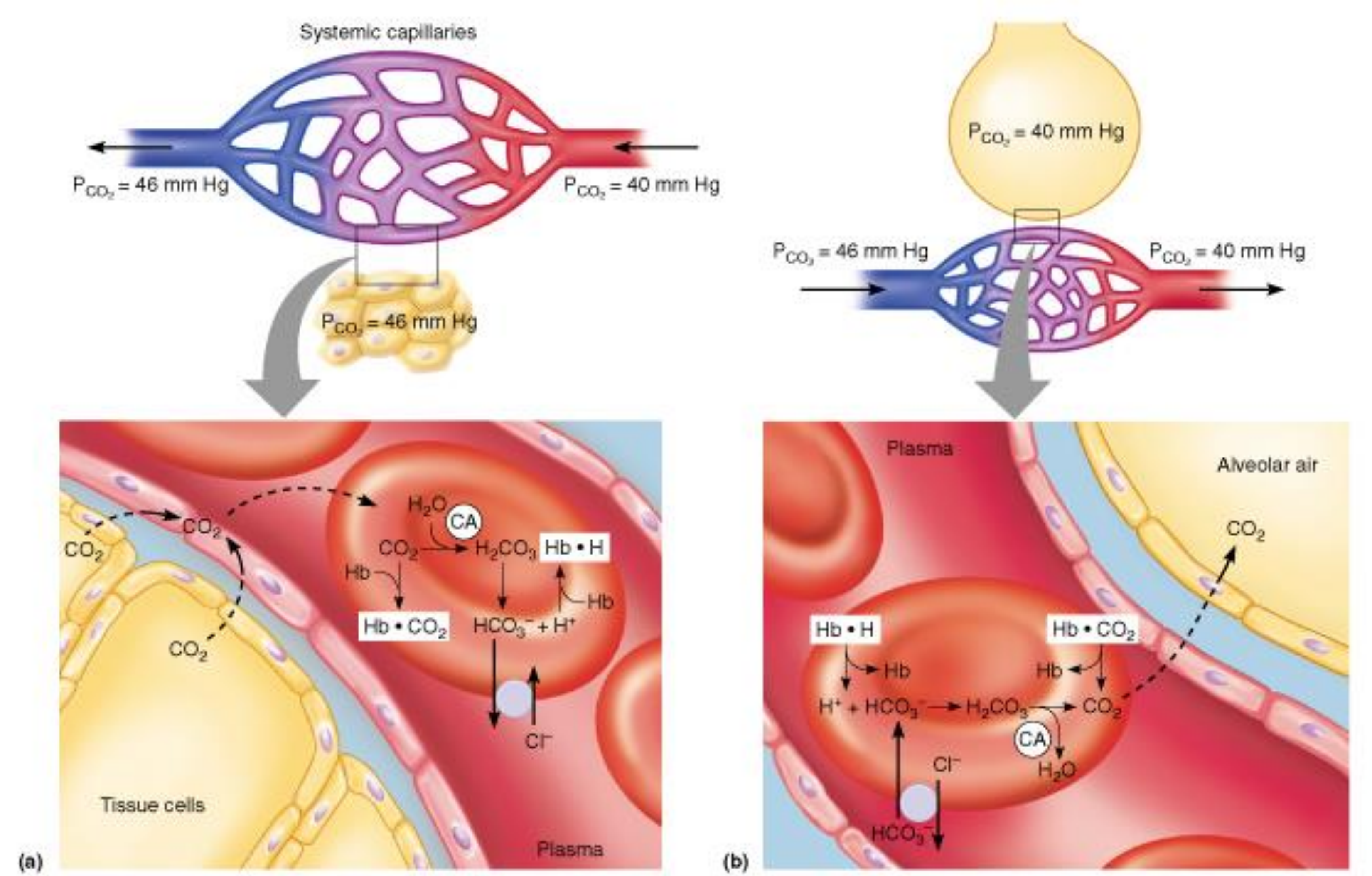
- Carbaminohemoglobin
  - CO_2 attached to a hemoglobin molecule
  - $Hb + CO_2 \leftrightarrow HbCO_2$
- ~ 5 - 8% of CO_2 is bound to Hb in RBCs
- CO_2 diffuses into RBCs and binds with the globin component (not the heme component) of Hb for transport to the lungs

Transport of Gases in the Blood: CO_2

The Chloride Shift

- CO_2 may be transported as $HbCO_2$ or H_2CO_3
  - H^+ ions or bicarbonate may accumulate in RBCs
- Hb functions as a buffer for H^+ ions
  - Hb binding to H^+ ions forms HHb as a buffer so that RBCs do not become too acidic
  - $Hb + H^+ \leftrightarrow HHb$
- The bicarbonate ion (H_2CO_3) diffuses out of the RBC into the plasma to be carried to the lungs
  - As bicarbonate ions leave the RBC, Cl^- ions enter the RBC

CO_2 Exchange and Transport in Systemic Capillaries and Veins



Systemic capillaries
P_{CO_2} = 46 mm Hg
P_{CO_2} = 40 mm Hg
P_{CO_2} = 46 mm Hg
CO_2
CO_2
CO_2
H_2O
CA
CO_2
H_2CO_3
Hb • H
Hb
Hb
Hb • CO_2
HCO_3^- + H^+
Cl^-
Tissue cells
Plasma
(a)
P_{CO_2} = 40 mm Hg
P_{CO_2} = 46 mm Hg
P_{CO_2} = 40 mm Hg
Plasma
Alveolar air
CO_2
Hb • H
Hb • CO_2
Hb
Hb
H^+ + HCO_3^-
H_2CO_3
CO_2
CA
H_2O
Cl^-
HCO_3^-
(b)

The Haldane effect

- Loading/Unloading of CO_2 onto Hb is *directly* related to:
- 1) The partial pressure of CO_2 (P_{CO2})
  - In areas of high P_{CO2}, carbaminohemoglobin forms
  - This helps unload CO_2 from tissues
- 2) The partial pressure of O_2 (P_{O2})
  - In areas of high P_{O2} (such as in the lungs), the amount of CO_2 transported by Hb decreases
  - This helps unload CO_2 from the blood
- 3) The degree of oxygenation of Hb
  - Deoxygenated Hb is able to carry more CO_2 than a Hb molecule loaded with O_2
  - The binding of O_2 to Hb decreases the affinity of Hb for CO_2

The Effect of O_2 on CO_2 Transport

REGULATION OF RESPIRATION

- The purpose of ventilation is to deliver O_2 to and remove CO_2 from cells at a rate sufficient to keep up with metabolic demands
- Breathing is under both involuntary and voluntary control
  - Normal breathing is rhythmic and involuntary
  - However, the respiratory muscles may be controlled voluntarily

Central Regulation of Ventilation

- The brainstem generates breathing rhythm
- Signals are delivered to the respiratory muscles via somatic motor neurons
- Phrenic nerve
  - Innervates the diaphragm
- Intercostal nerves
  - Innervate the internal and external intercostal muscles

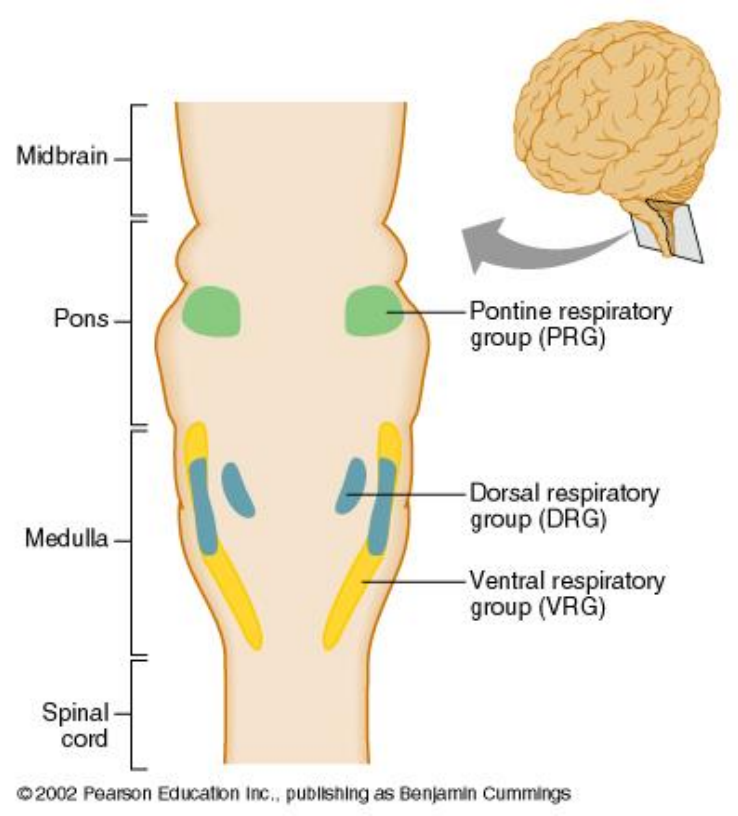
Neural Control of Breathing by Motor Neurons

- Central control of respiration is not completely understood
- Research indicates that respiratory control centers are located in the brainstem
- Respiratory control centers include…
  - Medullary Rhythmicity Area of the medulla oblongata
  - Pneumotaxic Area of the pons
  - Apneustic Center of the pons

Generation of the Breathing Rhythm by the Brainstem

Medullary Rhythmicity Area

- Includes two groups of neurons:
  - Dorsal Respiratory Group
  - Ventral Respiratory Group



The Dorsal Respiratory Group

- The medullary *inspiratory* center
- Functions to generate the basic respiratory rhythm
  - The respiratory cycle is repeated 12 - 15 times/minute
- Dorsal neurons have an intrinsic ability to spontaneously depolarize at a rhythmic rate
- Quiet breathing - Inhalation
  - The dorsal inspiratory neurons transmit nerve impulses via the phrenic and intercostal nerves to the diaphragm and external intercostal muscles
  - When these muscles contract, the lungs fill with air
- Quiet breathing - Exhalation
  - When the dorsal inspiratory neurons stop sending impulses, expiration occurs passively as the inspiratory muscles relax and the lungs recoil

Medullary Rhythmicity Area

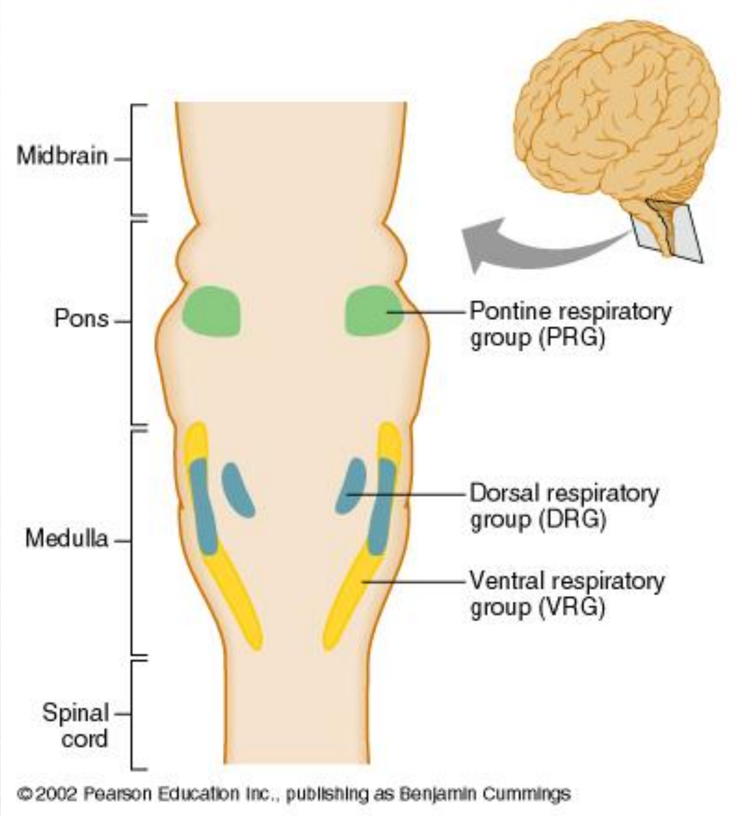
The Ventral Respiratory Group

- The medullary *expiratory* center
- Functions to promote expiration during forceful breathing
- If the rate and depth of breathing increases above a critical threshold, it stimulates a forceful expiration
- The ventral expiratory neurons transmit nerve impulses to the muscles of expiration
  - The internal intercostals
  - The abdominal muscles

Medullary Rhythmicity Area

Pneumotaxic Area

- Includes two groups of neurons:
  - Pontine Respiratory Group
  - The Central Pattern Generator



The Pontine Respiratory Group

- Facilitates the transition between inspiration and expiration
- Regulates the depth or the extent of inspiration
- Regulates the frequency of respiration

Pneumotaxic Area

The Central Pattern Generator

- A network of neurons scattered between the pons and the medulla
  - Exact location of these neurons is unknown
- Coordinates the control centers of the brainstem
- Regulates the rate of breathing
- Regulates the length of inspiration
  - Avoid over-inflation of the lungs
- Regulates the depth of breathing
  - ↑ pneumotaxic output = shallow, rapid breathing
  - ↓ pneumotaxic output = deep, slow breathing

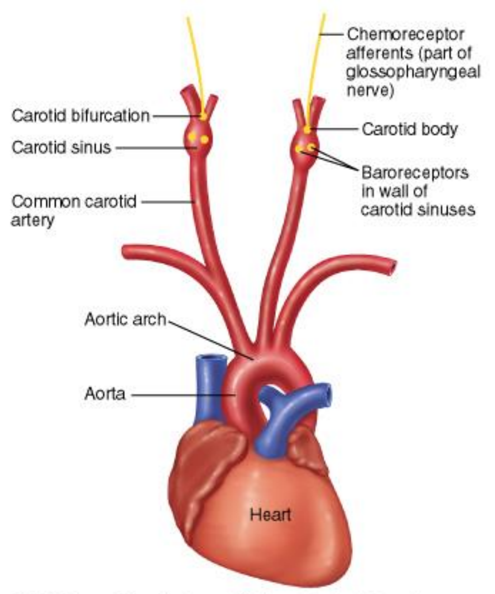
Pneumotaxic Area

Peripheral Input to Respiratory Centers

- Receptors and reflexes monitor and respond to stimuli
- Feed information (input) to the Central Pattern Generator
- Input received from…
  - Chemoreceptors
  - Pulmonary stretch receptors
    - Detect lung tissue expansion and may protect lungs from over inflation through the Hering-Breuer reflex
  - Irritant receptors
    - Detect inhaled particles (dust, smoke) and trigger coughing, sneezing, or bronchiospasm

Peripheral Chemoreceptors

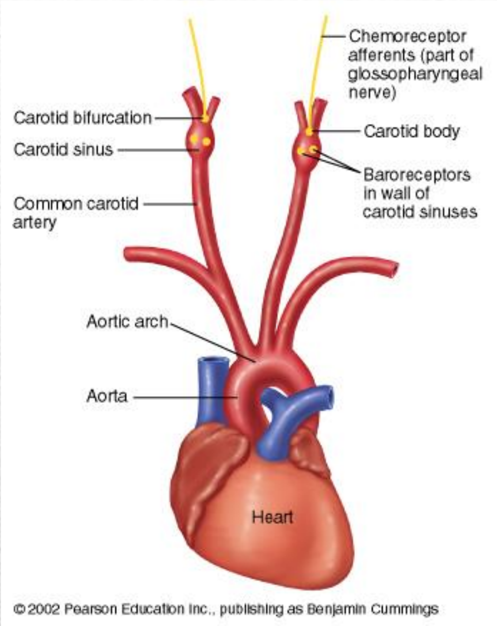
- Detect chemical concentration of blood and cerebrospinal fluid
- Location:
  - Carotid sinus
    - At its bifurcation into the internal and external carotid arteries
  - Connected to medulla by afferent neurons in the glossopharyngeal (CN IX) nerve
- Chemical concentration of the blood is most important
  - Changing levels of CO_2, O_2, and pH of the blood
  - Sensitive to low arterial O_2 concentrations (below 60 mmHg)



Peripheral Input to Respiratory Centers: Chemoreceptors

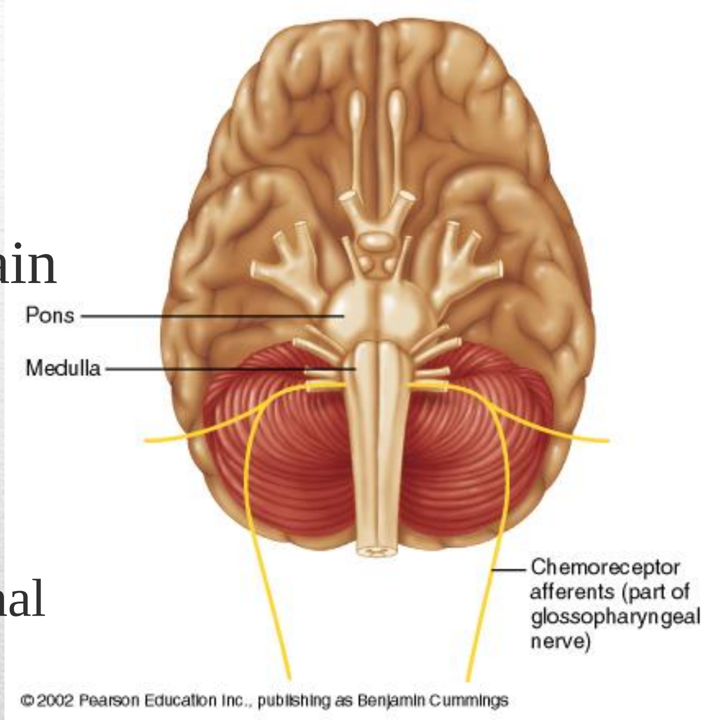
Peripheral Input to Respiratory Centers: Chemoreceptors

- Peripheral chemoreceptors are very sensitive to changes in arterial pH
- ↓ arterial pH (↑ H^+ ion concentration) occurs:
  - When arterial CO_2 levels increase
  - When lactic acid accumulates in the blood
- Therefore, ↓ arterial pH is the most powerful stimulant for respiration
- When O_2 concentration is low, ventilation increases

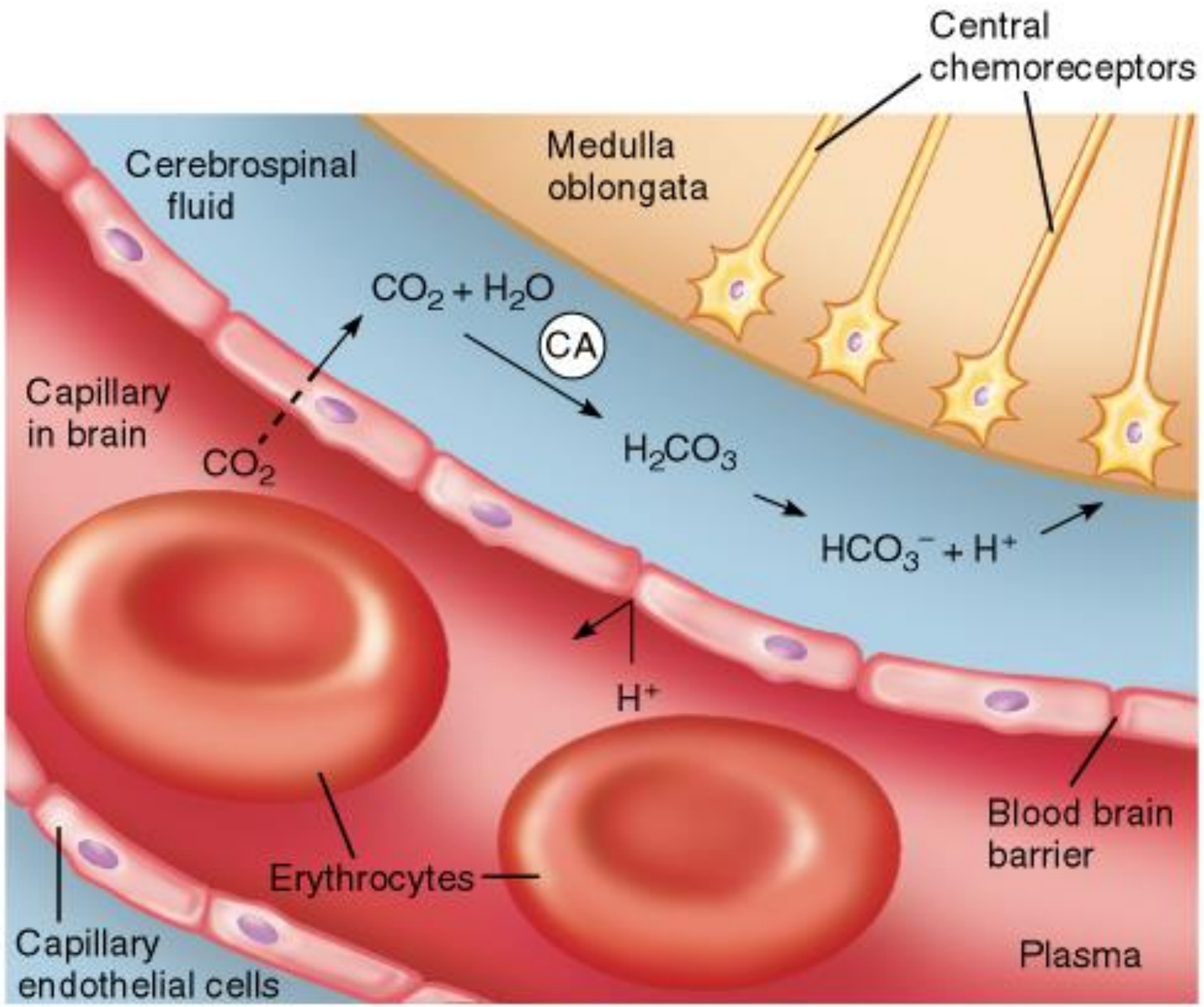


Central chemoreceptors

- Sensitive to H^+ ion concentration in cerebrospinal fluid
- Located in the medulla within the blood-brain barrier
- CO_2 is able to diffuse across the blood-brain barrier and combine with water to form carbonic acid
  - This reaction releases H^+ ions in the cerebrospinal fluid
  - CO_2 then combines with water in cerebrospinal fluid to form carbonic acid
- Stimulation of these central chemoreceptors increases respiration rate, thus increasing blood pH to homeostatic levels



Peripheral Input to Respiratory Centers: Chemoreceptors


Central chemoreceptors
Medulla oblongata
Cerebrospinal fluid
$CO_2 + H_2O$
CA
Capillary in brain
CO_2
H_2CO_3
$HCO_3^- + H^+$
H^+
Blood brain barrier
Erythrocytes
Capillary endothelial cells
Plasma

Chemoreceptor reflexes

- Chemoreceptors maintain normal levels of arterial CO_2 through chemoreceptor reflexes
- Increased CO_2 = increased concentration of H^+ ions (↓ pH)
  - This stimulates the chemoreceptors
- Decreased blood pH can be caused by
  - Exercise and accumulation of lactic acid
  - Breath holding
  - Other metabolic causes
- ↓ arterial pH causes the respiratory system to attempt to restore normal blood pH by…
  - ↑ ventilation to decrease CO_2 levels
  - This results in an increase in pH to normal levels

Conscious Control of Breathing

- Control over respiratory muscles is voluntary
  - Therefore, breathing patterns may be consciously altered
- Voluntary control is made possible by neural connections between higher brain centers (the cortex) and the brain stem
- Voluntary control includes…
  - Holding your breath
  - Emotional upset
  - Strong sensory stimulation (irritants) that alter normal breathing patterns

Hyperpnea

- An ↑ in the arterial CO_2 concentration with a resultant ↓ in CSF fluid pH
- This condition stimulates the…
  - Central chemoreceptors, and
  - Medullary respiratory centers
- Stimulates an increase in ventilation

Hyperventilation

- More CO_2 is exhaled resulting in ↓ arterial CO_2 concentration
- This returns arterial pH to normal levels

Disturbances in Respiration

Acid-Base Disturbances in Blood

- The average pH of body fluids is 7.38
  - This is slightly alkaline, but, acidic compared to blood
  - The pH of arterial blood is 7.4.
  - The pH of venous blood and extracellular fluid is 7.35
  - The pH of intracellular fluid is 7.0
    - This reflects the greater amounts of acidic wastes and CO_2 that are produced inside cells
- Acidosis
  - Arterial blood pH less than 7.35
- Alkalosis
  - Arterial blood pH greater than 7.45

The Respiratory System in Acid-Base Homeostasis

Hydrogen Ion Concentration Regulation

- Body pH is regulated by the respiratory system through the regulation of H^+ ion concentration in the blood
- Very important because metabolic reactions generally produce more acids than bases
- Acid-base buffers
  - Bind with H^+ ions when fluids become acidic
  - Release H^+ ions when fluids become alkaline
  - Convert strong acids into weaker acids
  - Convert strong bases into weaker bases
  - Examples:
    - Hemoglobin
    - Bicarbonate ions

The Respiratory System in Acid-Base Homeostasis

- Respiratory centers located in the brainstem help regulate pH by controlling the rate and depth of breathing
- Respiratory responses to changes in pH are not immediate, it requires several minutes to modify pH
- Respiratory responses to changes in pH are almost twice the buffering power of all the chemical buffers combined

The Respiratory System in Acid-Base Homeostasis

- pH disturbances result due to inadequate or improper functioning of respiratory mechanics
- ***Respiratory acidosis***
  - The most common type of acid-base imbalance
  - Accumulation of CO_2 as the result of shallow breathing, pneumonia, emphysema, or obstructive respiratory diseases
- ***Respiratory alkalosis***
  - Develops during hyperventilation
  - Excessive loss of CO_2
  - Treatment includes re-breathing air to increase arterial CO_2

Abnormalities of Acid-Base Balance