RESPIRATORY PHYSIOLOGY

By

EMOJEVWE, V.

DEPARTMENT OF PHYSIOLOGY

UNIVERSITY OF MEDICAL SCIENCES,ONDO

Objectives of this course

- Students should Know the meaning of respiration
- Explain how the intrapulmonary and intrapleural pressures vary during ventilation and relate these pressure changes to Boyle's law.
- Define the terms compliance and elasticity, and explain now these lung properties affect vehtilation.
- Discuss the significance of surface tension in lung mechanics, explain how the law of Laplace applies to lung function and describe the role of pulmonary surfactant.
- To Know the pulmonary function tests and their importance
- Pulmonary disease should have also been studied

Objectives (continued)

- Explain how inspiration and expiration are accomplished in unforced breathing and describe the accessory respiratory muscles used in forced breathing.
- Describe the roles of the medulla, pons, and cerebral cortex in the regulation of breathing.
- Explain how chemoreceptors in the medulla and the peripheral chemoreceptors in the aortic and carotid bodies respond to changes in P_{CO_2}, pH, and P_{O_2}.

Objectives (continued)

- Describe the loading and unloading reactions and explain how the extent of these reactions is influenced by the P_{0_2} and affinity of HB for 0_2.
- Explain how oxygen transport is influenced by changes in blood pH, temperature, and explain the effect and physiological significance of 2,3-DPG on oxygen transport.
- Describe the hyperpnea of exercise and explain how the anaerobic threshold is affected by endurance training.

Respiration

- **Definition:** It is the exchange of gases between the organism and its environment, utilization of O_2 and production of CO_2 by the organism.
- It Includes 3 separate functions:
- Ventilation:
  - Breathing.
- Gas exchange:
  - Between air and capillaries in the lungs.
  - Between systemic capillaries and tissues of the body.
- 0_2 utilization:
  - Cellular respiration.

Physiological Anatomy

- The system consist of

The nose, mouth

⬇

Tracheal and 2 main bronchi

⬇

Conducting bronchioles

⬇

Respiratory bronchioles

⬇

Alveolar ducts

⬇

Alveoli

Conducting Zone

- All the structures air passes through before reaching the respiratory zone.
- Warms and humidifies inspired air.
- Filters and cleans:
  - Mucus secreted to trap particles in the inspired air.
  - Mucus moved by cilia to be expectorated.

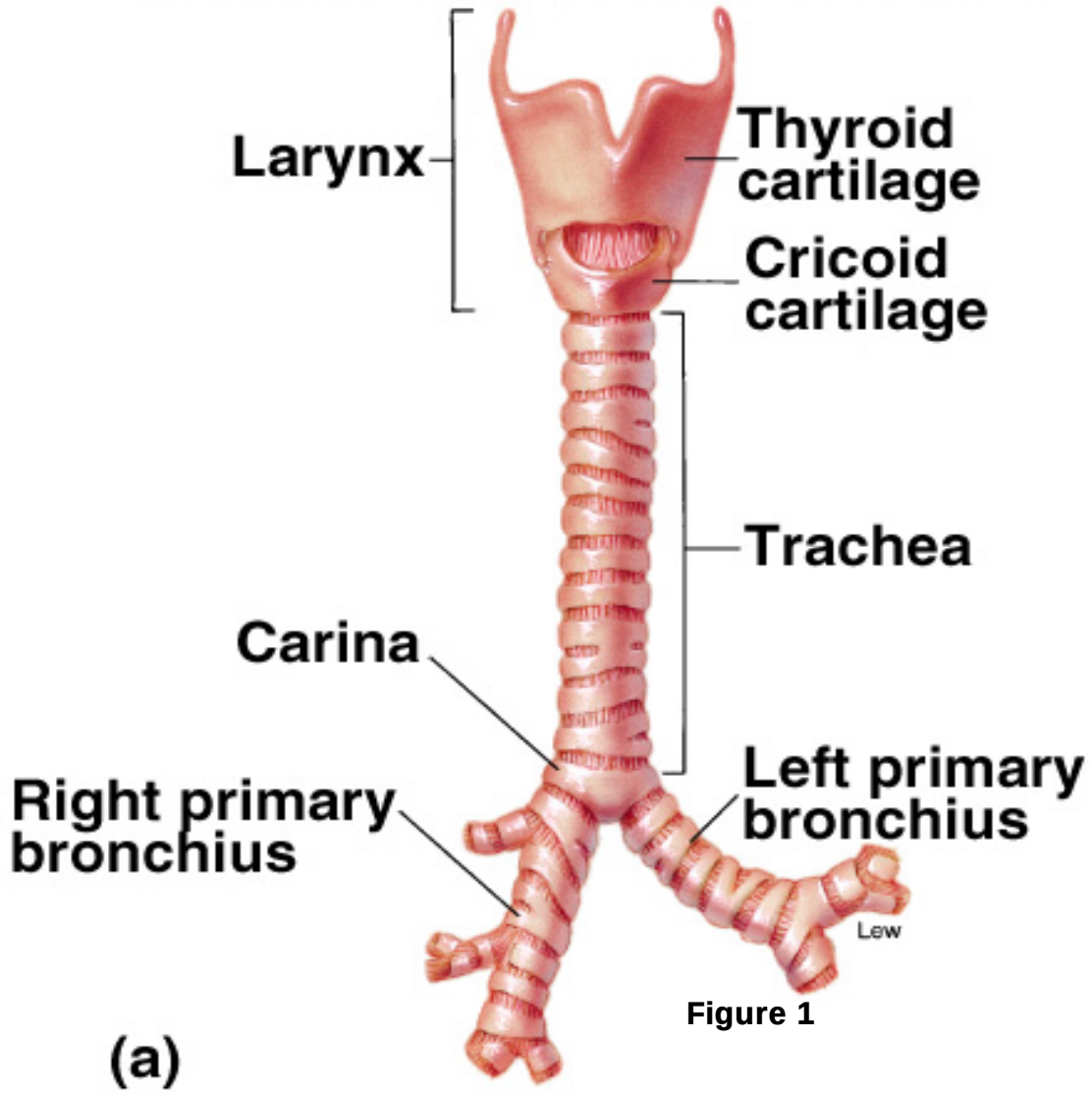


Figure 1

Respiratory Zone

- Region of gas exchange between air and blood.
- Includes respiratory bronchioles and alveolar sacs.
- Must contain alveoli.

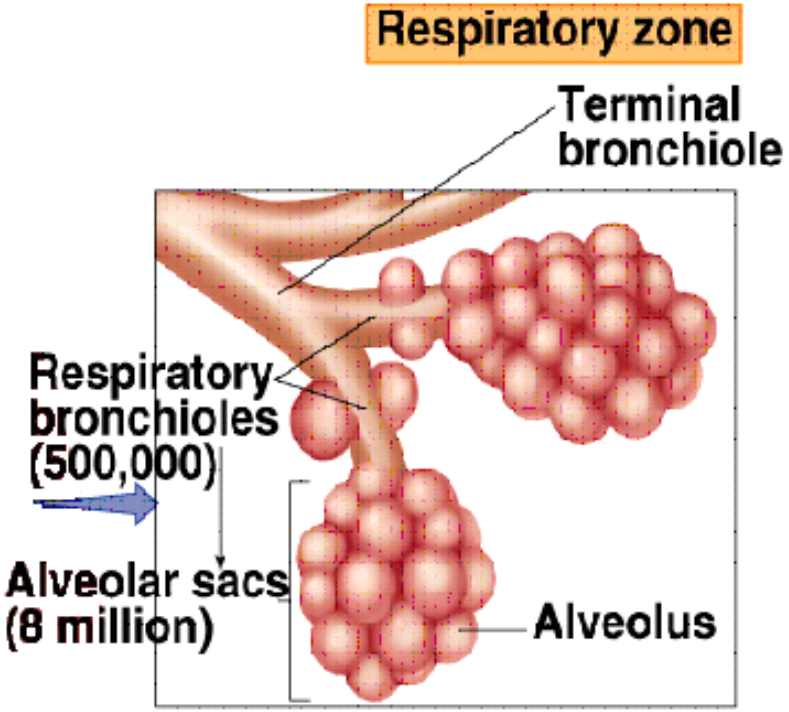


Figure 2

Alveoli

- ~ 300 million air sacs (alveoli).
  - Large surface area (60–80 m^2).
  - Each alveolus is 1 cell layer thick.
- 2 types of cells:
  - Alveolar type I:
    - Structural cells.
  - Alveolar type II:
    - Secrete surfactant.

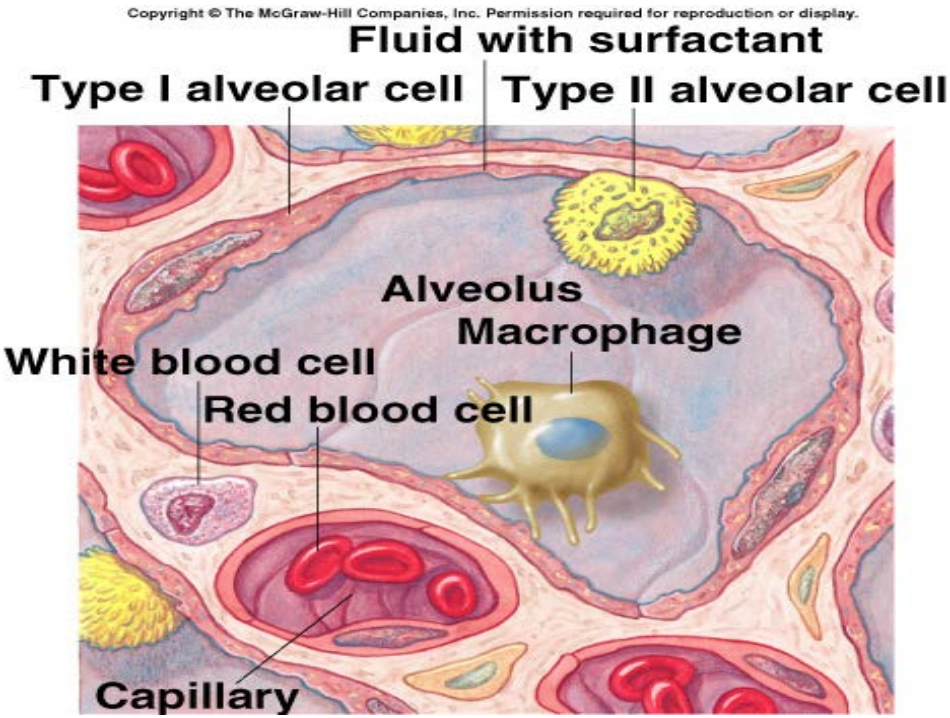


Figure 3

Physical Properties of the Lungs

- Compliance:
  - Distensibility (stretchability):
    - Ease with which the lungs can expand.
  - 100 x more distensible than a balloon.
    - Compliance is reduced by factors that produce resistance to distension.
- Elasticity:
  - Tendency to return to initial size after distension.
  - High content of elastin proteins.
    - Very elastic and resist distension.

Anatomical and Physiological Dead Space

- Not all of the inspired air reached the alveoli.
- As fresh air is inhaled it is mixed with air in the dead spaces.
  - **Anatomical dead space:** Conducting zone which does not participate in gaseous exchange
  - **Physiological dead space**: Anatomical dead space and part of respiratory zone where no gaseous exchange no longer take place
- Alveolar ventilation = F x (TV- DS).
  - F = frequency (breaths/min.).
  - TV = tidal volume.
  - DS = dead space.

Ventilation

- Mechanical process that moves air in and out of the lungs.
- [O_2] of air is higher in the lungs than in the blood, O_2 diffuses from air to the blood.
- $C0_2$ moves from the blood to the air by diffusing down its concentration gradient.
- Gas exchange occurs entirely by diffusion.
- Mechanics of ventilation: structural features that bring about breathing in and out and how they bring about this phenomenon

Mechanics of Ventilation:

- Respiration last about 4sec.
- It consist of inspiration which last about 1.5 Sec and expiration which last for 2.5 Sec
- Quiet Inspiration is brought about by actions of the diaphragm and the outward and forward movement of the Ribs and actions of external intercostal muscles
- Forceful inspiration is aided by sternocleidomastoids, scalene muscle, scapular elevator and Ant. serati

Quiet Inspiration

- Active process:
  - Contraction of diaphragm, increases thoracic volume vertically.
  - Contraction of internal intercostals increases thoracic volume laterally.
  - Increase in lung volume decreases pressure in alveoli, and air rushes in.
- Pressure changes:
  - Alveolar changes from 0 to –3 mm Hg.
  - Intrapleural changes from –4 to –6 mm Hg.
  - Transpulmonary pressure = +3 mm Hg.

Mechanics of Ventilation (Contd)

- Quiet expiration is by elastic recoil actions of the lungs and thoracic cage
- Forceful expiration is by actions of:
- Internal intercostal muscles, abdominal recti muscles and Posterior Inferior Sarrati muscles

Expiration

- Quiet expiration is a passive process.
  - After being stretched, lungs recoil.
  - Decrease in lung volume raises the pressure within alveoli above atmosphere, and pushes air out.
- Pressure changes:
  - Intrapulmonary pressure changes from –3 to +3 mm Hg.
  - Intrapleural pressure changes from –6 to –3 mm Hg.

Surface Tension

- Force exerted by fluid in alveoli to resist distension.
  - Lungs secrete and absorb fluid, leaving a very thin film of fluid.
  - This film of fluid causes surface tension.
- H_20 molecules at the surface are attracted to other H_20 molecules by attractive forces.
  - Force is directed inward, raising pressure in alveoli.

Surfactant

- Phospholipid produced by alveolar type II cells.
- Lowers surface tension.
  - Reduces attractive forces of hydrogen bonding by becoming interspersed between H_20 molecules.
- As alveoli radius decreases, surfactant's ability to lower surface tension increases.

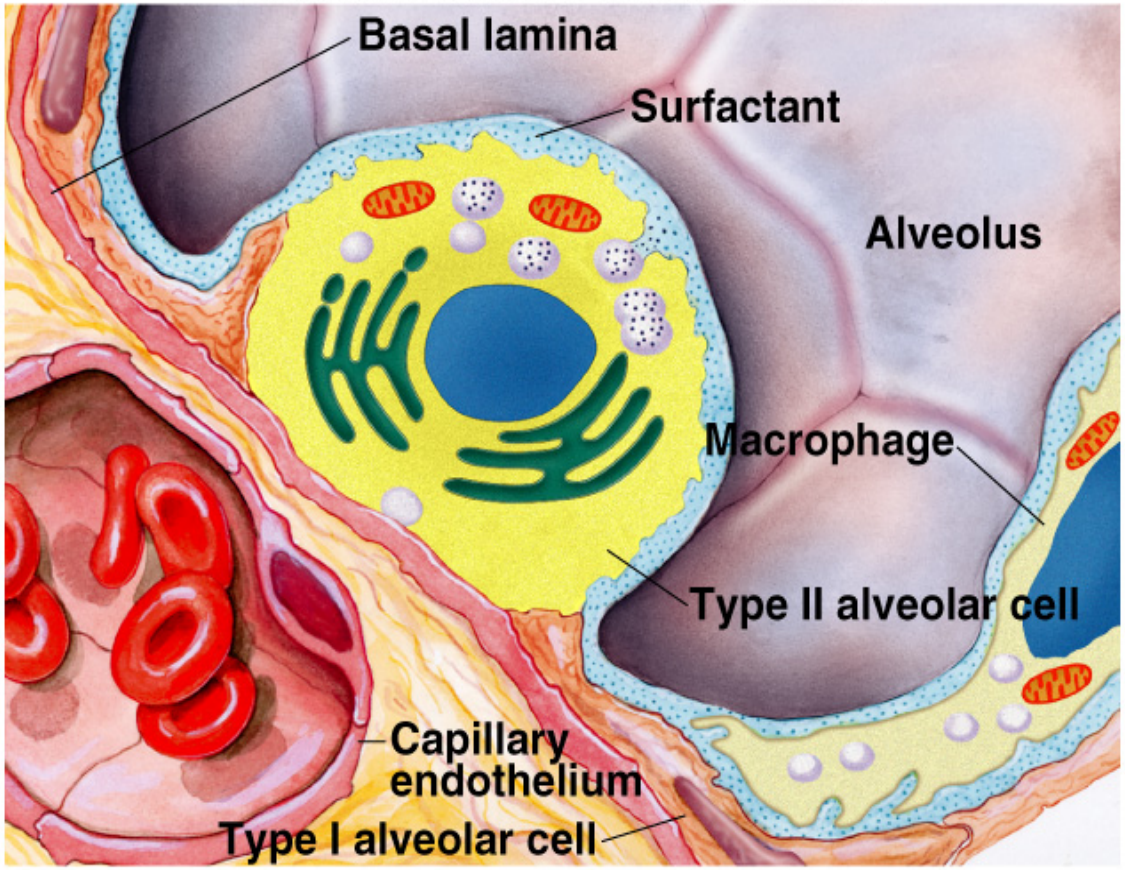


Figure 4

Gas Laws

- **Henry's Law:** States that at equilibrium, the amount of Gas dissolved in a given volume of fluid in a given temperature is proportional to the partial

- This law is important in the transfer of gases from the alveolar sacs into the plasma in pulmonary capillary and then into the RBCs

Gas Laws (contd)

- **General gas law:** Gases moves from area of higher pressure to area of lower pressure
- **Graham's law of diffusion:** Rate of diffusion of two gases are inversely proportional to the square root of their Molecular weight

- **Dalton's Law partial pressure:** the pressure exerted by any gas in a mixture of gases is the pressure it would exert if no other gas was present

Boyle's Law

- Changes in intrapulmonary pressure occur as a result of changes in lung volume.
  - Pressure of gas is inversely proportional to its volume.
- Increase in lung volume decreases intrapulmonary pressure.
  - Air goes in.
- Decrease in lung volume, raises intrapulmonary pressure above atmosphere.

Law of Laplace

- Pressure in alveoli is directly proportional to surface tension; and inversely proportional to radius of alveoli.
  - Pressure in smaller alveolus greater.

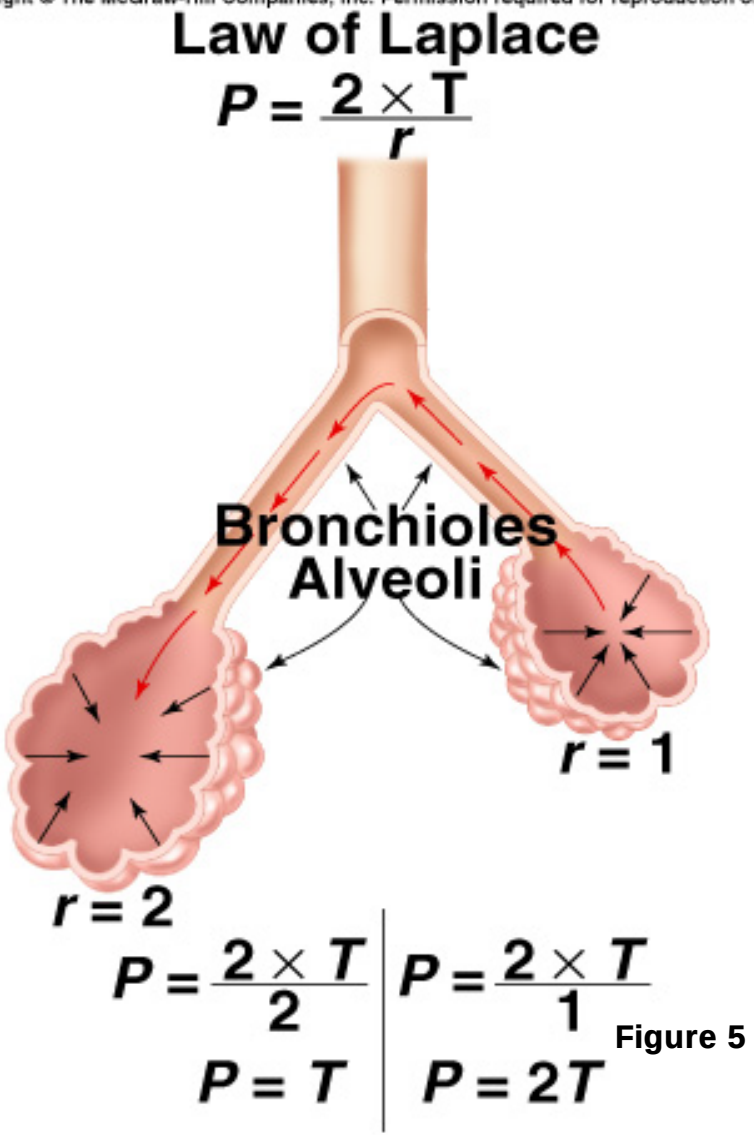


Figure 5

Lung Pressures

- Intrapulmonary pressure:
  - Intra-alveolar pressure (pressure in the alveoli).
- Intrapleural pressure:
  - Pressure in the intrapleural space.
  - Pressure is negative, due to lack of air in the intrapleural space.
- Transpulmonary pressure:
  - Pressure difference across the wall of the lung.
  - Intrapulmonary pressure – intrapleural

Pulmonary Ventilation

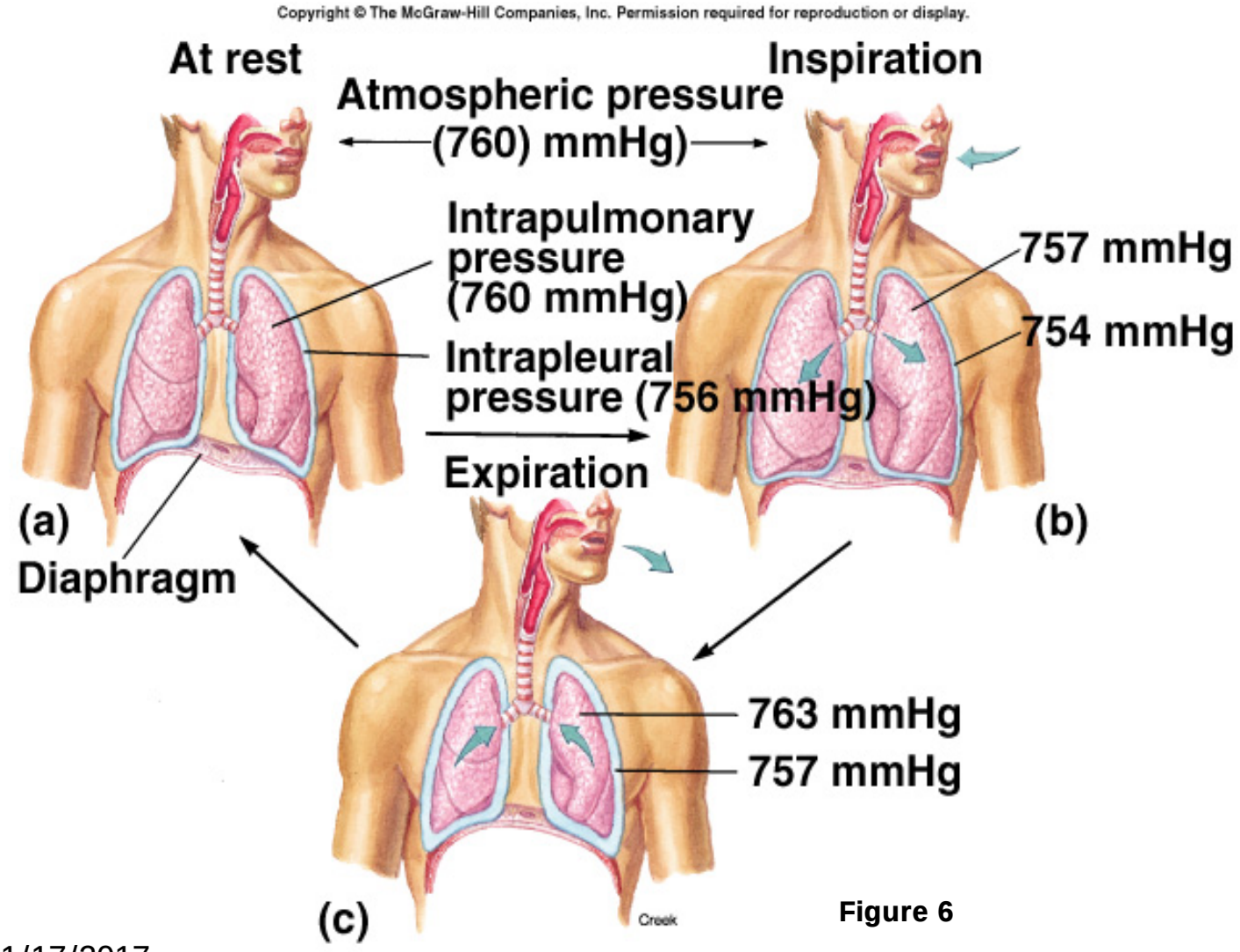


Figure 6

Pulmonary compliance

- It means the volume change produced by a unit change of pressure.
- It is the distensibility of the lungs and thoracic cage structures
- It obeys Hooke's law
  - 1. Compliance of lungs and thorax together: 130 mL/1 cm H2O pressure
  - 2. Compliance of lungs alone: 220 mL/1 cm H2O pressure.
- Work of breathing
  - Airway resistance work
  - Work done in overcoming Elastic resistance of lungs and thorax
  - Nonelastic viscous resistance work.

Pulmonary Function Tests

- These are tests done to asses the **functional status** of the respiratory system both in physiological and pathological conditions.
- These tests are carried out mostly by using spirometer.
- Subject breathes into a closed system in which air is trapped within a bell floating in H_20.
- The bell moves up when the subject exhales and down when the subject inhales.
- We have the digital type in unimed

☐ TYPES OF LUNG FUNCTION TESTS

- Lung function tests are of two types:
- 1. Static lung function tests: volume of air in the lungs regardless of time
- 2. Dynamic lung function tests: based on time (rate).

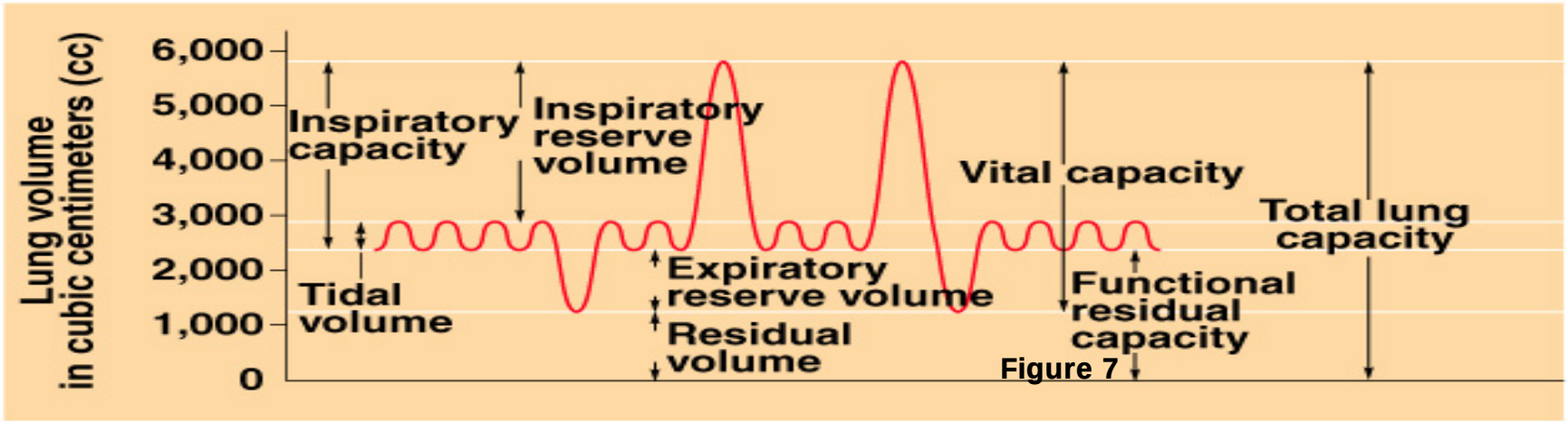


Figure 7

Static lung volumes

- volumes of air breathed by an individual.
- They do not overlap
- They can not be further divided
- When added together equal total lung capacity

Static Lung Volumes

- Tidal Volume: TV
  - The amount of gas inspired or expired with each normal breath.
  - About 500 ml

Static Lung Volumes

- Inspiratory Reserve Volume: IRV
  - Maximum amount of additional air (about 3500 ml) that can be inspired from the end of a normal inspiration.

Static Lung Volumes

- Expiratory Reserve Volume: ERV
  - The maximum volume of additional air that can be expired from the end of a normal expiration.The is about 1100ml

Static Lung Volumes

- Residual Volume: RV
  - The volume of air (about 1200ml) remaining in the lung after a maximal expiration. This lung volume which cannot be measured with a spirometer.
    - Gas dilution tech
      - nitrogen
      - helium
    - Body Plethysmograph

Static Lung Capacities

- Are subdivisions of the total volume that include two or more of the 4 basic lung volumes

Static Lung Capacities (Contd)

- Total Lung Capacity: TLC
  - The volume of air contained in the lungs at the end of a maximal inspiration.
  - It is the sum of the 4 basic lung volumes
  - TLC= RV+IRV+TV+ERV
  - Normal value is about 5800-6000ml

Static Lung Capacities (Contd)

- Vital Capacity: VC
  - The maximum volume of air that can be forcefully expelled from the lungs following a maximal inspiration.
  - It is the sum of inspiratory reserve volume, tidal volume and expiratory reserve volume.
  - VC= IRV+TV+ERV = TLC – RV
  - Value is 4,800 mL

Static Lung Capacities (Contd)

- Functional Residual Capacity: FRC
- The volume of air (about 2300) remaining in the lung at the end of a normal expiration.
  - It is the sum of residual volume and expiratory reserve volume.
  - FRC= RV+ERV

Static Lung Capacities (Contd)

- Inspiratory Capacity: IC
  - Maximum volume of air that can be inspired from end expiratory position.
  - It is the sum of tidal volume and inspiratory reserve volume. i.e IC= TV+IRV
  - This capacity is of less clinical significance than the other three.
  - Value is about 3,800 mL

Dynamic Lung Function Tests

- Tests based on time, i.e. the **rate at which air flows** into or out of lungs. These tests. It includes:
  - Forced vital capacity (FVC):
- **Forced expiratory volume (FEV):** Forced expiratory volume (FEV) is the volume of air, which can be expired forcefully in a given unit of time (after a deep inspiration).
- **Minute Volume (MV):** Is normally about 6 L [500 mL (TV) x 12 (breath Rate)].
- **Maximum ventilation volume or Maximum breathing capacity (MBC or MVV):** Is the largest volume of gas that can be moved into and out of the lungs in 1 minute by voluntary effort. The normal MVV is 125–170 L/min.
- **Peak expiratory flow rate (REFR):** The maximum rate at which air can be expired after a deep inspiration. In normal persons, it is 400 L/minute.

Respiratory Diseases

- Restrictive Disease:
  - Makes it more difficult to get air in to the lungs.
  - They “restrict” inspiration.
  - Decreased VC; Decreased TLC, RV, FRC
  - Includes:
    - Fibrosis
    - Sarcoidosis
    - Muscular diseases
    - Chest wall deformities

Respiratory Diseases

- Obstructive Disease
  - Make it more difficult to get air out of the lungs.
  - Decrease VC; Increased TLC, RV, and FRC
  - Includes:
    - Emphysema
    - Chronic bronchitis
    - Asthma

Restrictive a

- Restrictive disorder:
  - Vital capacity is reduced.
  - FVC is normal.
  - PEFR is less than 200
- Obstructive disorder:
  - VC is normal.
  - FEV_1 is < 80%.
  - PEFR is less than 100

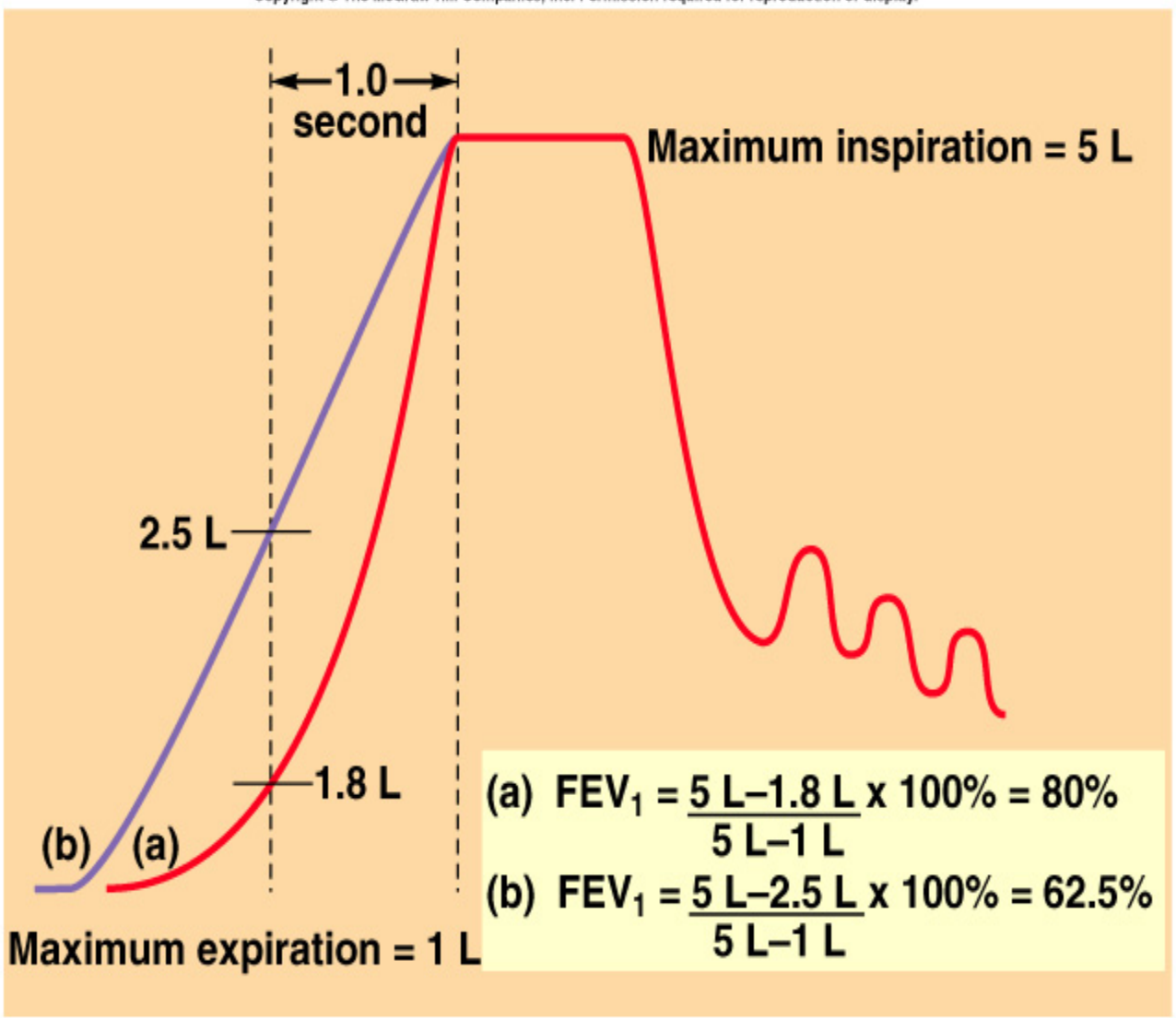


Figure 7

Pulmonary Disorders

- Dyspnea:
  - Shortness of breath.
- COPD (chronic obstructive pulmonary disease):
  - Asthma:
    - Obstructive air flow through bronchioles.
      - Caused by inflammation and mucus secretion.
        - Inflammation contributes to increased airway responsiveness to agents that promote bronchial constriction.
        - IgE, exercise.

Pulmonary Disorders (continued)

- Emphysema:
  - Alveolar tissue is destroyed.
  - Chronic progressive condition that reduces surface area for gas exchange.
    - Decreases ability of bronchioles to remain open during expiration.
      - Cigarette smoking stimulates macrophages and leukocytes to secrete protein digesting enzymes that destroy tissue.
- Pulmonary fibrosis:
  - Normal structure of lungs disrupted by accumulation of fibrous connective tissue proteins.

Lung Ventilation/Perfusion Ratios

- Ratio of lung ventilation to blood flow
- Functionally:
  - Alveoli at apex are underperfused (overventilated).
  - Alveoli at the base are underventilated (overperfused).

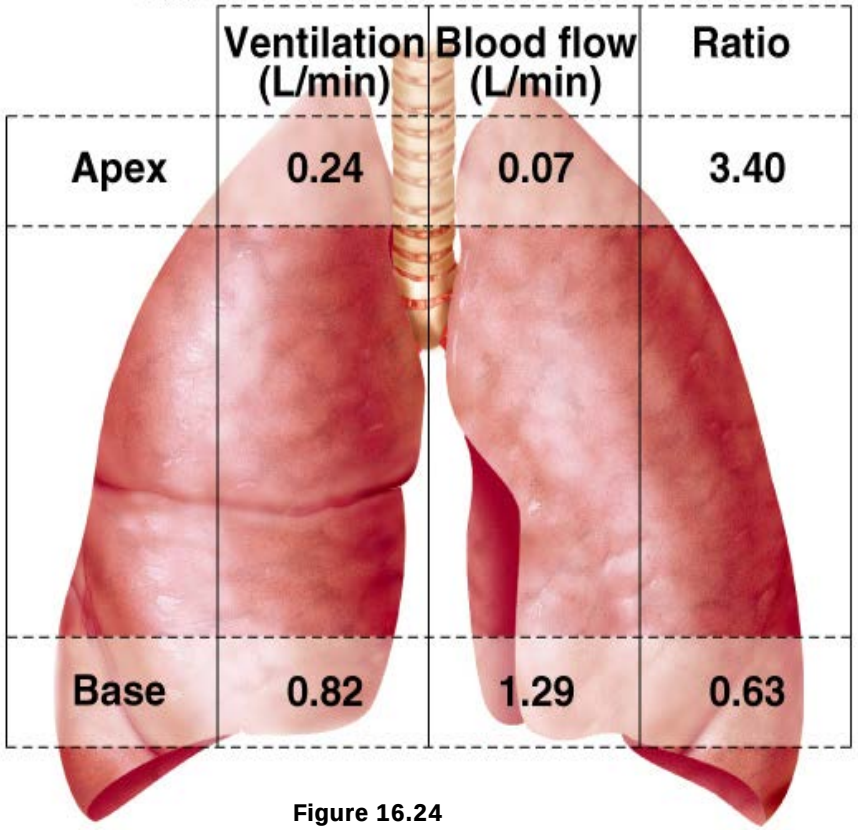


Figure 16.24

Pulmonary Gas Exchange

- Movement of gases into and within the pulmonary system is by diffusion and obeys laws such as graham's law of diffusion, fick's law, Henry's law, etc.
- It involves movement of O_2 and CO_2
- O_2 "flows downhill" from the air through the alveoli and blood into the tissues whereas CO_2 "flows downhill" from the tissues to the alveoli.
- It is done through the Respiratory membrane
- Gases are transported in blood to and from the tissues as the case may be.

Fick's Law of diffusion

- **Fick's Law of diffusion:** States that the rate of diffusion of a substance through a membrane is directly proportional to the area of the membrane, solubility of the substance and the concentration gradient of the substance across the membrane and inversely proportional to thickness of the membrane and the square root of the molecular weight of the substance.

$$D \propto \frac{\Delta P \times A \times S}{d \times \sqrt{MW}}$$

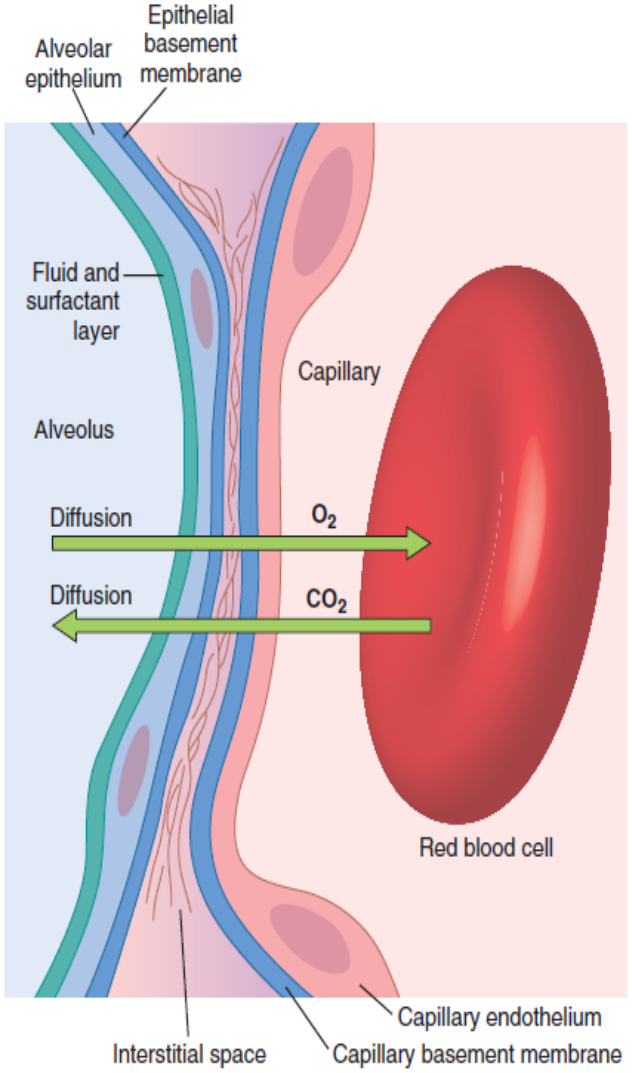
- This law is important in the exchange of gases at the respiratory membrane and tissue membrane

RESPIRATORY MEMBRANE (RM)

- It is the membranous structure in the respiratory unit through which exchange of respiratory gases takes place.
- **Respiratory Unit** composes of Respiratory bronchioles, alveoli ducts, atria and alveoli
- RM is formed by different layers of structures belonging to the alveoli and capillaries.
- it is very thin with total surface area of 70 square meter , average thickness of 0.5 μ and Average diameter 8 μ,
- The RBCs with a diameter of 7.4 μ actually squeeze through the capillaries.
- It is in close contact with RBC membrane to facilitates quick exchange of oxygen and carbon dioxide between the blood and alveoli.

Component of the RM

- A layer of fluid containing surfactant that lines the alveolus
- The alveolar epithelium, which is composed of thin epithelial cells
- An epithelial basement membrane
- A thin interstitial space between the alveolar epithelium and the capillary membrane
- A capillary basement membrane which fuses with the alveolar epithelial basement membrane
- The capillary endothelial



Factors that affect the rate of diffusion the the RM

- *Solubility of gas in fluid medium*
- *The thickness of the membrane,*
- *The surface area of the membrane,*
- *The diffusion coefficient of the gas in the substance of the membrane,*
- *The partial pressure difference of the gas between the two sides of the membrane.*
- *Molecular weight of the gas*

DIFFUSION COEFFICIENT AND DIFFUSION CAPACITY

- Diffusion coefficient is the measure of a substance diffusing through the concentration gradient.
- known as **diffusion constant.**
- It is related to size and shape of the molecules of the substance.
- D of Co_2 is 20 times O_2

- Diffusion capacity is the volume of a gas that diffuses through the membrane per minute for a partial pressure difference of 1 mm Hg.
- DC of O_2 is 21 ml/min/mm Hg.
- Mean PO_2 difference= 11mmhg
- Diffusion rate of O_2 is 230ml per min.

Role of the partial pressure of gases

- Partial pressure: is the individual pressure exerted independently by a particular gas within a mixture of gasses.
- The air we breath is a mixture of gasses: primarily nitrogen, oxygen, & carbon dioxide.
- The air blown into a balloon creates pressure that causes the balloon to expand (& this pressure is generated as all the molecules of nitrogen, oxygen, & carbon dioxide move about & collide with the walls of the balloon).
- The total pressure generated by the air is due in part to nitrogen, in part to oxygen, & in part to carbon dioxide. That part of the total pressure generated by oxygen is the 'partial pressure' of oxygen, while that generated by carbon dioxide is the 'partial pressure' of carbon dioxide. A gas's partial pressure, therefore, is a measure of how much of that gas is present (e.g., in the blood or alveoli).
- The partial pressure exerted by each gas in a mixture equals the total pressure times the fractional composition of the gas in the mixture. So, given that total atmospheric pressure (at sea level) is about 760 mm Hg and, further, that dry air is about 21% oxygen, then the partial pressure of oxygen in the dry air is 0.21 times 760 mm Hg or 160 mm Hg.

Partial Pressure: (contd)

- $P_{ATM} = P_{N_2} + P_{0_2} + P_{C0_2} + P_{H_20} = 760$ mm Hg.
  - 0_2 is humidified in alveoli to 105 mm Hg.
    - H_20 contributes to partial pressure (47 mm Hg).
      - P_{0_2} (sea level) = 150 mm Hg.
  - $P_{C0_2} = 40$ mm Hg.

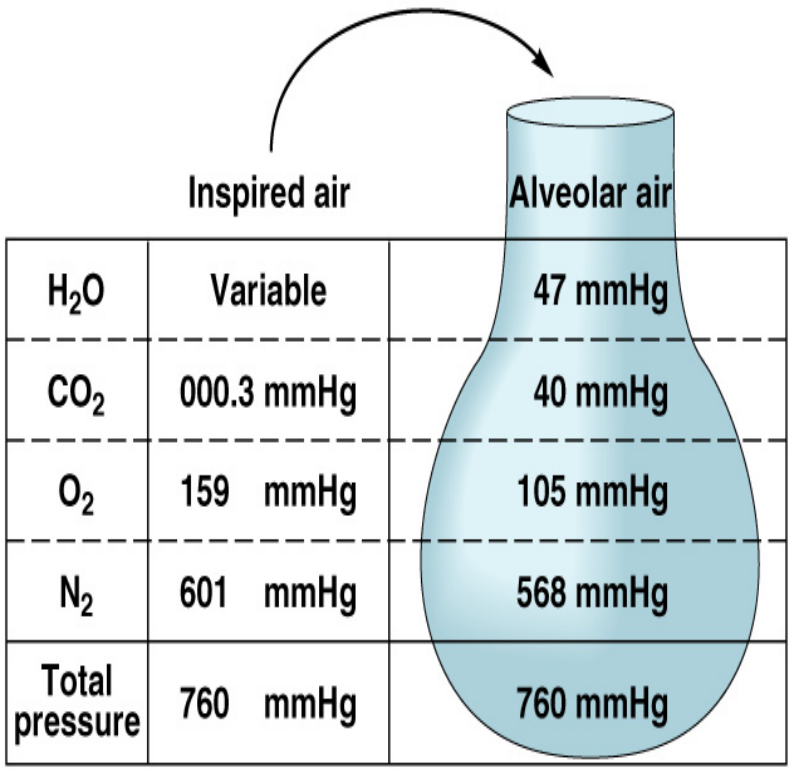


Figure 8

Diffusion of Oxygen and Carbon IV Oxide

This occurs in phases

Diffusion of Oxygen:

- From Atmosphere into alveoli
- From Alveoli into Blood
- From Blood into Tissue

Diffusion of Carbon IV Oxide

- From Tissue Into Blood
- From Blood into Alveoli
- From alveoli into the Atmosphere

This is explained below:

At any given step, there is a Pressure gradient that permits the flow of the gas(s) froma region of higher partial presure to lower partial presure.

In the atmosphere

- PO_2 = 160 mm Hg
- PCO_2 = 0.30 mm Hg

In the Alveoli

- PO_2 = 100 mm Hg
- PCO_2 = 40 mm Hg

In the Alveolar capillaries

- PO_2 = 40 mm Hg (relatively low because this blood has just returned from the systemic circulation & has lost much of its oxygen)
- PCO_2 = 45 mm Hg to 46 mm Hg (relatively high because the blood returning from the systemic circulation has picked up carbon dioxide)

- While in the alveolar capillaries, the diffusion of gasses occurs: oxygen diffuses from the alveoli into the blood & carbon dioxide from the blood into the alveoli.

Leaving the alveolar capillaries

- PO_2 = 100 mm Hg
- PCO_2 = 40 mm Hg

Blood leaving the alveolar capillaries returns to the left atrium & is pumped by the left ventricle into the systemic circulation.

This blood travels through arteries & arterioles and into the systemic, or body, capillaries. As blood travels through arteries & arterioles, no gas exchange occurs.

Entering the systemic capillaries

- PO_2 = 100 mm Hg
- PCO_2 = 40 mm Hg

Body cells (resting conditions)

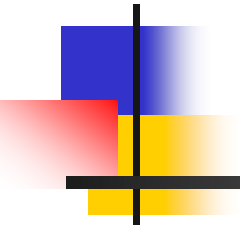
- PO_2 = 40 mm Hg
- PCO_2 = 45 mm Hg

Because of the differences in partial pressures of oxygen & carbon dioxide in the systemic capillaries & the body cells, oxygen diffuses from the blood & into the cells, while carbon dioxide diffuses from the cells into the blood.

Leaving the systemic capillaries

- PO_2 = 40 mm Hg
- PCO2 = 45 mm Hg

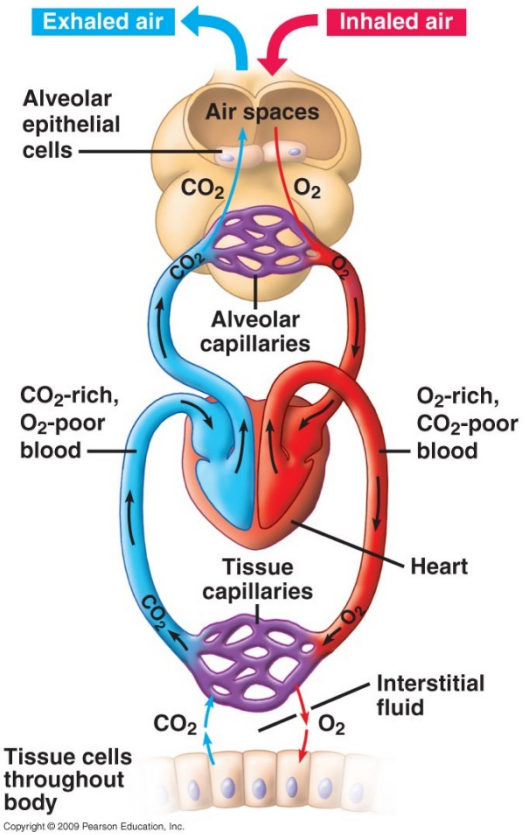
Blood leaving the systemic capillaries returns to the heart (right atrium) via venules & veins (and no gas exchange occurs while blood is in venules & veins). This blood is then pumped to the lungs (and the alveolar capillaries) by the right ventricle.



TRANSPORT OF RESPIRATORY GASES

Respiratory Gas Transport

- Blue colored side is O_2 poor
  - Blood from capillaries to heart which transports to alveoli for exchange
- Red side is O_2 rich
  - Blood from alveoli return to heart which transports to tissues
- Gas exchange via diffusion across a pressure gradient
  - Air is a mix of gases with pressure
  - Each type of gas contributes a **partial pressure**
    - Each gas type moves down individual gradients



TRANSPORT OF OXYGEN IN THE ARTERIAL BLOOD

Shunt flow

- About 98 percent of the blood that enters the left atrium from the lungs has just passed through the alveolar capillaries and has become oxygenated up to a PO_2 of about 104 mm Hg.
- Another 2 percent of the blood has passed from the aorta through the bronchial circulation, which supplies mainly the deep tissues of the lungs and is not exposed to lung air.
- This blood flow is called “shunt flow,” meaning that blood is shunted past the gas exchange areas.
- Upon leaving the lungs, the PO_2 of the shunt blood is approximately that of normal systemic venous blood—about 40 mm Hg.

Venous Admixture

- When this blood combines in the pulmonary veins with the oxygenated blood from the alveolar capillaries, (*venous admixture) of blood* causes the PO_2 of the blood entering the left heart and pumped into the aorta to fall to about 95 mm Hg.

TRANSPORT OF OXYGEN

- **Oxygen Delivery (DO_2):-**The volume of O_2 delivered to the systemic vascular bed per minute
- It is the product of cardiac output and arterial concentration of O_2
- Factors that influence O_2 delivered it are:
  - Amount of O_2 entering the lungs
  - Adequacy of pulmonary gas exchange
  - Blood flow to the tissue which depends on CO and degree of vascular constriction
  - Oxygen carrying capacity of blood which depends on affinity of Hb to O_2 , dissolved in plasma and combined with Hb
- Oxygen is transported in two forms:
  - 3% is dissolved in plasma
  - 97% combined with Hemoglobin

Transport of Oxygen dissolved in plasma

- Oxygen dissolves in water of plasma and is transported in this **physical form.**
- About 0.3 mL/100 mL of plasma.
- It forms only about 3% of total oxygen in blood.
- The value is low because of poor solubility of oxygen in water content of plasma.
- However saturation of plasma with Oxygen exposes the RBCs to high Oxygen tension
- Transport of oxygen in this form becomes important during the conditions like muscular exercise to meet the excess demand of oxygen by the tissues.

Transport of Oxygen combined with Hemoglobin

- Under normal conditions, oxygen is carried to the tissues almost entirely by hemoglobin.
- When PO_2 is high, as in the pulmonary capillaries, O_2 binds with the hemoglobin, but when PO_2 is low, as in the tissue capillaries, O_2 is released from the hemoglobin.
- This is the basis for almost all O_2 transport from the lungs to the tissues.
- The combination here is oxygenation and not oxidation

Combination of O_2 with Hemoglobin

- The dynamics of the reaction of hemoglobin with O_2 make it a particularly suitable O_2 carrier.
- Hemoglobin is a protein made up of four subunits, each of which contains a **heme** moiety attached to a polypeptide chain of globin
- In normal adults, most of the hemoglobin molecules contain 2α and 2β.
- Heme is a complex made up of a porphyrin and one atom of ferrous iron.
- Each of the four iron atoms can bind reversibly one O_2 molecule.
- The iron stays in the ferrous state, so that the reaction is an **oxygenation,** as $Hb + O_2 \rightleftarrows HbO_2$.
- Since it contains four Hb units, the hemoglobin molecule can also be represented as Hb_4, and it actually reacts with four molecules of O_2 to form Hb_4O_8. this is self cathalytic reaction
- This is why Oxegen-Hb dissociation curve is step rise
- The reaction is rapid, requiring less than 0.01 s.
- The formation of Hb_4O_2 is slow but the Hb_4O_2 catalyzes the formation of the next till Hb_4O_8 is formed
- The deoxygenation (reduction) of Hb_4O_8 in the tissue is also very rapid

Oxygen Carrying Capacity Of Hemoglobin

- The amount of oxygen transported by 1 gram of hemoglobin.
- It is about 1.34 mL/g.

Oxygen carrying capacity of blood

- The amount of oxygen transported by blood.
- Normal hemoglobin content in blood is 15 g%.
- Since oxygen carrying capacity of hemoglobin is 1.34 mL/g, blood with 15 g% of hemoglobin should carry 20.1 mL% of oxygen (i.e. 20.1 mL of oxygen in 100 mL of blood).
- But, blood with 15 g% of hemoglobin carries only 19 mL% of oxygen
- The amount of dissolved O_2 is a linear function of the PO_2 (0.003 mL/dL blood/mm Hg PO_2). That is 0.30 mL in solution
- Oxygen carrying capacity of blood is only 19 mL% because the hemoglobin is not fully saturated with oxygen.
- It is saturated only for about 95%.

Oxyhemoglobin Dissociation Curve

- Graphic illustration of the % oxyhemoglobin saturation at different values of $P0_2$.
  - Loading and unloading of 0_2.
    - Steep portion of the sigmoidal curve, small changes in $P0_2$ produce large differences in % saturation (unload more 0_2).
- Decreased pH, increased temperature, and increased 2,3 DPG:
  - Affinity of hemoglobin for 0_2 decreases.
    - Greater unloading of 0_2:
      - Shift to the curve to the right.

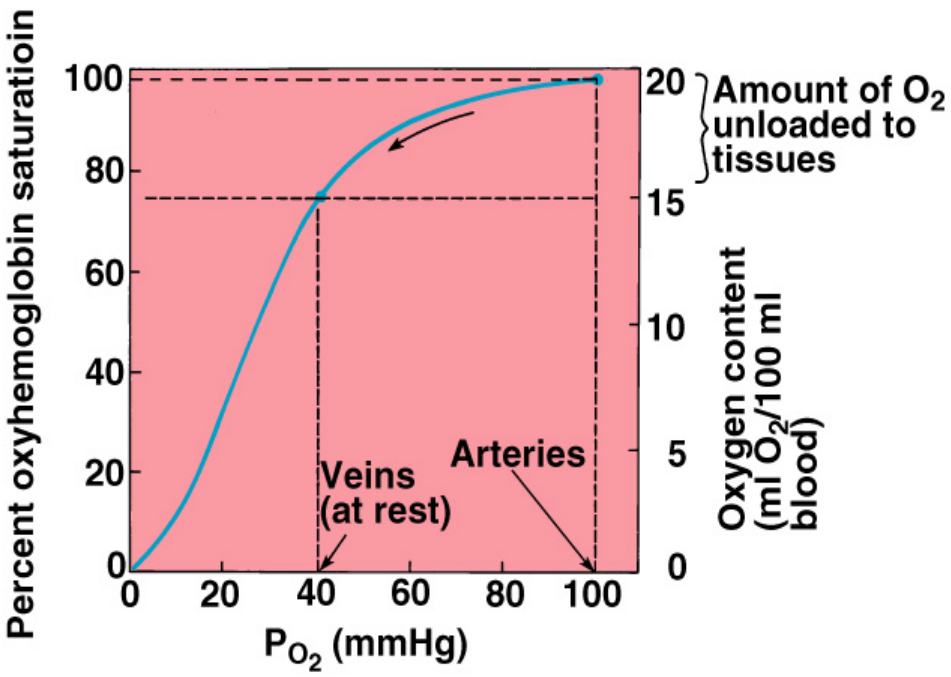


Figure 16.34

Effects of pH and Temperature

- Affinity is decreased when pH is decreased.
- Increased temperature and 2,3-DPG:
  - Shift the curve to the right.

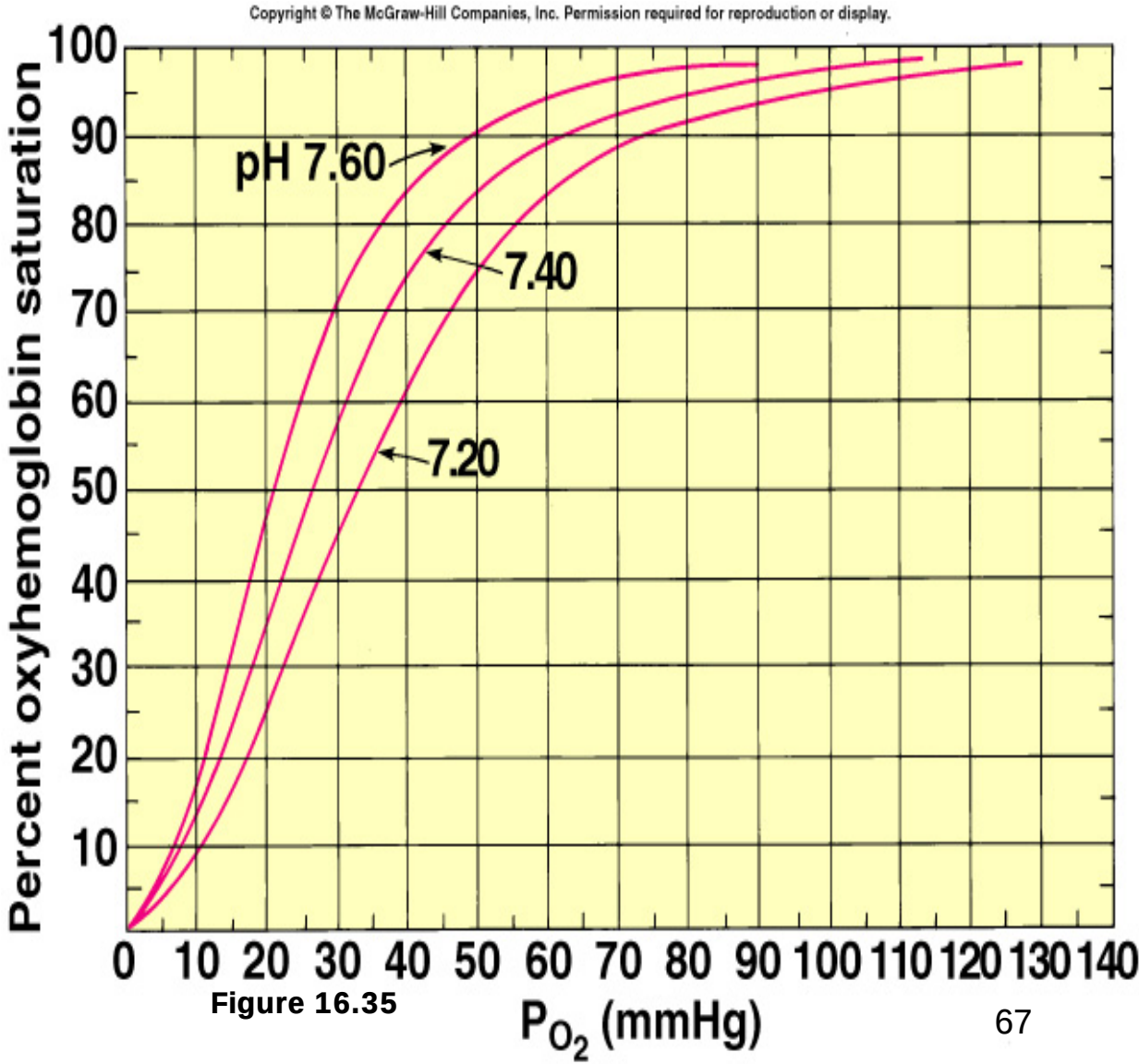
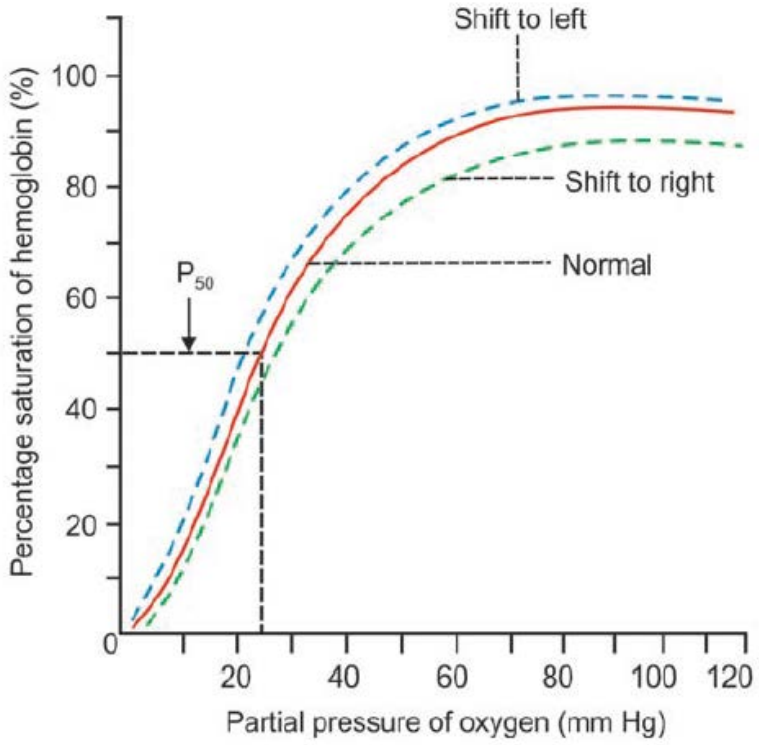


Figure 16.35

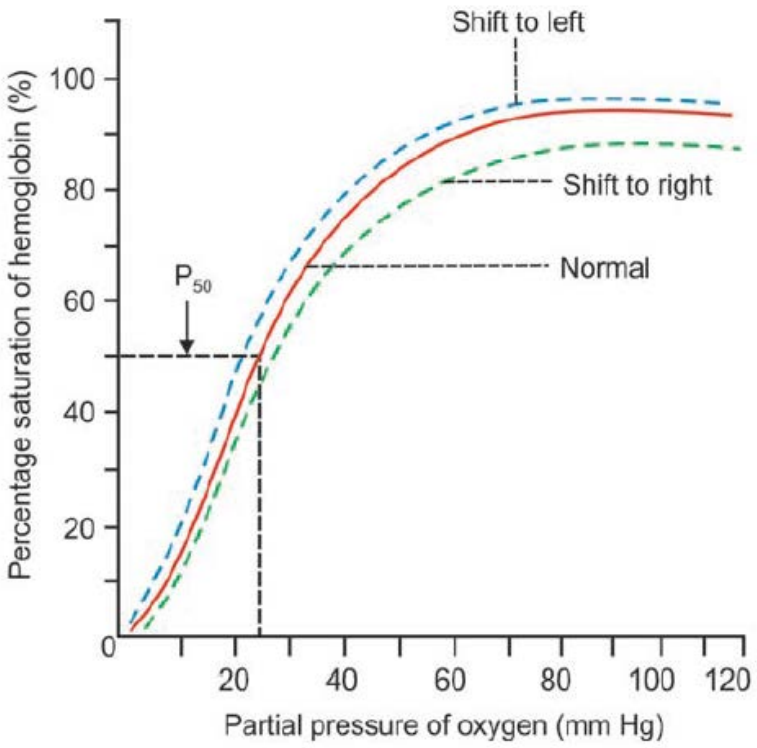
THE OXYGEN-HEMOGLOBIN DISSOCIATION CURVE

- A curve that demonstrates the relationship between PO_2 and percentage saturation of Hb with Oxygen.
- It is sigmoid in shape
- The oxygen-hemoglobin dissociation curve 'shifts' under certain conditions.



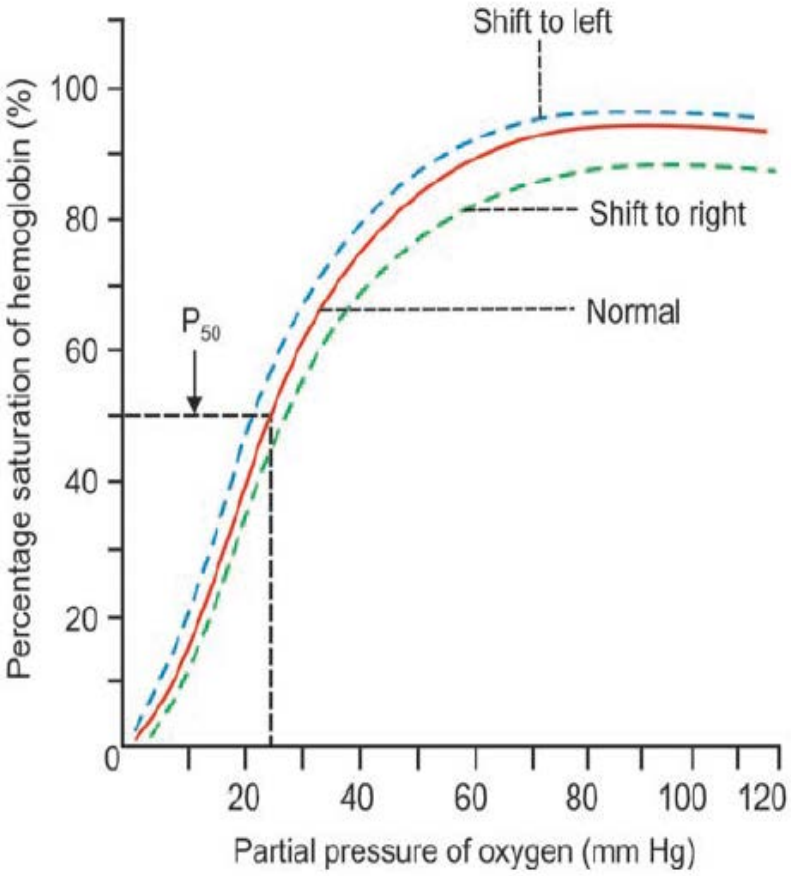
Factors that shift the curve to the Right

- Increased in bod temperature
- Increase in PCO_2
- Reduction in pH
- Increase in 2,3-diphosphoglycera e (DPG)



Factors that shift the curve to the Left

- Decrease in body temperature
- decrease in PCO_2
- Increase in pH
- Decrease in 2,3-diphosphoglycerate
- Presence of Foetal H



Transport of Carbon Dioxide

Carbon Dioxide is transported in four forms:

- Dissolved in plasma (7%)
- As carbonic acid (negligible)
- As bicarbonate (63%)
- As carbamino compounds (30%).

Fate of Carbon Dioxide in Blood

- The solubility of CO_2 in blood is about 20 times that of O_2; therefore considerably more CO_2 than O_2 is present in simple solution at equal partial pressures.
- The CO_2 that diffuses into red blood cells is rapidly hydrated to H_2CO_3 because of the presence of carbonic anhydrase.
- The H_2CO_3 dissociates to H^+ and HCO_3^-, and the H^+ is buffered, primarily by hemoglobin, while the HCO_3^- enters the plasma.
- Some of the CO_2 in the red cells reacts with the amino groups of hemoglobin and other proteins (R), forming **carbamino compounds**

Fate of Carbon Dioxide in Blood (contd)

- These factors change when tissues become more active. For example, when a skeletal muscle starts contracting, the cells in that muscle use more oxygen, make more ATP, & produce more waste products (CO_2). Making more ATP means releasing more heat; so the temperature in active tissues increases. More CO_2 translates into a lower pH. That is so because this reaction occurs when CO_2 is released:

$$CO_2 + H_20 \text{ -----> } H_2CO_3 \text{ -----> } HCO_3\text{-} + H+$$

- more hydrogen ions = a lower (more acidic) pH.
- So, in active tissues, there are higher levels of CO_2, a lower pH, and higher temperatures.

Fate of Carbon Dioxide in Blood (contd)

- At lower PO_2 levels, red blood cells increase production of a substance called 2,3-diphosphoglycerate.
- These changing conditions (more CO_2, lower pH, higher temperature, & more 2,3-diphosphoglycerate) in active tissues cause an alteration in the structure of hemoglobin, which, in turn, causes hemoglobin to give up its oxygen.
- In other words, in active tissues, more hemoglobin molecules give up their oxygen **(Bohr's effect).**

Fate of Carbon Dioxide in Blood (contd)

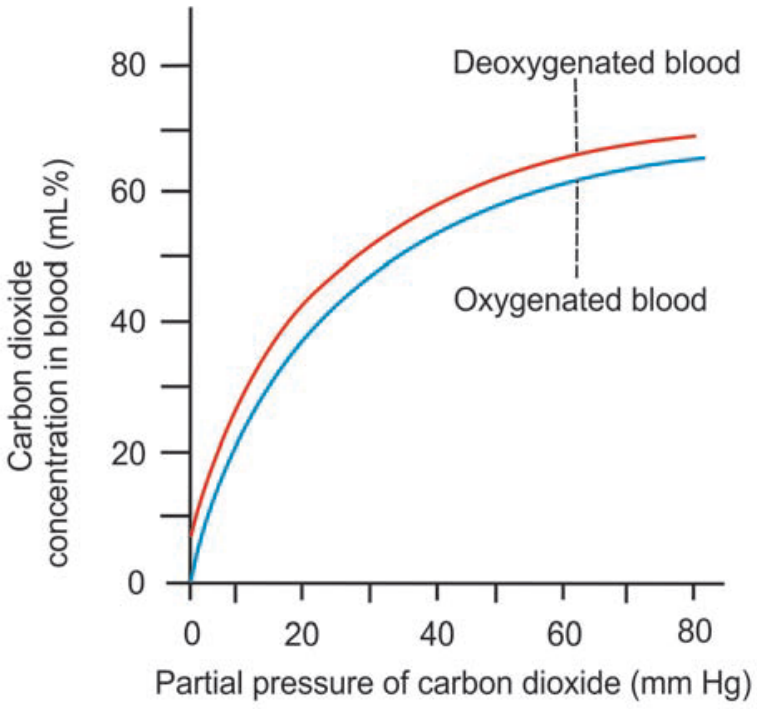
- Since deoxygenated hemoglobin binds more H^+ than oxyhemoglobin does and forms carbamino compounds more readily, binding of O_2 to hemoglobin reduces its affinity for CO_2 **(Haldane effect).**
- Consequently, venous blood carries more CO_2 than arterial blood, CO_2 uptake is facilitated in the tissues, and CO_2 release is facilitated in the lungs.
- About 11% of the CO_2 added to the blood in the systemic capillaries is carried to the lungs as carbamino-CO_2.
- In the plasma, CO_2 reacts with plasma proteins to form small amounts of carbamino compounds, and small amounts of CO_2 are hydrated; but the hydration reaction is slow in the absence of carbonic anhydrase.

Chloride Shift

- In plasma, plenty of sodium chloride which dissociates into sodium and chloride ions
- Since the rise in the HCO_3^- content of red cells is much greater than that in plasma as the blood passes through the capillaries, about 70% of the HCO_3^- formed in the red cells enters the plasma.
- When the negatively charged bicarbonate ions move out of RBC into the plasma, the negatively charged chloride ions move into the RBC in order to maintain the **electrolyte equilibrium**
- This process is mediated by **Band 3,** a major membrane protein.
- This exchange is called the **chloride shift.**
- Because of it, the Cl^- content of the red cells in venous blood is therefore significantly greater than in arterial blood.
- The chloride shift occurs rapidly and is essentially complete in 1 second.

CARBON DIOXIDE HEMOGLOBIN DISSOCIATION CURVE

- A curve that demonstrates the relationship between PCO_2 and percentage saturation of Hb with CC
- It is Parabolic in shape
- It is affected by:
  - Level of PO_2 (excess O_2 shift the curve to the Right)
  - Degree of de-oxygenation of Hb
  - Rate of tissue metabolism



Control of Respiration

Objectives

At the end of the module you should be able to:

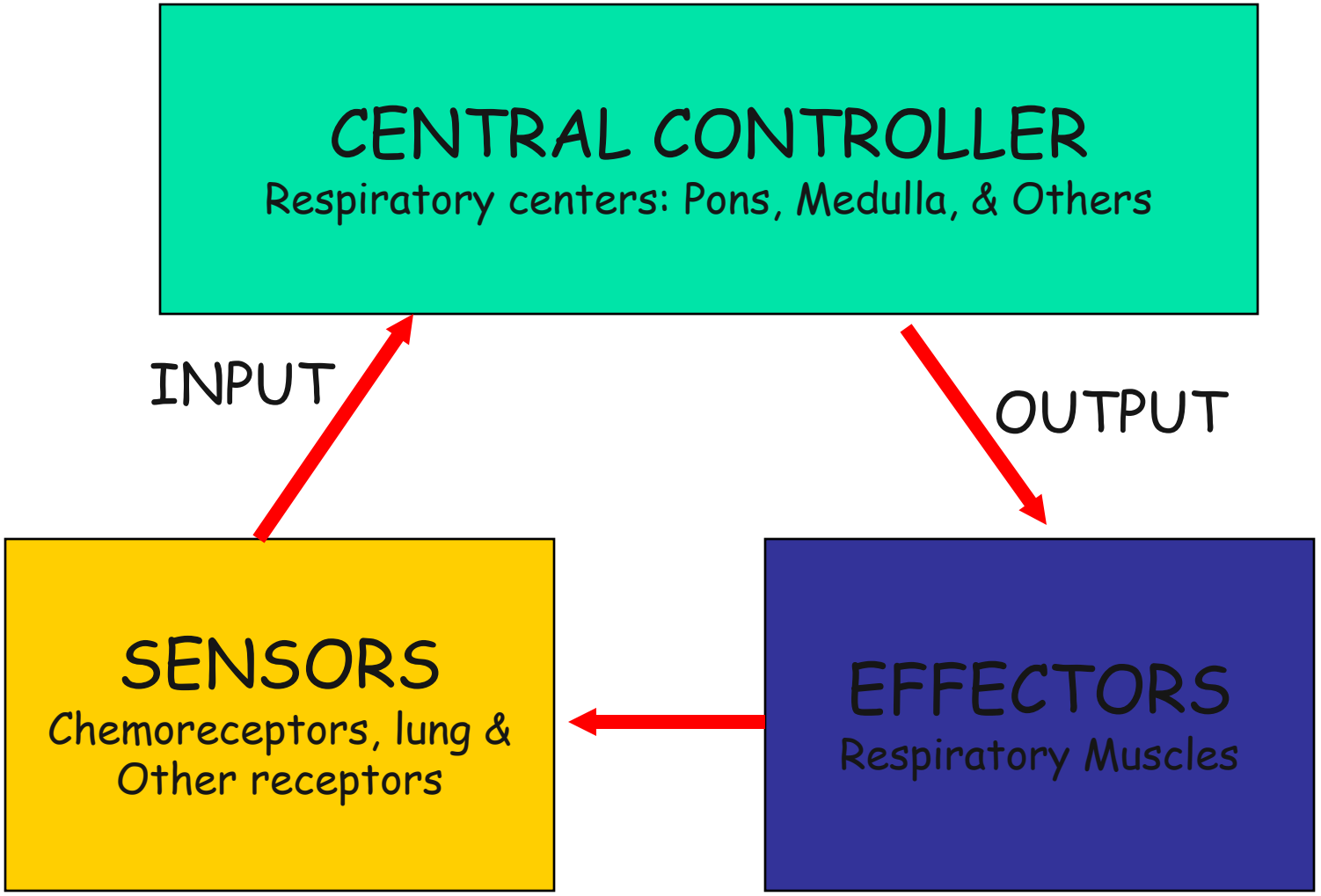
- Describe the function of the respiratory centers in the medulla oblongata.
- Describe the function of the apneustic center and pneumotaxic center in the pons.
- List 3 conditions that would depress the respiratory centers of the medulla oblongata.
- Describe the function of the central chemoreceptors.

Objectives

At the end of the module you should be able to:

- Describe the function of the peripheral chemoreceptors
- Describe the function of the Hering-Breuer reflex.
- Describe the function of the deflation reflex.
- Describe the function of the irritant reflex.
- Describe the function of the juxtapulmonary capillary receptors.
- Describe the function of the Paradoxical reflex of Head (to be taken as assignment) .

Control of Respiration



I. Respiratory Center and Formation of the Respiratory Rhythm

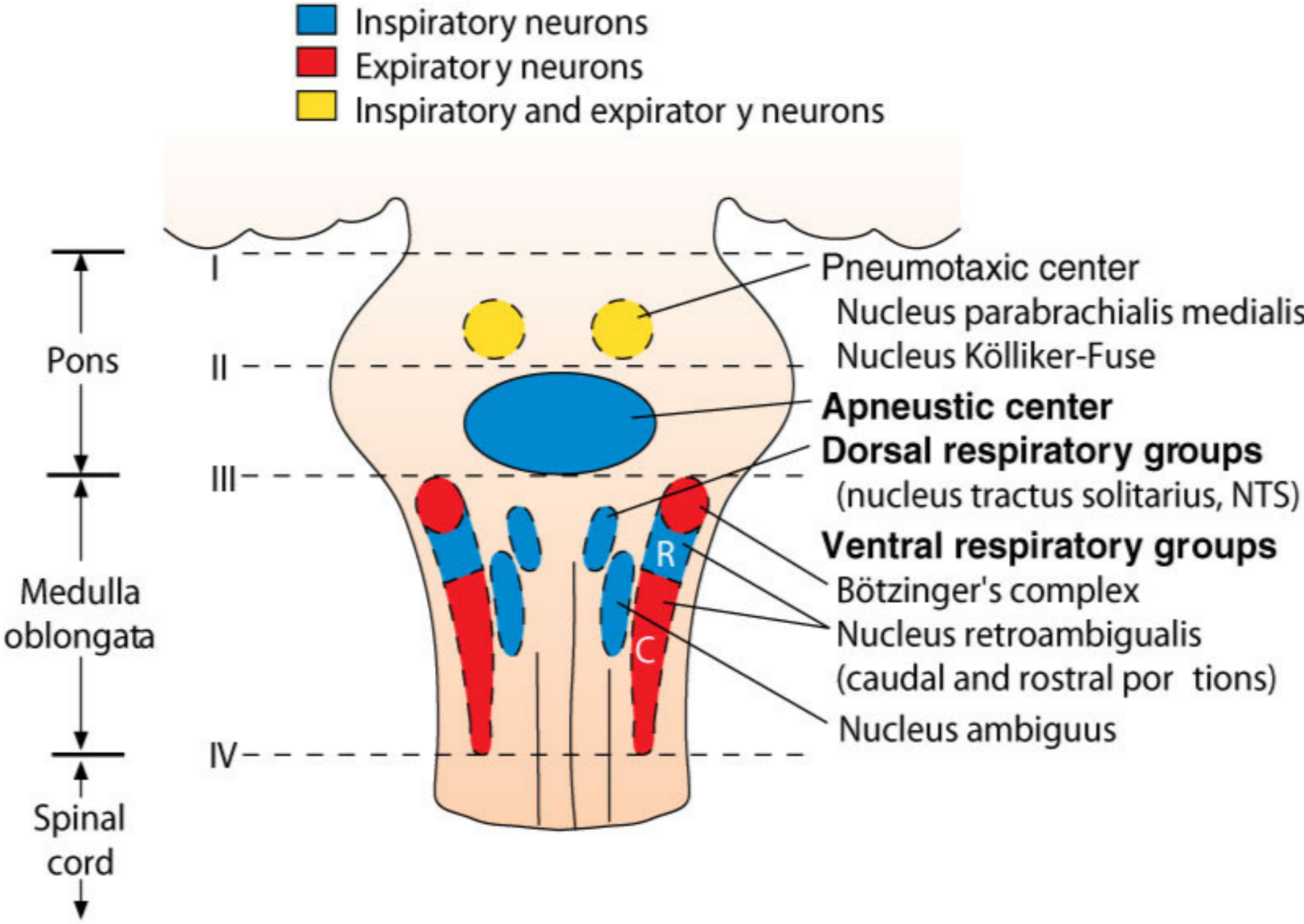
1 Respiratory Center

Medulla Oblongata

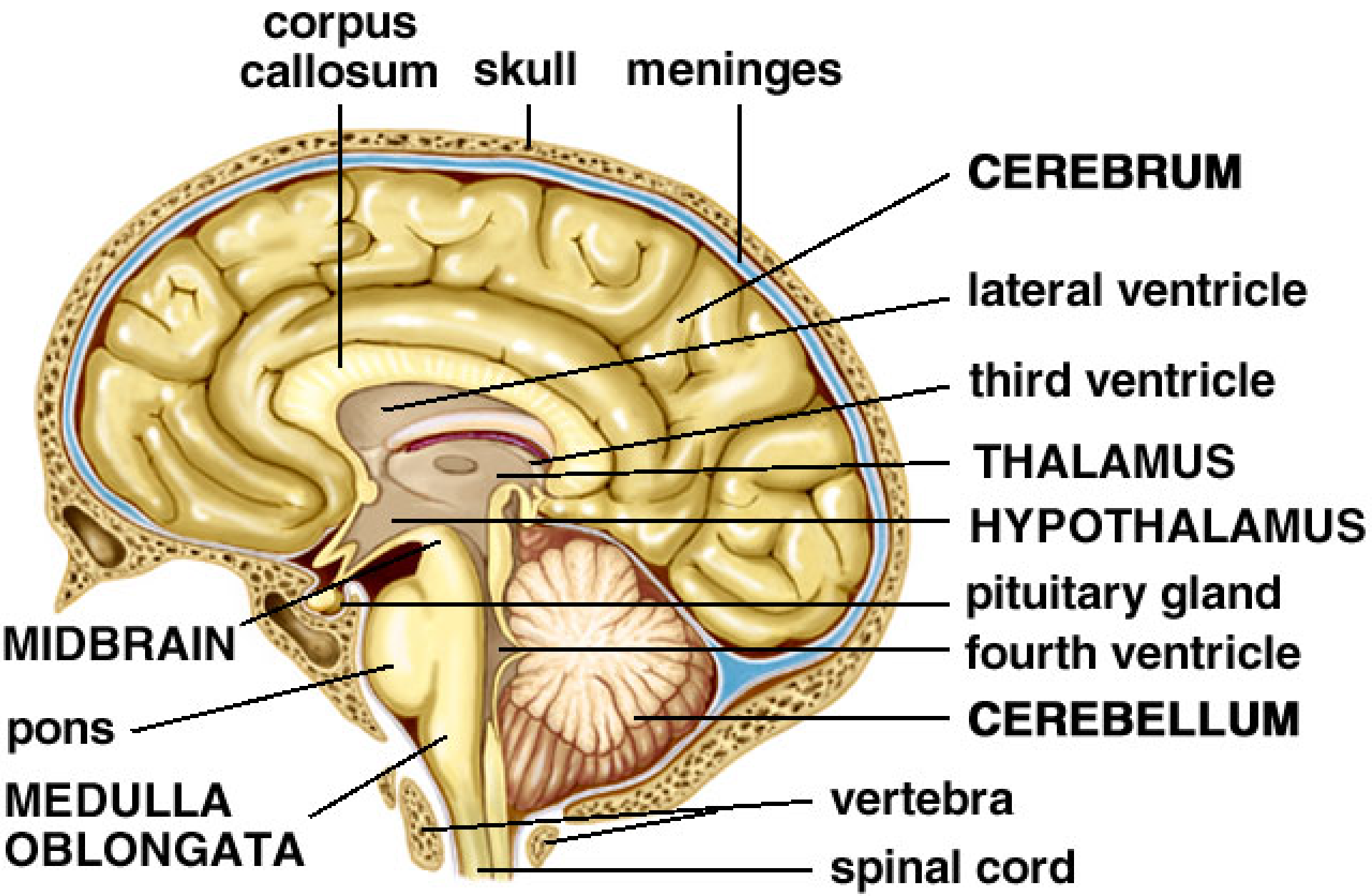
- The lower portion of the brainstem.
  - Inferior to the pons
  - Anterior to the cerebellum
- Associated with vital involuntary reflexes (sneezing, coughing) and regulation of cardiovascular and respiratory activity.
- Two dense bilateral groups of neurons
  - Dorsal Respiratory Groups
    - Mainly inspiratory cells that innervate inspiratory muscles
    - Also receives input from IX & X cranial nerves, peripheral receptors and impulses from the cerebral cortex.
  - Ventral Respiratory Groups
    - Both inspiratory & expiratory cells

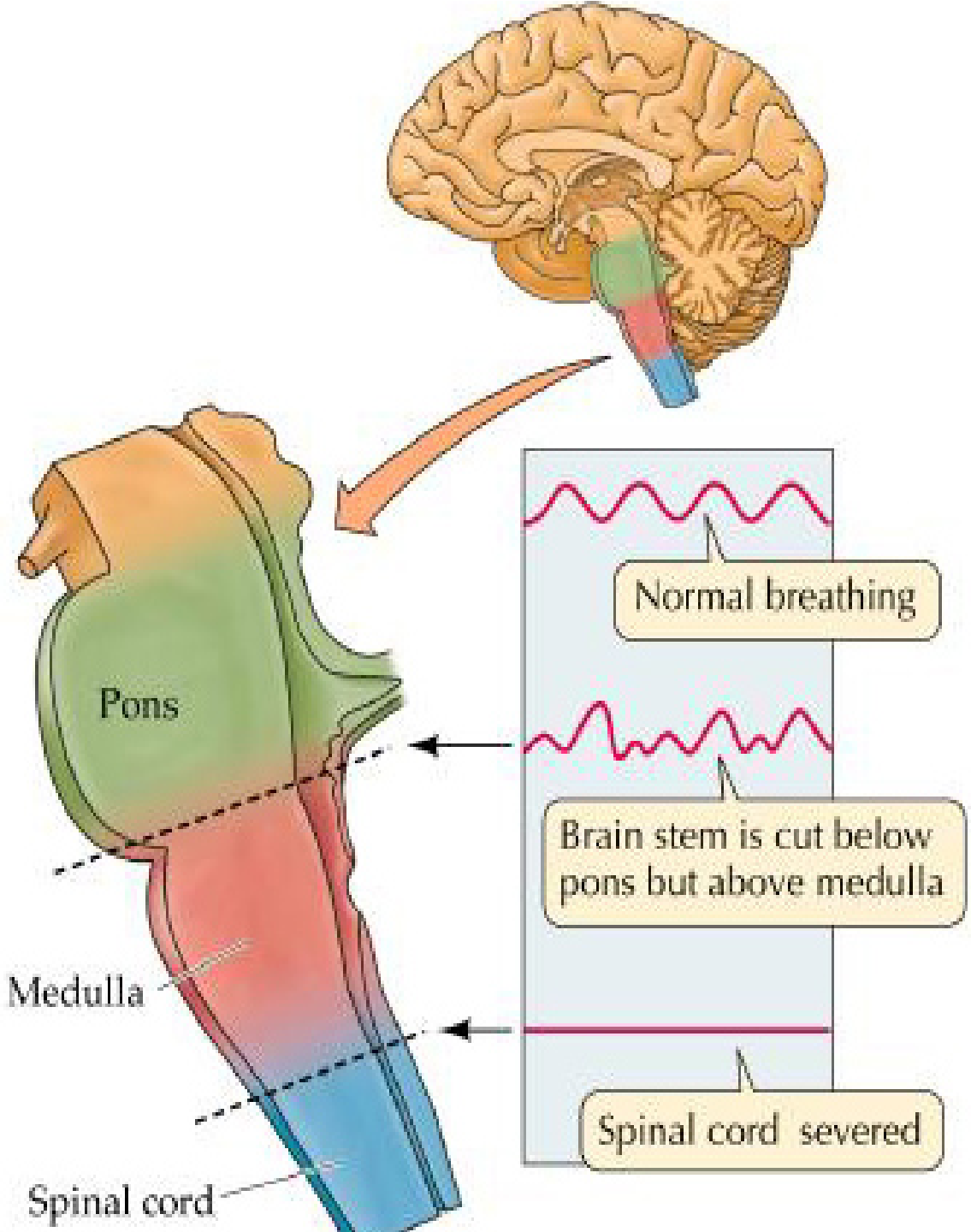
Pons

- Located superiorly to the medulla oblongata.
- Two respiratory centers
  - Apneustic Center (APC)
    - Directly above medulla
    - Inspiratory cut-off switch
    - Usually is inactivated by other impulses
  - Pneumotaxic Center (PNC)
    - Superior to APC
    - Controls Apneustic center and “fine-tunes” breathing by sending inhibitory impulses to medulla.


Inspiratory neurons
Expiratory neurons
Inspiratory and expiratory neurons
Pons
Medulla oblongata
Spinal cord
I
II
III
IV
R
C
Pneumotaxic center
Nucleus parabrachialis medialis
Nucleus Kölliker-Fuse
Apneustic center
Dorsal respiratory groups
(nucleus tractus solitarius, NTS)
Ventral respiratory groups
Bötzinger's complex
Nucleus retroambigualis
(caudal and rostral portions)
Nucleus ambiguus

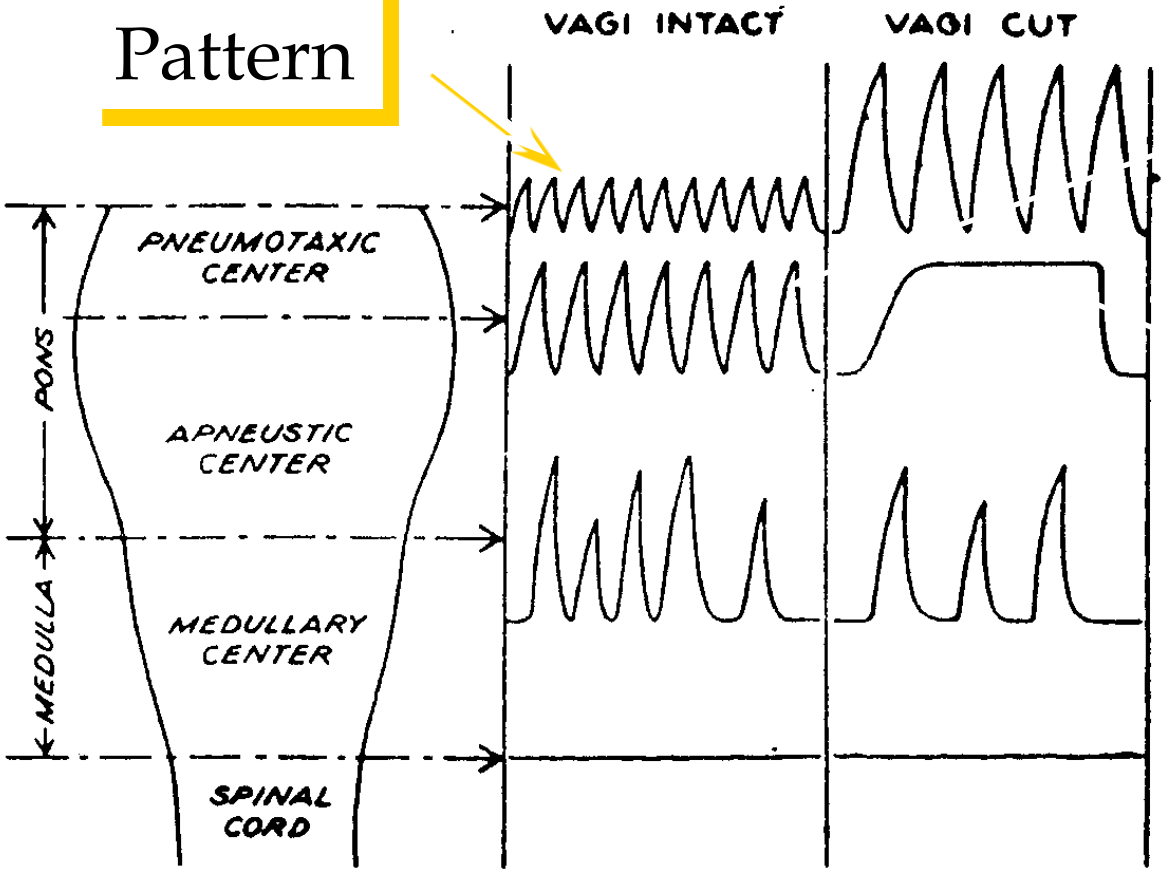
The Human Brain




Pons
Medulla
Spinal cord
Normal breathing
Brain stem is cut below pons but above medulla
Spinal cord severed

Brainstem Transection

Normal Pattern



Increased Inspiratory Depth

Apneustic Breathing

Gasping Patterns

Respiratory Arrest

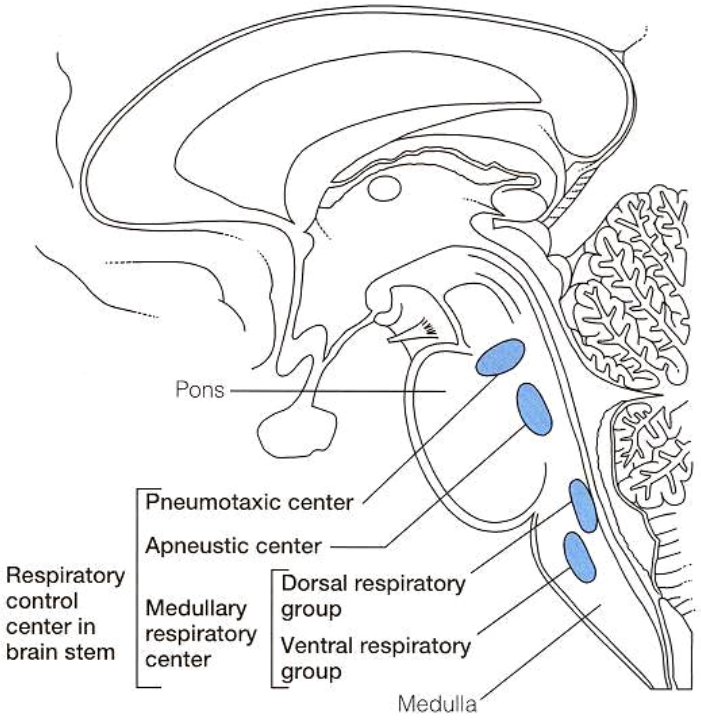
Two respiratory nuclei in medulla oblongata

Inspiratory center (dorsal respiratory group, DRG)

- more frequently they fire, more deeply you inhale
- longer duration they fire, breath is prolonged, slow rate

Expiratory center (ventral respiratory group, VRG)

- involved in *forced* expiration



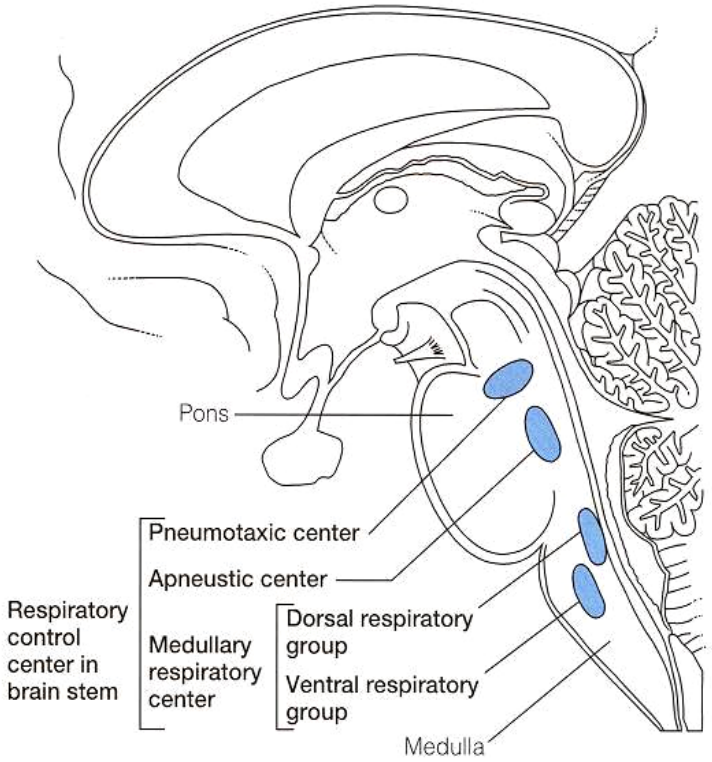
Respiratory Centers in Pons

Pneumotaxic center (upper pons)

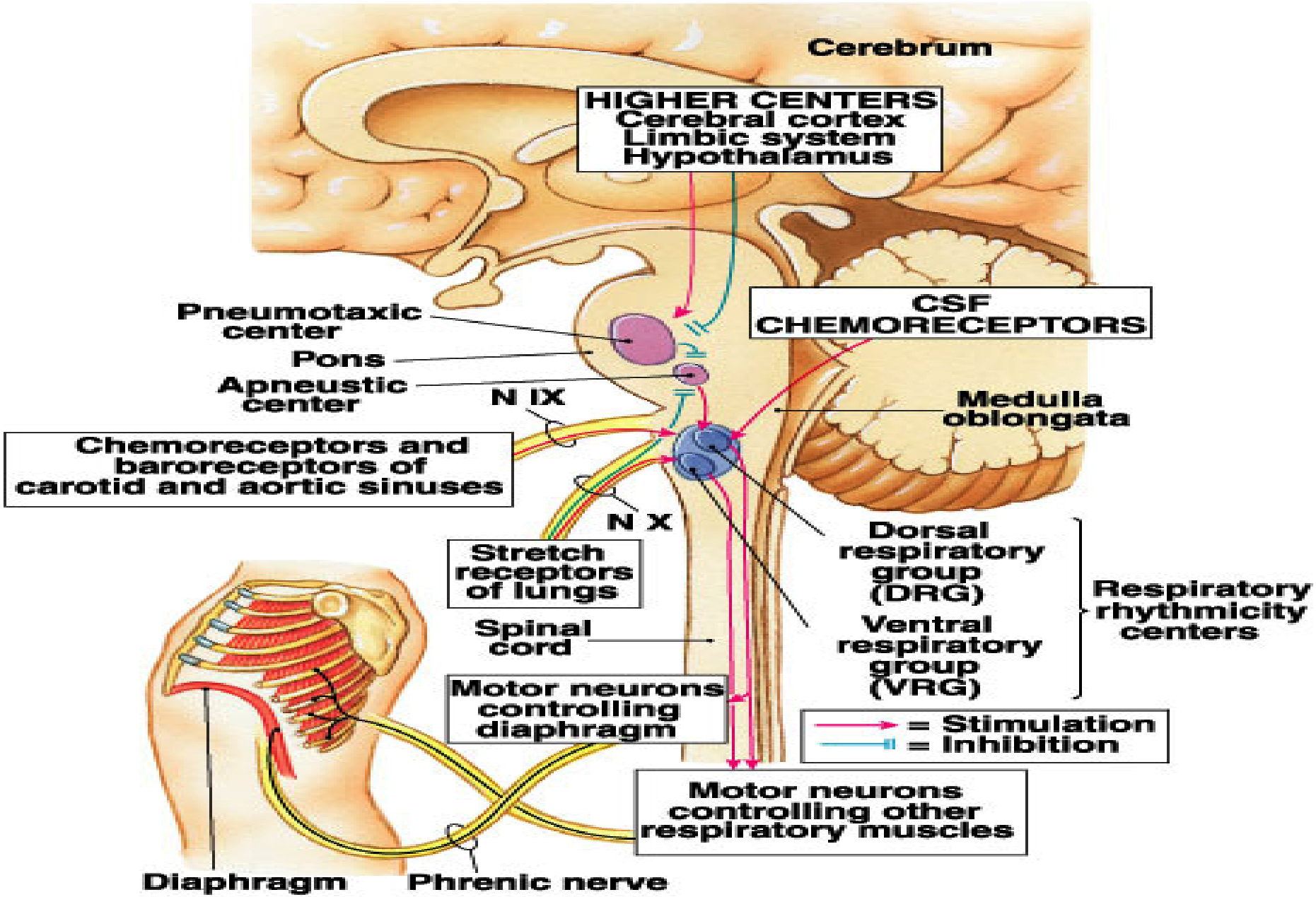
- Sends continual inhibitory impulses to inspiratory center of the medulla oblongata,
- As impulse frequency rises, breathe faster and shallower

Apneustic center (lower pons)

- Stimulation causes apneusis
- Integrates inspiratory cutoff information



Respiratory Structures in Brainstem



2. Rhythmic Ventilation (Inspiratory Off Switch)

- **Starting inspiration**
  - Medullary respiratory center neurons are continuously active (spontaneous)
  - Center receives stimulation from
    - Peripheral and central receptors
    - brain concerned with voluntary respiratory movements and emotion
  - Combined input from all sources causes action potentials to stimulate respiratory muscles

- **Increasing inspiration**
  - More and more neurons are activated
- **Stopping inspiration**
  - Neurons receive input from pontine group and stretch receptors in lungs.
  - Inhibitory neurons activated and relaxation of respiratory muscles results in expiration.
  - Inspiratory off switch.

3. Higher Respiratory Centers

Modulate the activity of the more primitive controlling centers in the medulla and pons.

Allow the rate and depth of respiration to be controlled voluntarily.

During speaking, laughing, crying, eating, defecating, coughing, and sneezing. ….

Adaptations to changes in environmental temperature --Panting

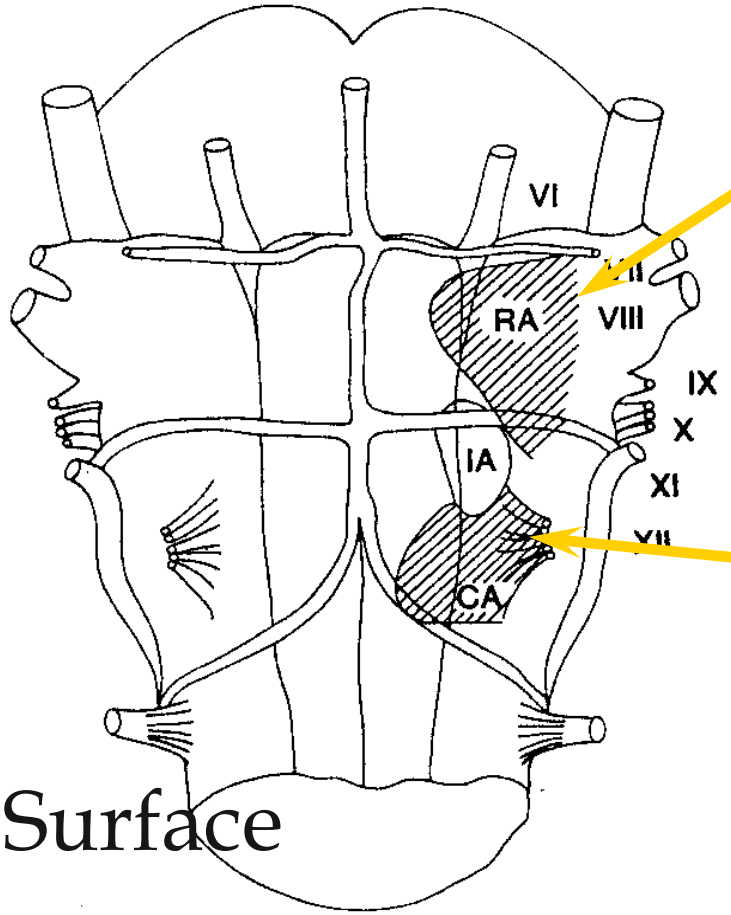
II Pulmonary Reflex

1.Chemoreceptor Reflex

Two Sets of Chemoreceptors Exist

- Central Chemoreceptors
  - Responsive to increased arterial PCO_2
  - Act by way of CSF $[H^+]\uparrow$.
- Peripheral Chemoreceptors
  - Responsive to decreased arterial PO_2
  - Responsive to increased arterial PCO_2
  - Responsive to increased H^+ ion concentration.

Central Chemoreceptor Location

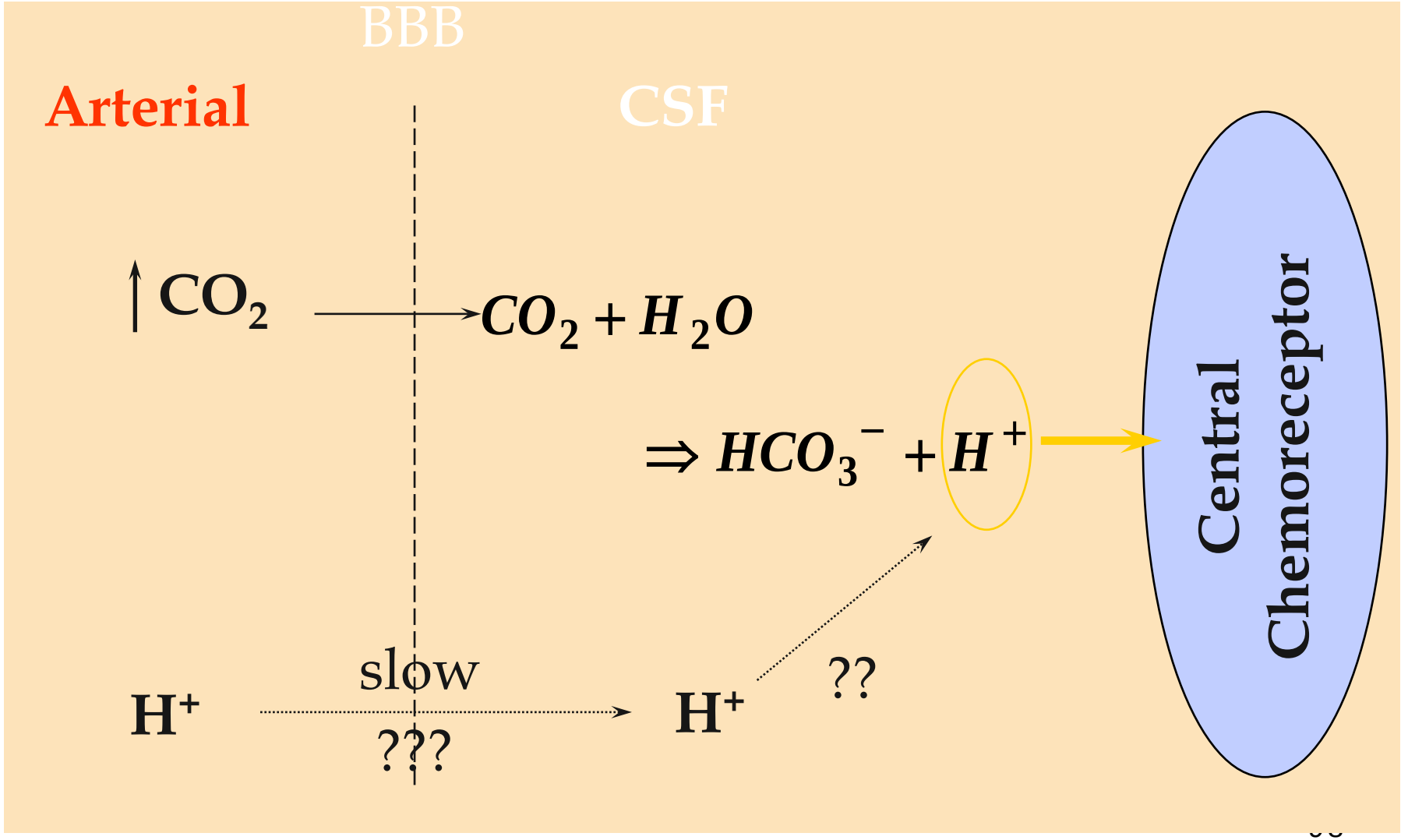


Rostral Medulla

Caudal Medulla

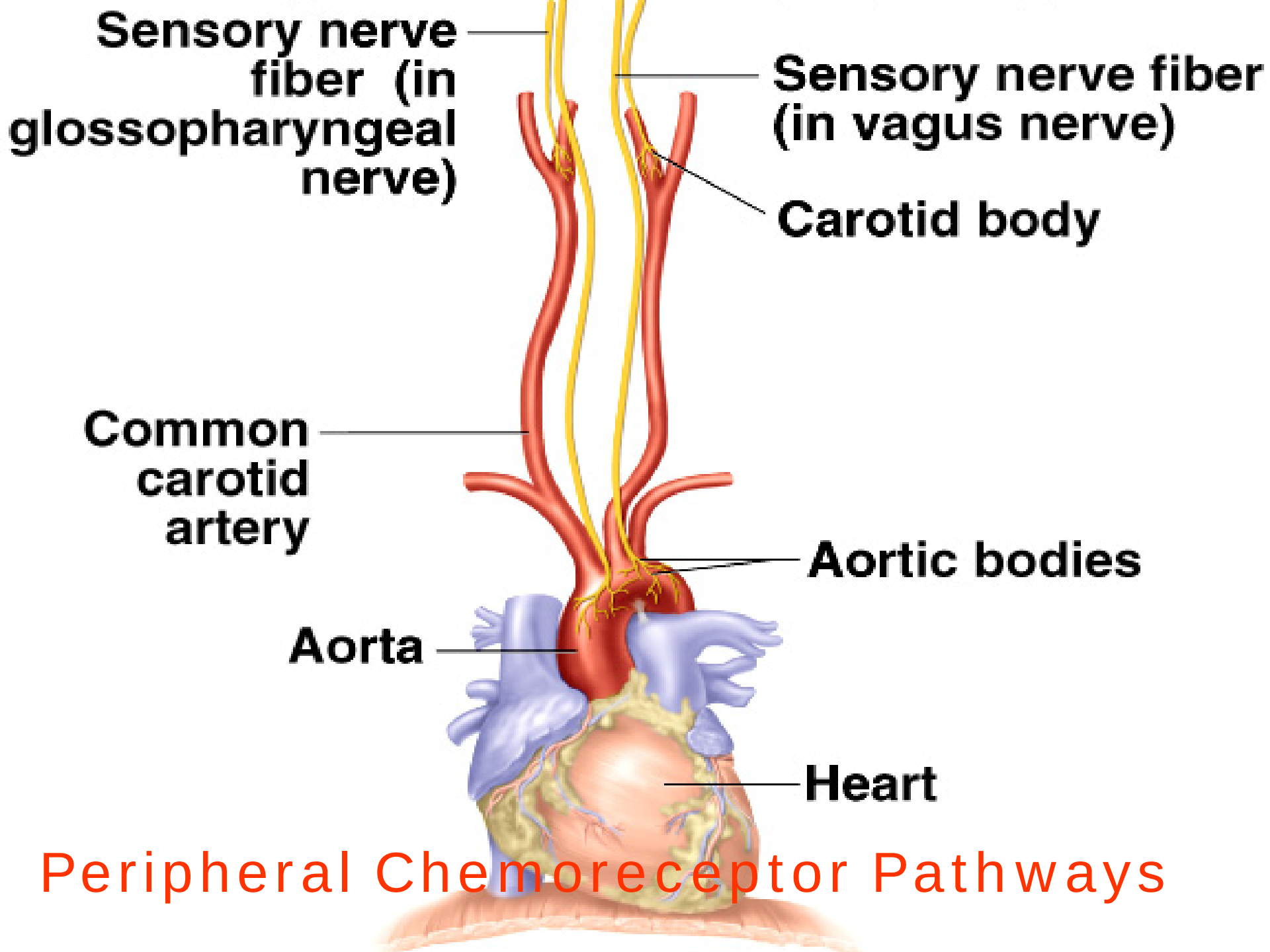
Ventral Surface

Central Chemoreceptor Stimulation

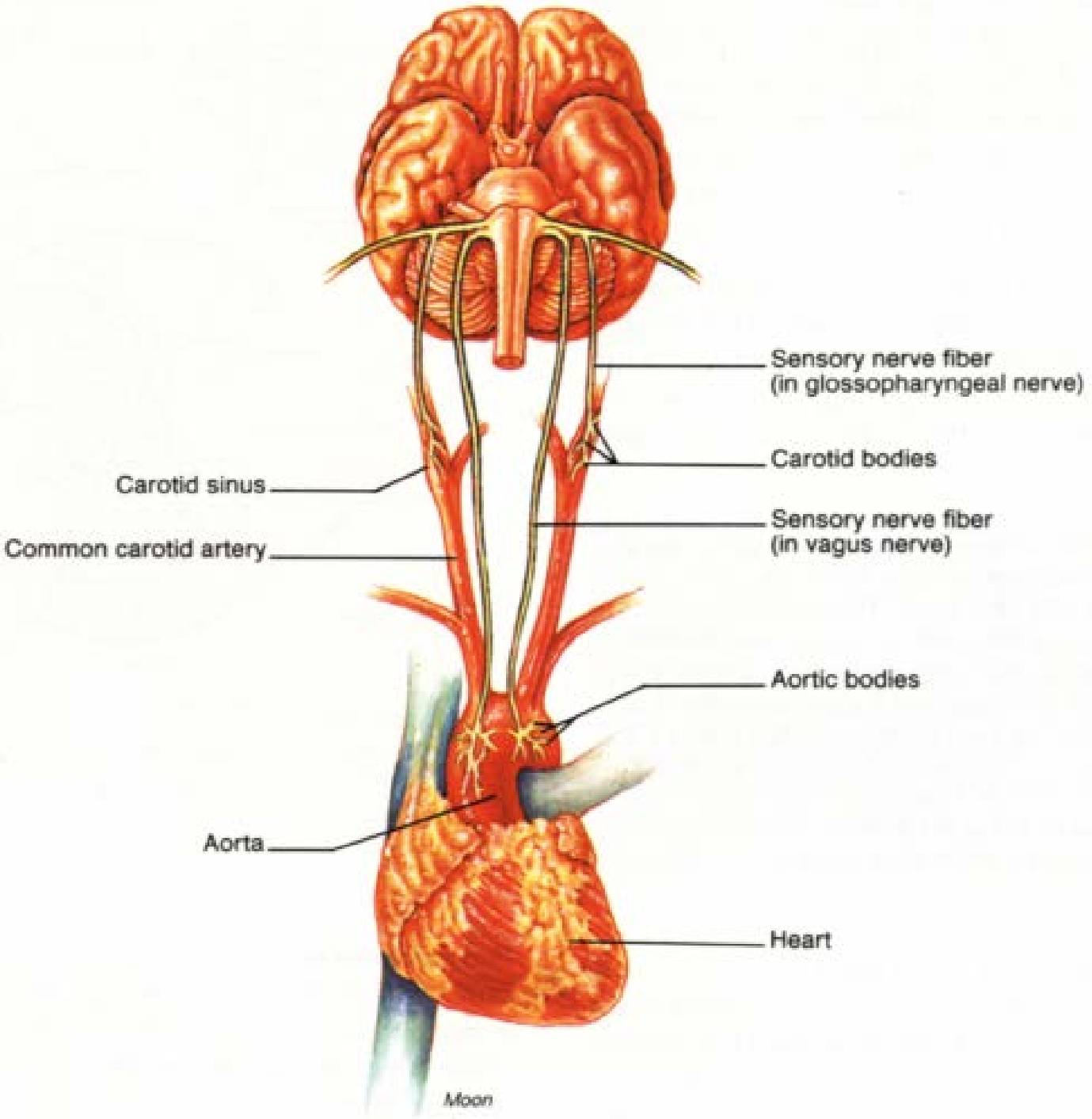


Peripheral Chemoreceptors

- Carotid bodies
  - Sensitive to: P_aO_2, P_aCO_2, and pH
  - Afferents in glossopharyngeal nerve.
- Aortic bodies
  - Sensitive to: P_aO_2, P_aCO_2, but <u>not</u> pH
  - Afferents in vagus



Peripheral Chemoreceptor Pathways


Sensory nerve fiber
(in glossopharyngeal nerve)
Carotid bodies
Carotid sinus
Sensory nerve fiber
(in vagus nerve)
Common carotid artery
Aortic bodies
Aorta
Heart
Moon

Carotid Body Function

- High flow per unit weight:

  (2 L/min/100 g)

- High carotid body VO_2 consumption:

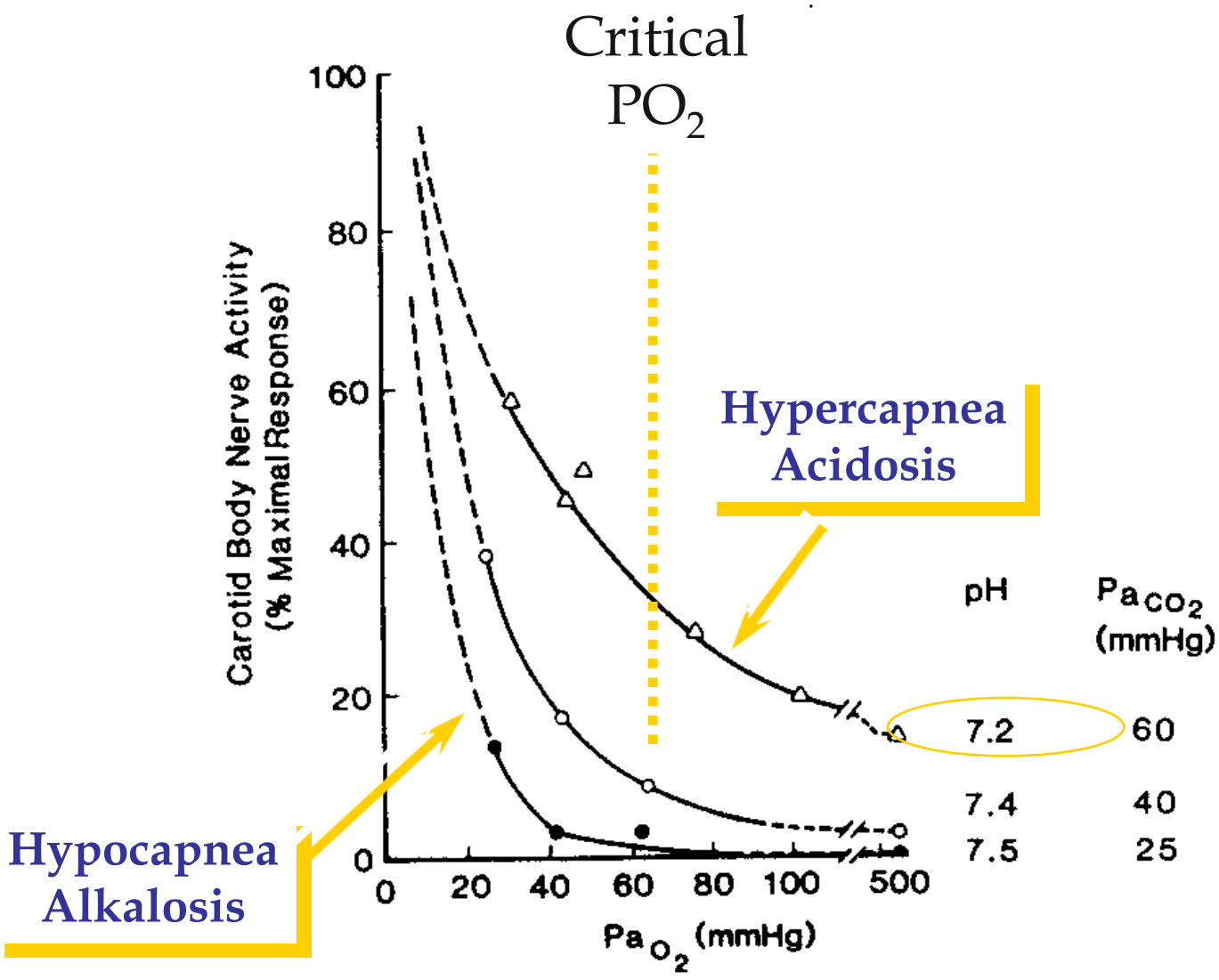
  (8 ml O_2/min/100g)

- Tiny a-v O_2 difference:

  Receptor cells “see” arterial PO_2.

- Responsiveness begins at P_aO_2 (not the oxygen content) <u>below about 60 mmHg.</u>

Carotid Body Response



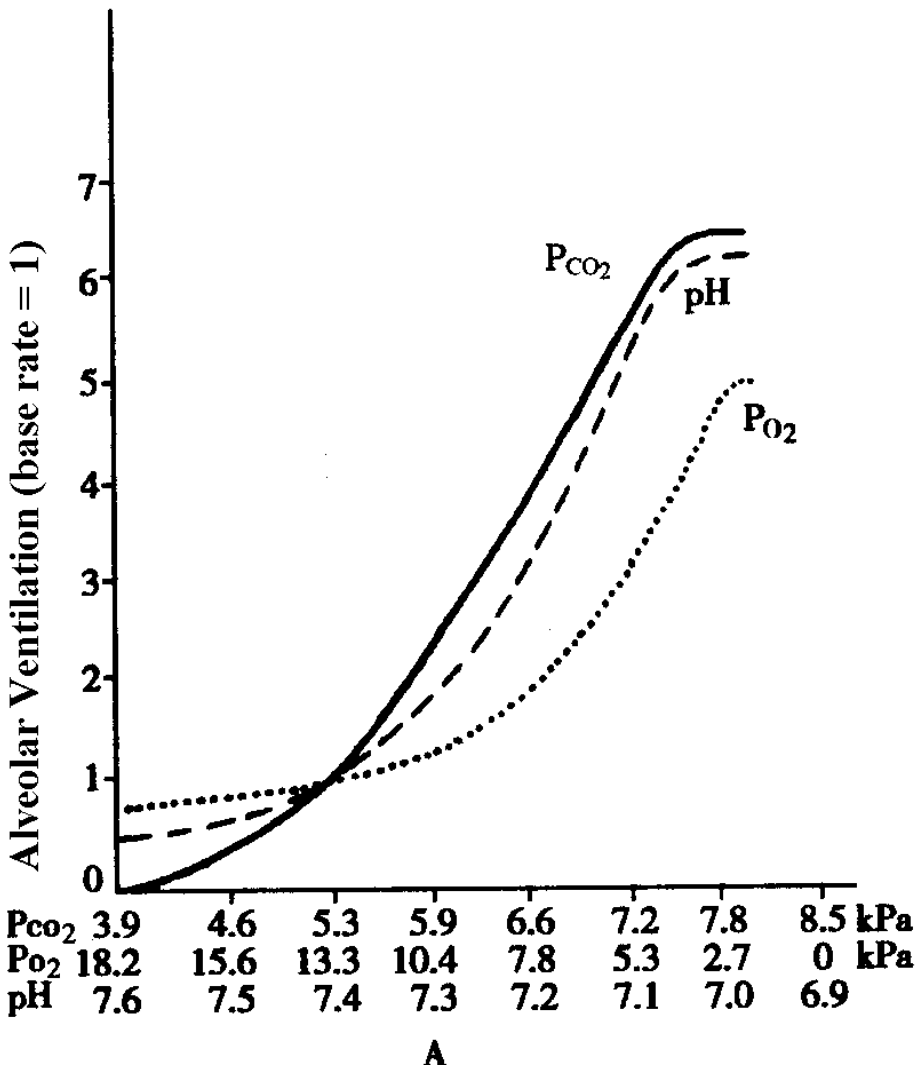
Carbon Dioxide

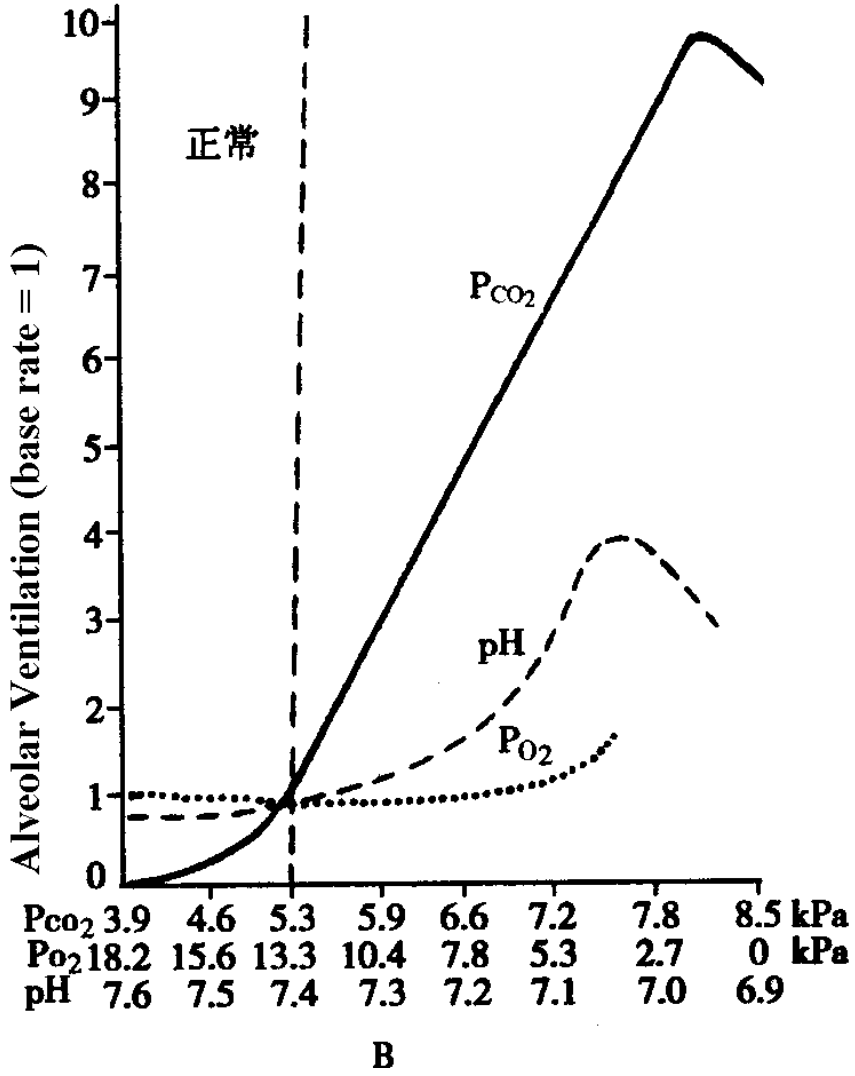
- Indirect effects
  - through H^+ in CNS
- Direct effects
  - ↑ CO_2 may directly stimulate peripheral chemoreceptors and trigger ↑ ventilation more quickly than central chemoreceptors
- Receptor adaption
- If the PCO_2 is too high, the respiratory center will be inhibited.

Oxygen

- Direct inhibitory effect of hypoxemia on the respiratory center
- Chronic hypoxemia, $PO_2 < 60$ mmHg, can significantly stimulate ventilation
  - Emphysema, pneumonia
  - high altitudes after several days
- Receptor: Slow Adaption
  - More important in chronic hypoxemia

Overall Response to Pco_2, Po_2 and pH





Change of One Factor Only, with control other factors

Change of one factor, without control of the other factors

Chemoreceptor Control of Breathing

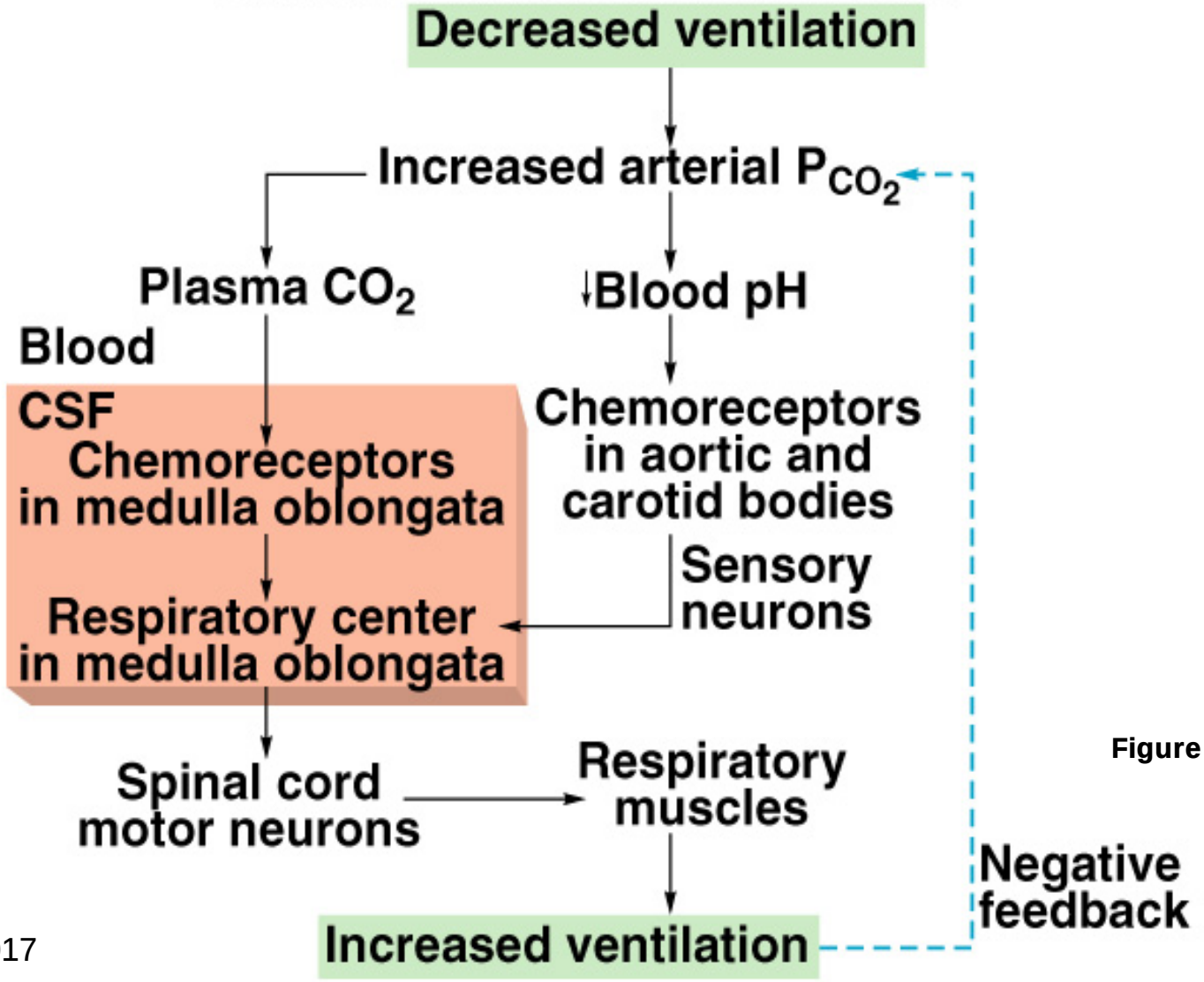
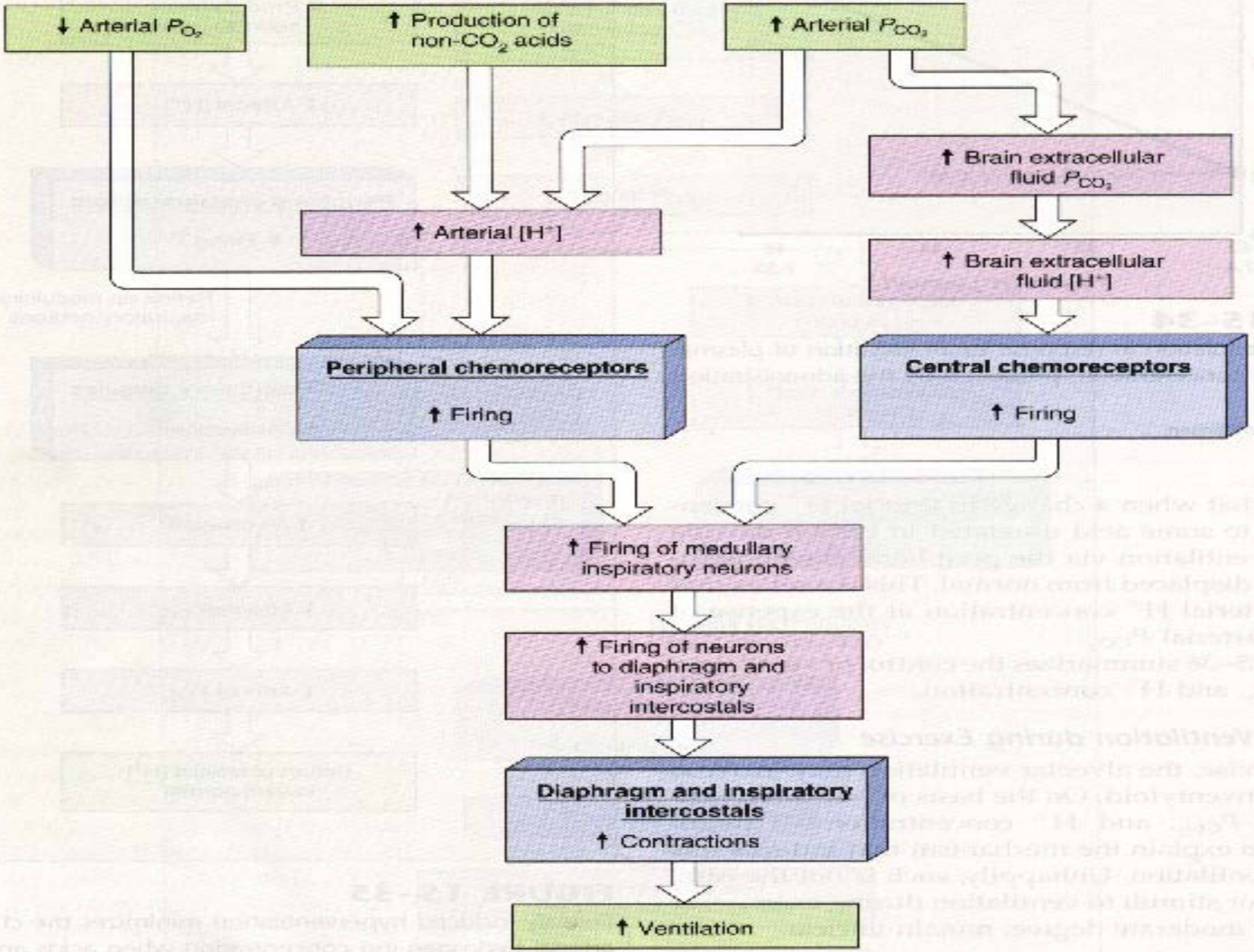


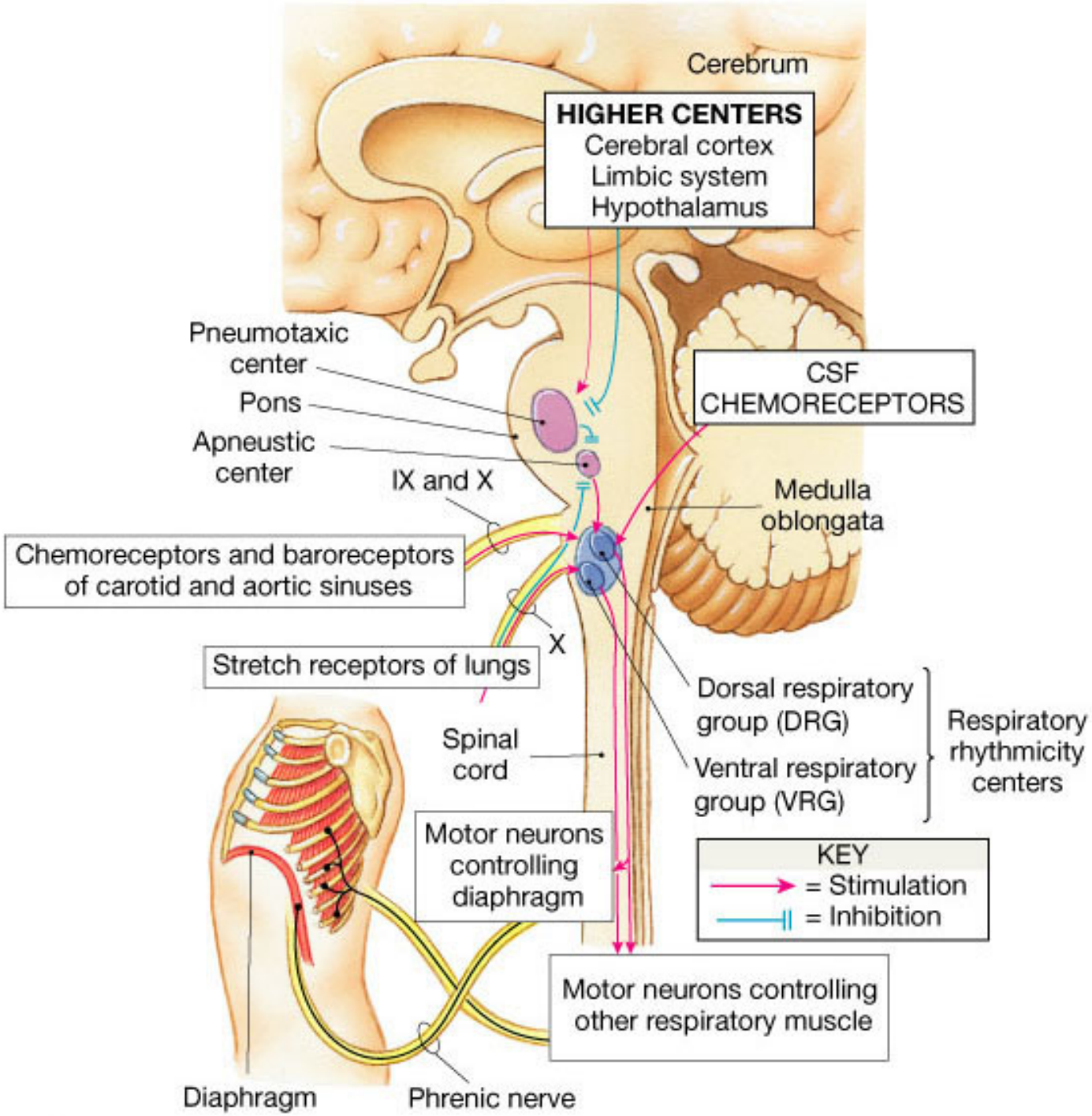
Figure 16.20


↓ Arterial P_{O_2}
↑ Production of non-CO_2 acids
↑ Arterial P_{CO_2}
↑ Brain extracellular fluid P_{CO_2}
↑ Arterial [H^+]
↑ Brain extracellular fluid [H^+]
Peripheral chemoreceptors
↑ Firing
Central chemoreceptors
↑ Firing
↑ Firing of medullary inspiratory neurons
↑ Firing of neurons to diaphragm and inspiratory intercostals
Diaphragm and inspiratory intercostals
↑ Contractions
↑ Ventilation

2. Neuroreceptor reflex

Hering-Breuer Reflex or Pulmonary Stretch Reflex

- Including pulmonary inflation reflex and pulmonary deflation reflex
- Receptor: Slowly adapting stretch receptors (SARs) in bronchial airways.
- Afferent: vagus nerve
- Pulmonary inflation reflex:
  - Terminate inspiration.
  - By speeding inspiratory termination they increase respiratory frequency.
  - **Sustained stimulation of SARs:** causes activation of expiratory neurons


Cerebrum
HIGHER CENTERS
Cerebral cortex
Limbic system
Hypothalamus
Pneumotaxic center
Pons
Apneustic center
CSF CHEMORECEPTORS
IX and X
Medulla oblongata
Chemoreceptors and baroreceptors of carotid and aortic sinuses
X
Stretch receptors of lungs
Dorsal respiratory group (DRG)
Ventral respiratory group (VRG)
Respiratory rhythmicity centers
Spinal cord
Motor neurons controlling diaphragm
KEY
= Stimulation
= Inhibition
Motor neurons controlling other respiratory muscle
Diaphragm
Phrenic nerve

Significance of Hering-Breuer

- Normal adults. Receptors are not activated at end normal tidal volumes.
  - Become Important during exercise when tidal volume is increased.
  - Become Important in Chronic obstructive lung diseases when lungs are more distended.
- Infants. Probably help terminate normal inspiration.

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:
    - Capsaicin:
      - Produces apnea followed by rapid, shallow breathing.
    - Histamine and bradykinin:
      - Released in response to noxious agents.
  - Irritant receptors are rapidly adaptive receptors.
- Hering-Breuer reflex:
  - Pulmonary stretch receptors activated during inspiration.
    - Inhibits respiratory centers to prevent undue tension on lungs.

RESPIRATORY ADJUSTMENT DURING EXERCISE

RESPIRATORY ADJUSTMENT DURING EXERCISE

- Muscular exercise brings about various changes in the body
- The changes depends on the degree of exercise
- **Exercise exert effects on:**
  - Pulmonary ventilation
    - Increased minute volume due to increase in TV and BR
    - Affected by:
      - Body temperature, acidosis, proprioceptors, chemoreceptors and actions of higher brain centers

Exercise also exert effects on:

- **Diffusion capacity** is increased from 21ml/min at rest up to 45-50ml/min during moderate exercise due to increase in blood flow through capillaries
- **Oxygen consumption by tissues:** this is enhanced and The amount of oxygen utilized by the muscles is directly proportional to the amount of oxygen available.
- **Respiratory quotient:** This is the molar ratio of carbon dioxide production to oxygen consumption.
  - Respiratory quotient in resting condition is 1.0 and during exercise it increases to 1.5 to 2. However, at the
- **Oxygen dept:** This is the amount of O_2 required by muscles when recovering from severe exercise.
  - It is for the reversal of metabolic processes that occurs during the exercise.
  - It increases about six time the normal O_2consumption rate
- **VO_2 Max:** It is the amount of oxygen consumed under maximal aerobic metabolism.
  - It is the product of maximal cardiac output and maximal amount of oxygen consumed by the muscle.
  - It increased about 50% during Exercise

Some Other Patterns of Respiration

1. **Periodic Breathing**

- Biot's breathing: There is a period of apnea in an apparent eupnea. The transition to apnea and eupnea is sharp. It is found mostly in pathological situations like in meningitis.

- Cheyne-Stoke's Breathing: Ventilation increases and decreases to an apnea. The transition is gradual unlike in Biot's breathing. It may be physiological, e.g. in sleeping infants, hyperventilation or high altitude, or pathological as in chronic heart failure.

2. Hyperventilation:

- This is the movement of air greater than is necessary to maintain the arterial PO_2 at 100 mmgH and the PCO_2 at 40 mmHg.
- It can occur voluntarily or in disease conditions like epidemic encephalitis as well as in pain, fear and anxiety.
- The general effects at the end of the over breathing are hyperoxia (aPO_2 =140 mmHg) and hypocapnia ($aPCO_2$ =15 mmHg) and are characterized by:
  - Respiratory alkalaemia: This is due to the hypocapnia. The plasma pH may rise to as much as 7.55. the alkalosis causes hypereflexia due to loss of Ca^{2+} from cell membrane and reduced serum ionized Ca^{2+} which results in increased irritability of the cells.
  - The kidney excretes alkaline urine containing HCO_3 to compensate for the alkalaemia.
  - In the CVS, there may be an increase in the cardiac output.
  - Neurological changes: Consciousness is dull and there is dizziness due to a reduction of the cerebral blood flow as a result of vasoconstriction; increased excitability of the motor nerves and tetany.

3. Breath Holding

- Breath holding may be referred to as voluntary apnea.
- It is an important act used to protect the lungs from noxious external environment. It last about 40-50sec (breaking point) in Man at which point it is voluntarily terminated due to hypercapnia.
- It can also be influenced by hypoxia and lack of carotid bodies may also increase it.
- At breaking point:
  - Arterial PO_2 is low (aPO_2 falls to about 56mmHg)
  - $aPCO_2$ is about 50 mmHg instead of 45 mmHg
  - H^+ is high

RESPIRATORY CONTROL OF ACID /BASE BALANCE

Respiratory Regulation of Acid base balance

- The respiratory system acts as a feedback regulatory system in the control of H^+ concentration in the body.
- Rate of alveolar ventilation affect the hydrogen ion concentration of the body fluids (vise vasa)
- This results from a direct action of H^+ on the respiratory center in the medullar and through the chemoreceptors
- The control is inefficient since stimulus is lost before the pH reaches 7.4

Respiratory Acidosis and Alkalosis.

- **Acidosis:** Any disturbance of alveolar ventilation that prevents CO2 excretion from proceeding at the rate that is sufficient to satisfy the existing body needs
  - This is different from metabolic acidosis in which the body produces excessive quantity of acid.
  - There is a compensation increase in bicarbonate.
  - The major causes of this are impairment of alveolar ventilation, reduced respiratory center activity, hypoxic diseases like thoracic abnormalities.
  - All of which generally result in alveolar hypoventilation.
- **Respiratory alkalosis:** Is alveolar ventilation in excess of that required by the body for the normal excretion of CO2
  - This is different from metabolic alkalosis in which the body secrete less acid
  - the aPOC2 falls to inappropriately low levels (hypocapnia)
  - Hormones like progesterone, epinephrine and disease like hyperthyroidism may cause alveolar hyperventilation.

EFFECT OF CHANGE IN BAROMETRIC PRESSURE ON RESPIRATION

Respiratory adjustment at High Altitude (Lower barometric pressure)

- At high altitude:
  - The barometric pressure is less than 760mmHg
  - iPO_2 and $aPCO_2$ are reduced
  - Consequently hypoxia result which stimulate respiration
  - At 400m, aPO_2 falls below a critical level of 35mmHg and hypoxia becomes severe
  - Above 700m consciousness is lost

Respiratory adjustment at High Altitude (Contd)

- Other effects of:
  - Hyperventilation which will result in
    - Alkalosis
    - Reduction in activities of central chemoreceptor
  - Increase in heart rate
  - Erhythropoiesis, polycythemia and increased viscosity of blood will occur after acclimatization

Acclimatization to High Altitude

- Adjustments in respiratory function when moving to an area with higher altitude:
  - Changes in ventilation:
    - Hypoxic ventilatory response produces hyperventilation by stimulating peripheral chemoreceptors
      - This will cause respiratory alkalosis due to excess loss of Co_2
      - Increase in H.R and C.O due to increase sympathetic drive
    - Increases total minute volume.
    - Increased tidal volume.
  - Increased hemoglobin production and RBCs count
    - Kidneys secrete erythropoietin.
  - Affinity of hemoglobin for 0_2:
    - Action of 2,3-DPG decreases affinity of hemoglobin for 0_2 and increases 0_2 delivery to the tissue

- The following changes will also occur:
  - Excretion of Alkaline urine to correct alkalosis
  - Increased cell Mitochondria
  - Increased vascularity of the tissue
  - Release of (about 10 times) more NO to double blood flow
  - Angiogenesis (development of new vessels) due to the hypoxic tissues releasing angiogenic factors such as *VEGF*, *FGF*

Mountain sickness

- Condition characterized by adverse effects of hypoxia at high altitude.
- Common in first time visitors
- It occurs within a day in these persons, before they get acclimatized to the altitude.
- It could be acute or chronic

Mountain sickness (contd.)

- Symptoms (they occur due to low Po_2)
  - Headache, depression, disorientation, irritability, lack of sleep, weakness and fatigue due to **cerebral edema.**
  - Increase in Heart rate and force of contraction of heart
  - Loss of appetite, nausea and vomiting (due to expansion of gases in GI tract).
  - Breathlessness due to pulmonary edema
  - In Chronic state, congestive heart failure occurs due to increased viscosity caused by excessive polycythemia

Respiratory adjustment at low altitude
(High barometric pressure)

- An increased in depth increases Barometric pressure
  - This will increase gas pressure
    - Nitrogen: nitrogen narcosis and dysbarism
    - Oxygen: toxicity
  - As well as body pressure (thoracic cage)
    - Fixation of chest wall to increase inspiratory effort and may cause edema to the external presser
    - Barotrauma

EFFECT ON NITROGEN

- Some gases including N_2 will now dissolve in plasma which should not be a problem, particularly when the individual is returned to the atmosphere very slowly.
- In a rapid return to the atmosphere, N_2 bubbles appears in blood
- This will block vessels to heart and CNS and cause pain in tissues (“the bends”).
- This is referred to as decompression sickness or Caisson’s disease or Dysbarism.
- The treatment for this is to quickly return the subject and bring him up slowly to the surface or wash-off the N_2 by breathing O_2- helium before decent.
- N_2 itself is toxic. With increasing PN_2, there is CNS depression (anaesthetic effects), euphoria and narcosis, which is equivalent to alcoholic intoxication.

Effect on Oxygen

- Oxygen can also be toxic at depths of 100 m and below.
- It is a function of intracellular partial pressure of oxygen (iPO_2) and the length of time of exposure.
- When the iPO_2 reses to above 165 mmHg, hyperroxia results.

  Characterized by:-

  - Lung damage with a decrease in surfactant;
  - Coughing and pain during breathing are the first symptoms
  - Convulsions and unconsciousness develops.

Effects on body pressure

- **Barotrauma:**
  - When the rising pressure compresses the gas-filled spaces, particularly the ear, they are damaged (air drum may be pushed inwards)
  - water flows into the inner ear causing nausea, dizziness and difficulty in orientation.
- **Pressure on the chest:**
  - Increase in inspiratory effort as the chest is pushed to an expiratory position.
  - Blood from the periphery is pushed into the chest which may result in pulmonary Oedema.