The Respiratory System physiology

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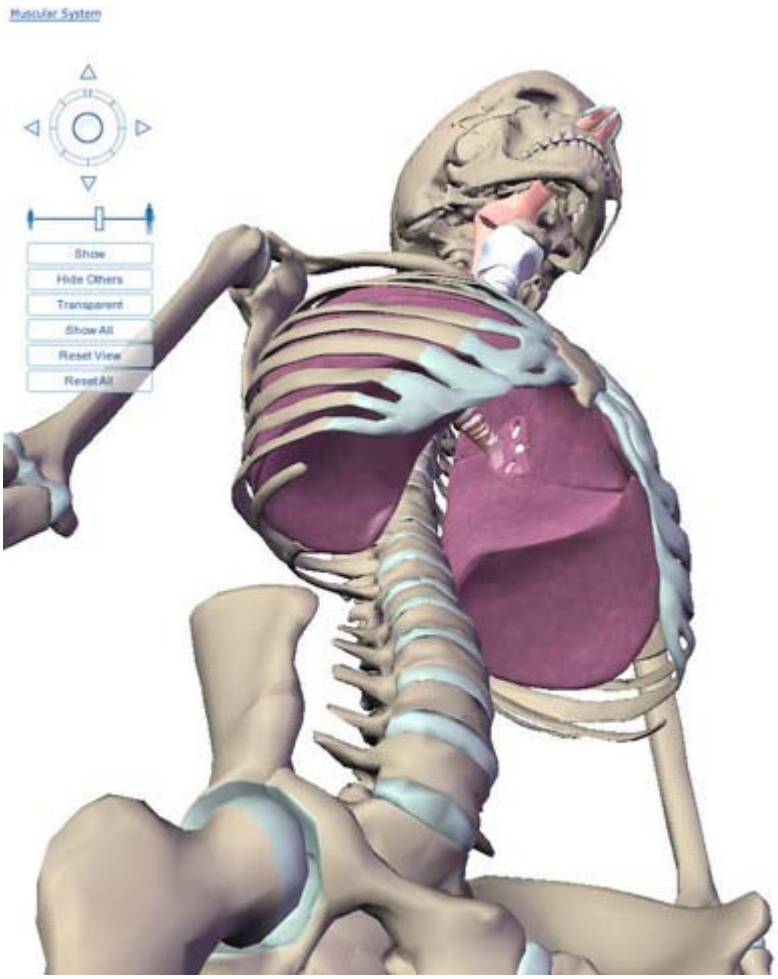


Introduction

- Respiration has two meanings in biology.
  - At the cellular level, it refers to the O_2 requiring chemical reactions that take place in the mitochondria and are the chief source of energy in the eukaryotic cells.
  - At the level of the whole organism, it designates the process of taking in O_2 from the environment and returning CO_2 to it.
- O_2 consumption is directly related to energy expenditure.
  - Energy requirements are usually calculated by measuring O_2 intake or CO_2 release.
  - Energy expenditure at rest is known as **basal metabolism**.

The function of the **respiratory system** is to deliver air to the lungs. Oxygen in the air diffuses out of the lungs and into the blood, while carbon dioxide diffuses in the opposite direction, out of the blood and into the lungs. Respiration includes the following processes:

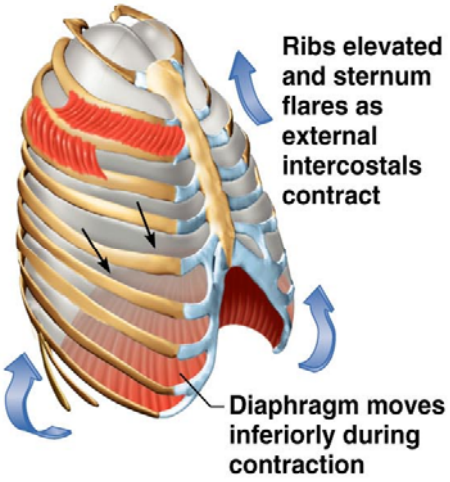
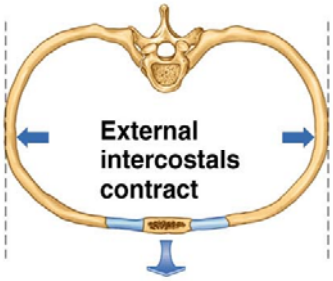
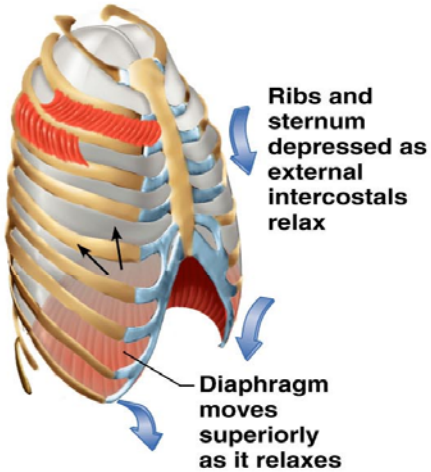
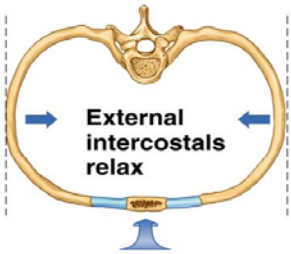
- Pulmonary ventilation is the process of breathing—inspiration (inhaling air) and expiration (exhaling air).
- External respiration is the process of gas exchange between the lungs and the blood. Oxygen diffuses into the blood, while CO_2 diffuses from the blood into the lungs.

- Gas transport, carried out by the cardiovascular system, is the process of distributing the oxygen throughout the body and collecting CO_2 and returning it to the lungs.
- Internal respiration is the process of gas exchange between the blood, the interstitial fluids (fluids surrounding the cells), and the cells. Inside the cell, cellular respiration generates energy (ATP), using O_2 and glucose and producing waste CO_2.

Diffusion and Air Pressure

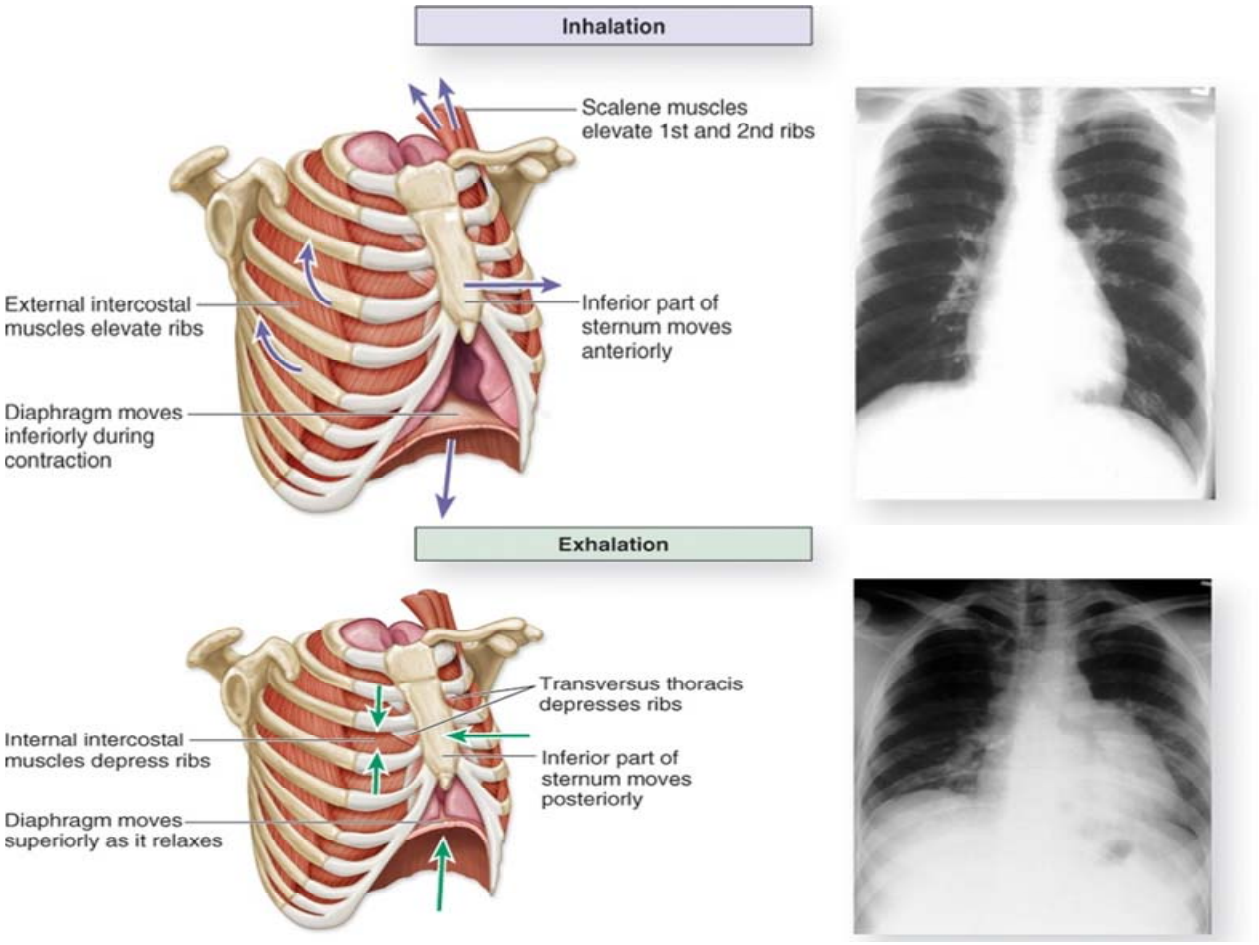
- In every organism from amoeba to elephant, gas exchange--the exchange of O_2 and CO_2 between cells and the surrounding environment--takes place by diffusion.
    - Diffusion--the net movement of particles from a region of higher concentration to a region of lower concentration as a result of their random movement.
- In describing gases, scientists speak of the pressure of a gas rather than its concentration.
    - At sea level, air exerts a pressure of one (1) atm. (15 lb/in^2)
        - This pressure is enough to support a column of mercury 760 mm high.

    - **Dalton's Law of Partial Pressure**--The total pressure of a mixture of gases is sum of the pressures of the separate gases in the mixture.
        - The pressure of each gas is proportional to its concentration.
            - O_2 makes up 21% of the composition of dry air therefore 21% of the total air pressure or 160 mm of Hg results from the pressure of O_2--partial pressure of O_2--designated as pO_2--if H_2O is present then pO_2 =155 mm Hg.
- If a liquid containing no dissolved gases is exposed to air at atmospheric pressure, each of the gases in the air diffuses into the liquid until the partial pressure of each gas in the liquid is equal to the partial pressure of the gas in the air.
    - pO_2 of blood means the pressure of dry gas with which the dissolved O_2 in the blood is in equilibrium.
        - For example, blood with a pO_2 of 40 mm Hg would be in equilibrium with air in which the partial pressure of O_2 was 40 mm Hg.
        - If blood with a pO_2 of 40 mm Hg was exposed to the usual mixture of air, O_2 will move from the air to the blood until the pO_2 = 155 mm Hg.
- Conversely, if a liquid containing a dissolved gas is exposed to air in which the partial pressure of that gas is lower than the liquid, the gas will leave the liquid until the partial pressures of the air and the liquid are equal.
- In summary, gases move from a region of higher partial pressure to a region of lower partial pressure.

	Sequence of events	Changes in anterior-posterior and superior-inferior dimensions	Changes in lateral dimensions
Inspiration	① Inspiratory muscles contract (diaphragm descends; rib cage rises) ↓ ② Thoracic cavity volume increases ↓ ③ Lungs stretched; intrapulmonary volume increases ↓ ④ Intrapulmonary pressure drops (to –1 mm Hg) ↓ ⑤ Air (gases) flows into lungs down its pressure gradient until intrapulmonary pressure is 0 (equal to atmospheric pressure)		
Expiration	① Inspiratory muscles relax (diaphragm rises; rib cage descends due to recoil of costal cartilages) ↓ ② Thoracic cavity volume decreases ↓ ③ Elastic lungs recoil passively; intrapulmonary volume decreases ↓ ④ Intrapulmonary pressure rises (to +1 mm Hg) ↓ ⑤ Air (gases) flows out of lungs down its pressure gradient until intrapulmonary pressure is 0		

Breathing

- Breathing, or pulmonary ventilation, consists of two phases
  - Inspiration – air flows into the lungs
  - Expiration – gases exit the lungs



Breathing

In mammals, the diaphragm divides the body cavity into the

- **abdominal cavity**, which contains the viscera (e.g., stomach and intestines) and the
- **thoracic cavity**, which contains the heart and lungs.

The inner surface of the thoracic cavity and the outer surface of the lungs are lined with **pleural membranes** which adhere to each other. If air is introduced between them, the adhesion is broken and the natural elasticity of the lung causes it to collapse. This can occur from trauma. And it is sometimes induced deliberately to allow the lung to rest. In either case, reinflation occurs as the air is gradually absorbed by the tissues.

Because of this adhesion, any action that increases the volume of the thoracic cavity causes the lungs to expand, drawing air into them.

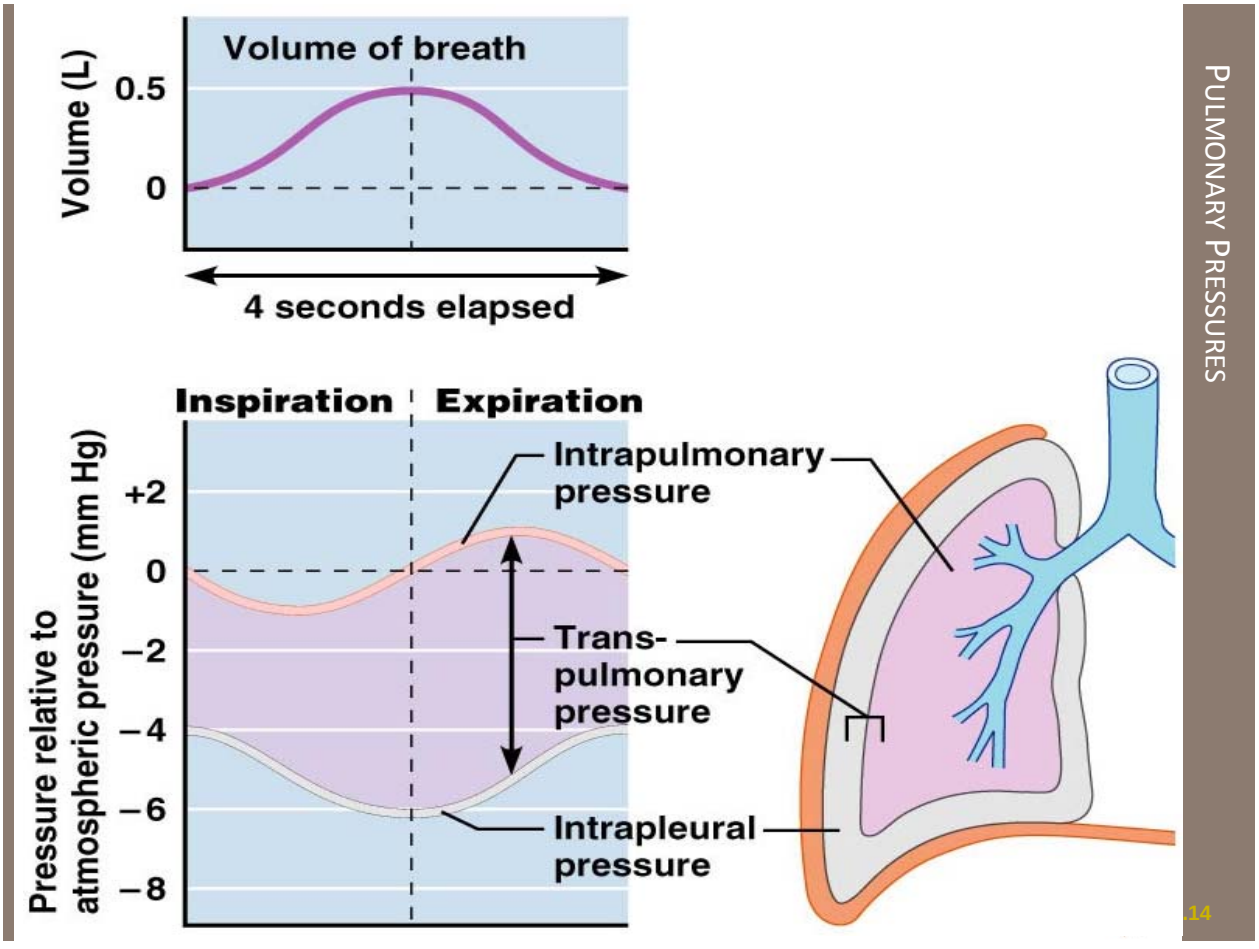
- During inspiration (inhaling),
  - The external intercostal muscles contract, lifting the ribs up and out.
  - The diaphragm contracts, drawing it down .
- During expiration (exhaling), these processes are reversed and the natural elasticity of the lungs returns them to their normal volume. At rest, we breath 15-18 times a minute exchanging about 500 ml of air.
- In more vigorous expiration,

- The internal intercostal muscles draw the ribs down and inward
- The wall of the abdomen contracts pushing the stomach and liver upward.

Under these conditions, an average adult male can flush his lungs with about 4 liters of air at each breath. This is called the **vital capacity**. Even with maximum expiration, about 1200 ml of **residual air** remain.

The table shows what happens to the composition of air when it reaches the alveoli. Some of the oxygen dissolves in the film of moisture covering the epithelium of the alveoli. From here it diffuses into the blood in a nearby capillary. It enters a red blood cell and combines with the hemoglobin therein.

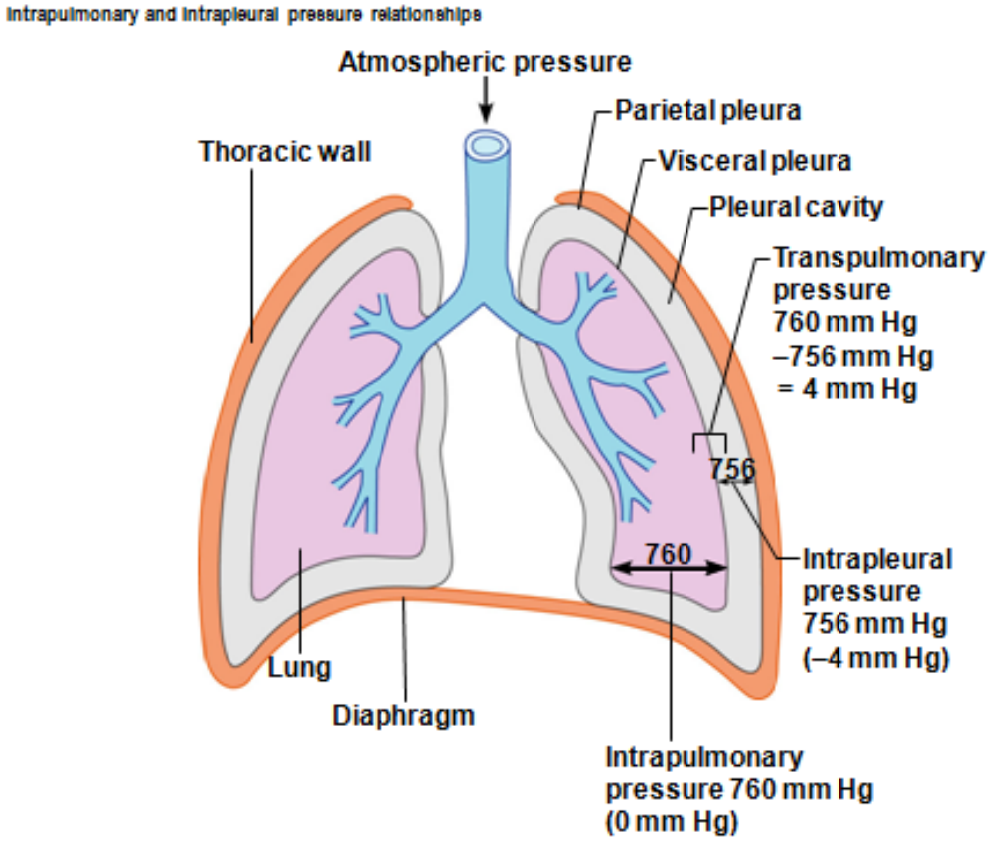
At the same time, some of the carbon dioxide in the blood diffuses into the alveoli from which it can be exhaled.



Pressure Relationships in the Thoracic Cavity

- Respiratory pressure is always described relative to atmospheric pressure
- Atmospheric pressure (P_{atm})
  - Pressure exerted by the air surrounding the body
  - Negative respiratory pressure is less than P_{atm}
  - Positive respiratory pressure is greater than P_{atm}
- Intrapulmonary pressure (P_{pul}) – pressure within the alveoli

- Intrapleural pressure (P_{ip}) – pressure within the pleural cavity

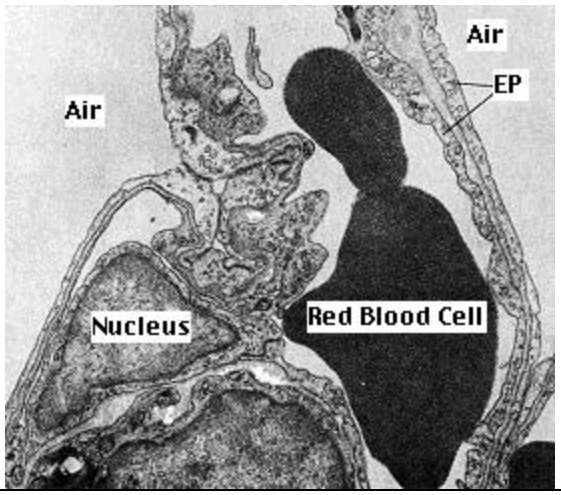


Pressure Relationships

- Intrapulmonary pressure and intrapleural pressure fluctuate with the phases of breathing
- Intrapulmonary pressure always eventually equalizes itself with atmospheric pressure
- Intrapleural pressure is always less than intrapulmonary pressure and atmospheric pressure
- Two forces act to pull the lungs away from the thoracic wall, promoting lung collapse
  - **Elasticity of lungs** causes them to assume smallest possible size
  - **Surface tension of alveolar fluid** draws alveoli to their smallest possible size
- Opposing force – elasticity of the chest wall pulls the thorax outward to enlarge the lungs

Composition of atmospheric air and expired air in a typical subject. Note that only a fraction of the oxygen inhaled is taken up by the lungs.

Component	Atmospheric Air (%)	Expired Air (%)
N_2 (plus inert gases)	78.62	74.9
O_2	20.85	15.3
CO_2	0.03	3.6
H_2O	0.5	6.2
	100.0%	100.0%



Forces Acting on the Lungs

1. **Lung recoil** refers to forces that develop in the lung wall during expansion.

a. Recoil increases as the lung enlarges.

b. Recoil always acts to collapse the lung.

2. **Intrapleural pressure** (also called pleural pressure, or **PPL**) is the pressure in the thin film of fluid between the lung and chest wall (Figure 3–2).

a. PPL is generally subatmospheric (~ −5 cm H20).

b. Negative subatmospheric pressures act to expand the lung, whereas positive pressures act to collapse the lung.

c. When PPL exceeds recoil forces the lungs expand.

d. When recoil forces exceed PPL the lungs decrease in volume.

3. **Alveolar pressure** (**PA**) is the pressure of the alveolar air (see Figure 3–2).

a. PA drives airflow into and out of the lungs.

b. If PA equals 0 (ie, no airflow), then PA is the same as atmospheric pressure.

c. PA is less than 0 during respiration; PA is greater than 0 during expiration.

4. **Transpulmonary pressure** (**PTP**) is the difference between the pressure inside the lung (alveolar pressure) and the pressure outside the lung (intrapleural pressure). PTP determines the degree of inflation of the lung.

Lung Collapse

- Caused by equalization of the intrapleural pressure with the intrapulmonary pressure

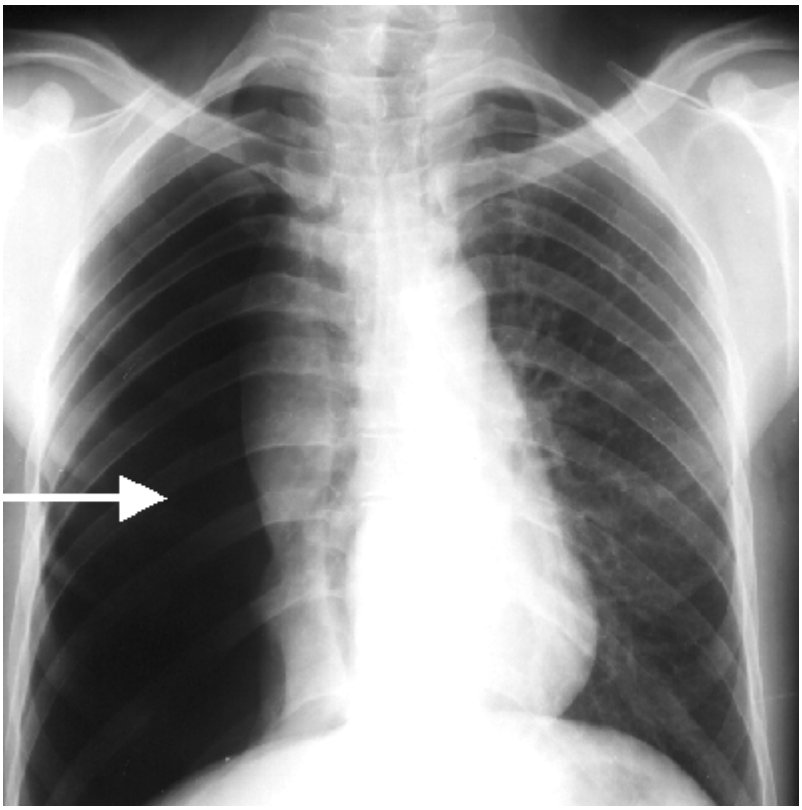
- Transpulmonary pressure keeps the airways open
  - Transpulmonary pressure – difference between the intrapulmonary and intrapleural pressures **($P_{pul} - P_{ip}$)**

Pneumothorax is the presence of air in the pleural space.

a. If the chest is opened, the intrapleural pressure changes to equal atmospheric pressure.

b. Lung recoil decreases to zero as the lung collapses.

c. The chest wall expands.



Pulmonary Ventilation

- A mechanical process that depends on volume changes in the thoracic cavity
- Volume changes lead to pressure changes, which lead to the flow of gases to equalize pressure

Boyle's Law

- Boyle's law – the relationship between the pressure and volume of gases

$$P_1V_1 = P_2V_2$$

  - P = pressure of a gas in mm Hg
  - V = volume of a gas in cubic millimeters
  - Subscripts 1 and 2 represent the initial and resulting conditions, respectively

Inspiration

- The diaphragm and external intercostal muscles (inspiratory muscles) contract and the rib cage rises
- The lungs are stretched and intrapulmonary volume increases
- Intrapulmonary pressure drops below atmospheric pressure (–1 mm Hg)

- Air flows into the lungs, down its pressure gradient, until intrapleural pressure = atmospheric pressure

Expiration

- Inspiratory muscles relax and the rib cage descends due to gravity
- Thoracic cavity volume decreases
- Elastic lungs recoil passively and intrapulmonary volume decreases
- Intrapulmonary pressure rises above atmospheric pressure (+1 mm Hg)
- Gases flow out of the lungs down the pressure gradient until intrapulmonary pressure is 0

Muscles of Breathing

A. Inspiration

1. The **diaphragm** is the major muscle of inspiration.

a. This dome-shaped muscle is located between the thorax and the abdomen.

b. It is innervated by phrenic nerves.

c. The diaphragm moves down during inspiration and up during expiration.

d. Quiet breathing is accomplished almost entirely by the diaphragm.

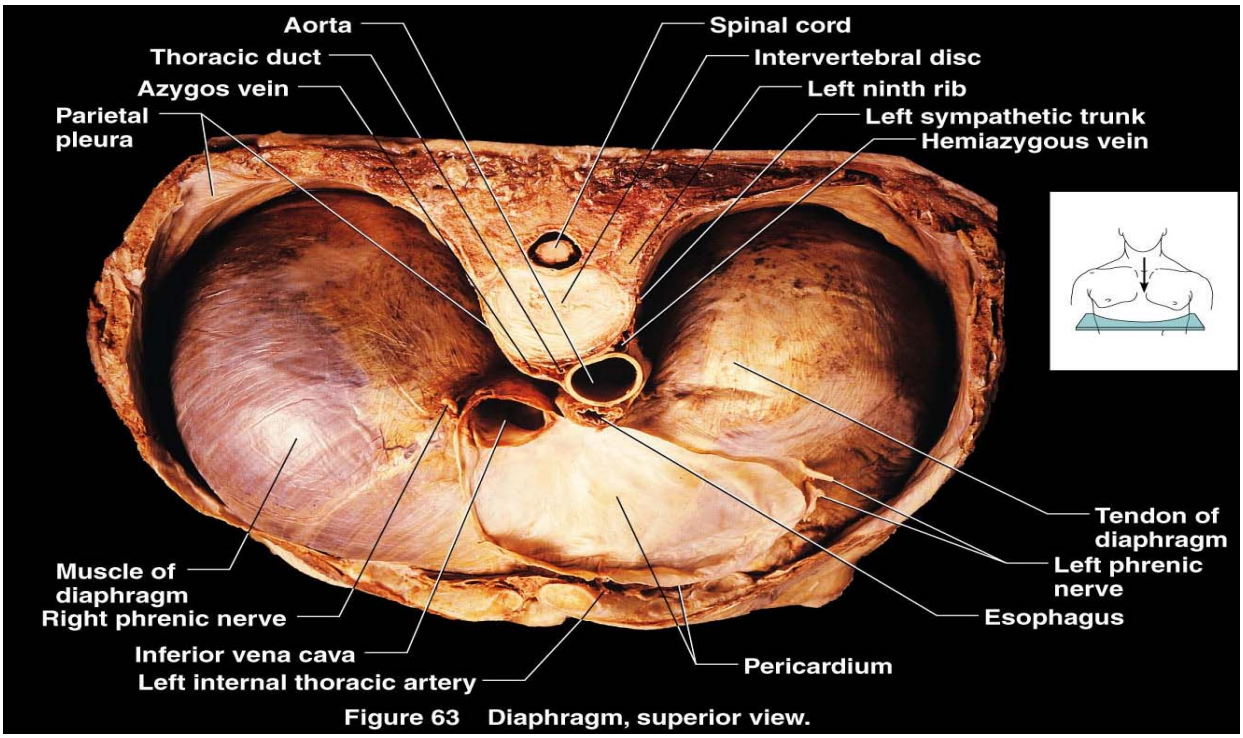
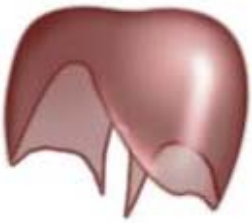
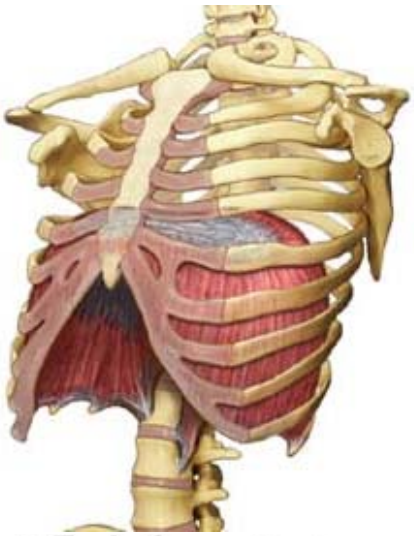


Figure 63 Diaphragm, superior view.



The diaphragm is shaped like a parachute



End of expiration

Muscles of inspiration

Sternocleido-mastoid

Scalenes

Pectoralis minor

External inter-costals

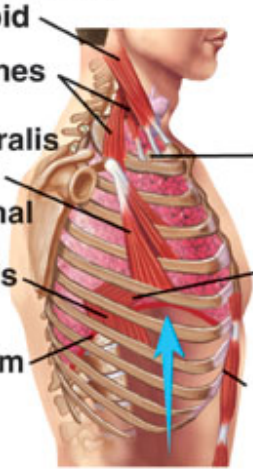
Dia-phragm

Clavicle (cut)

Internal inter-costals

Ab-dominal muscles

Muscles of expiration

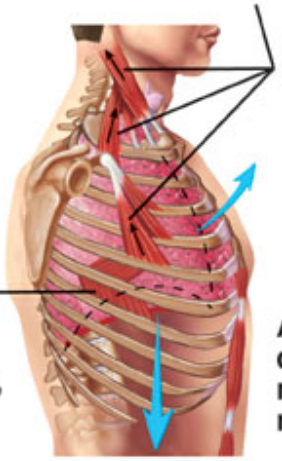


Diaphragm relaxed

(a)

End of inspiration

Labored breathing: Additional muscles contract, causing additional expansion of the thorax.

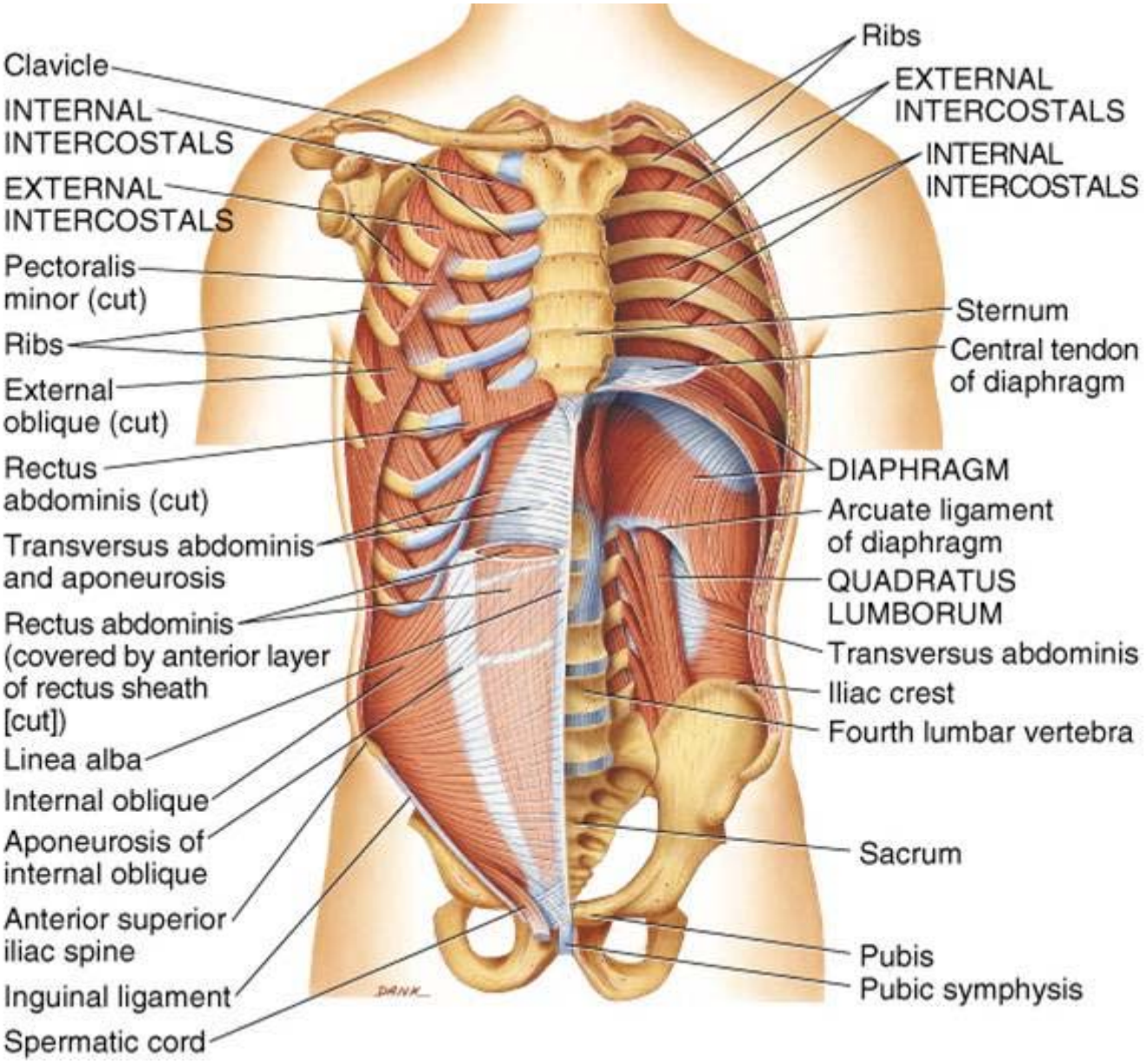


Quiet breathing: The external intercostal muscles contract, elevating the ribs and moving the sternum.

Ab-dominal muscles relax.

The diaphragm contracts, increasing the superior–inferior dimension of the thoracic cavity.

(b)



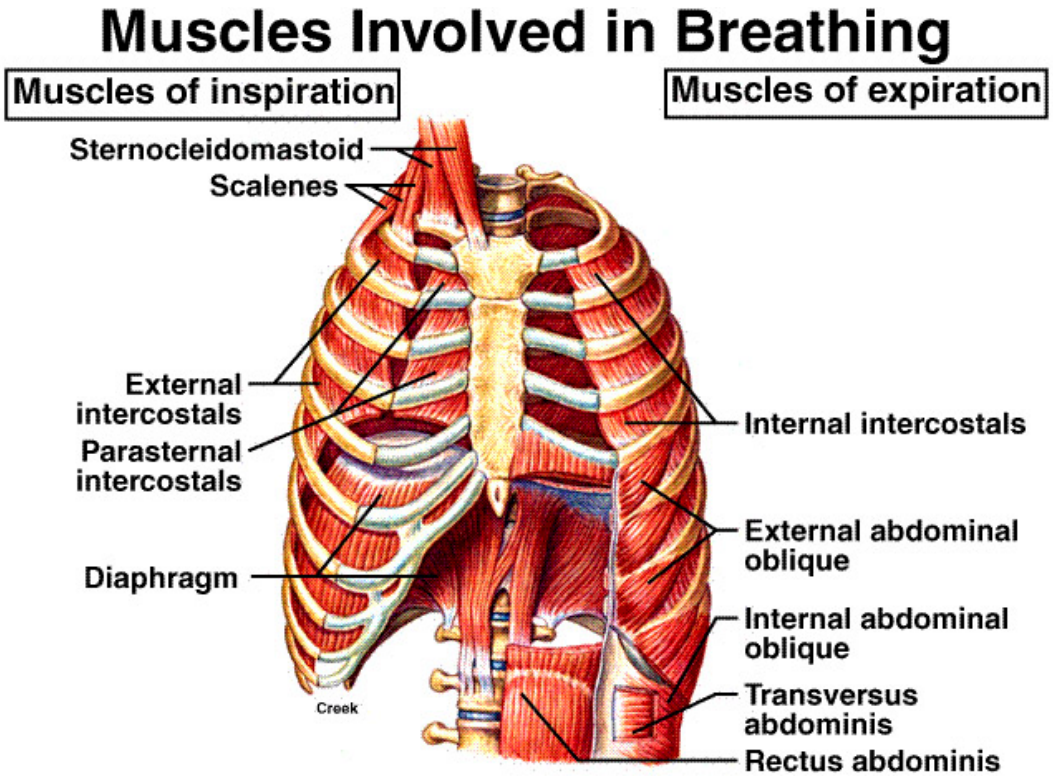
2. External intercostals are important muscles for active inspiration, for example, during exercise, singing, playing wind instruments, and sighing.

a. These muscles are located between the ribs and are oriented such that contraction elevates the ribs and increases thickness of the thoracic cage, thereby drawing air into the lungs.

b. They are innervated by intercostal nerves that come from the spinal cord at the level of the rib attached to a given intercostal muscle.

3. The **accessory inspiratory muscles** are:

- the scalene
- sternomastoid muscles
- the alae nasi (used in nostril flaring).

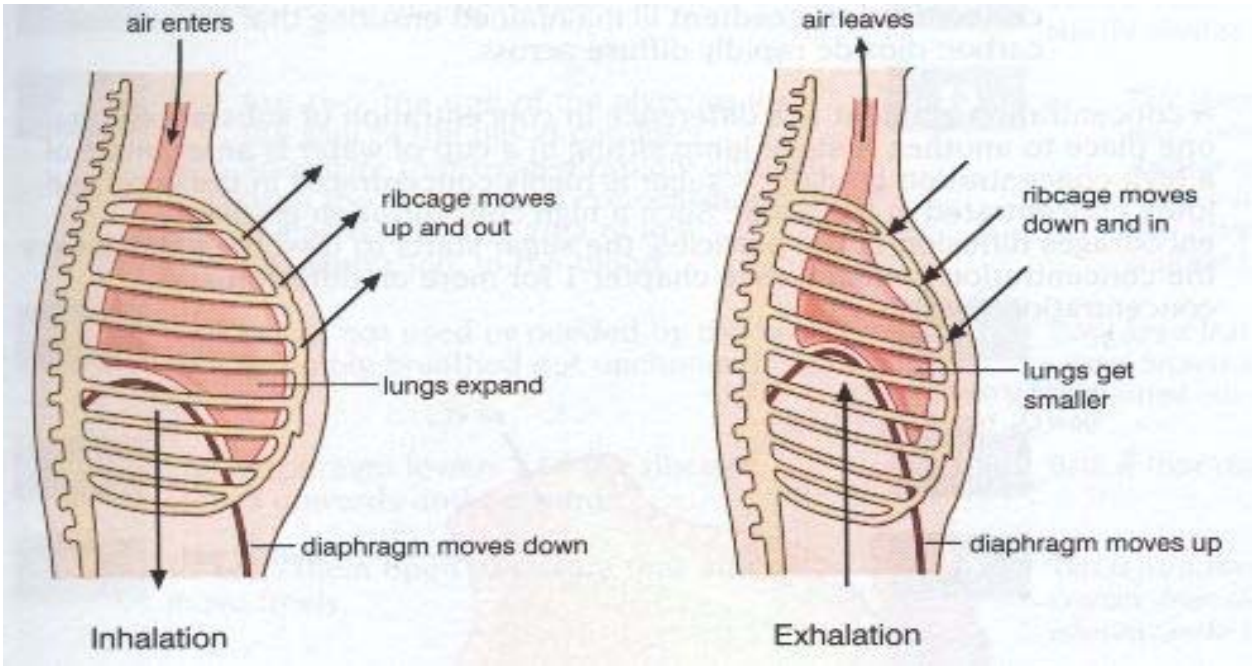


B. Expiration

1. The muscles of expiration are passive during quiet breathing and active during exercise.

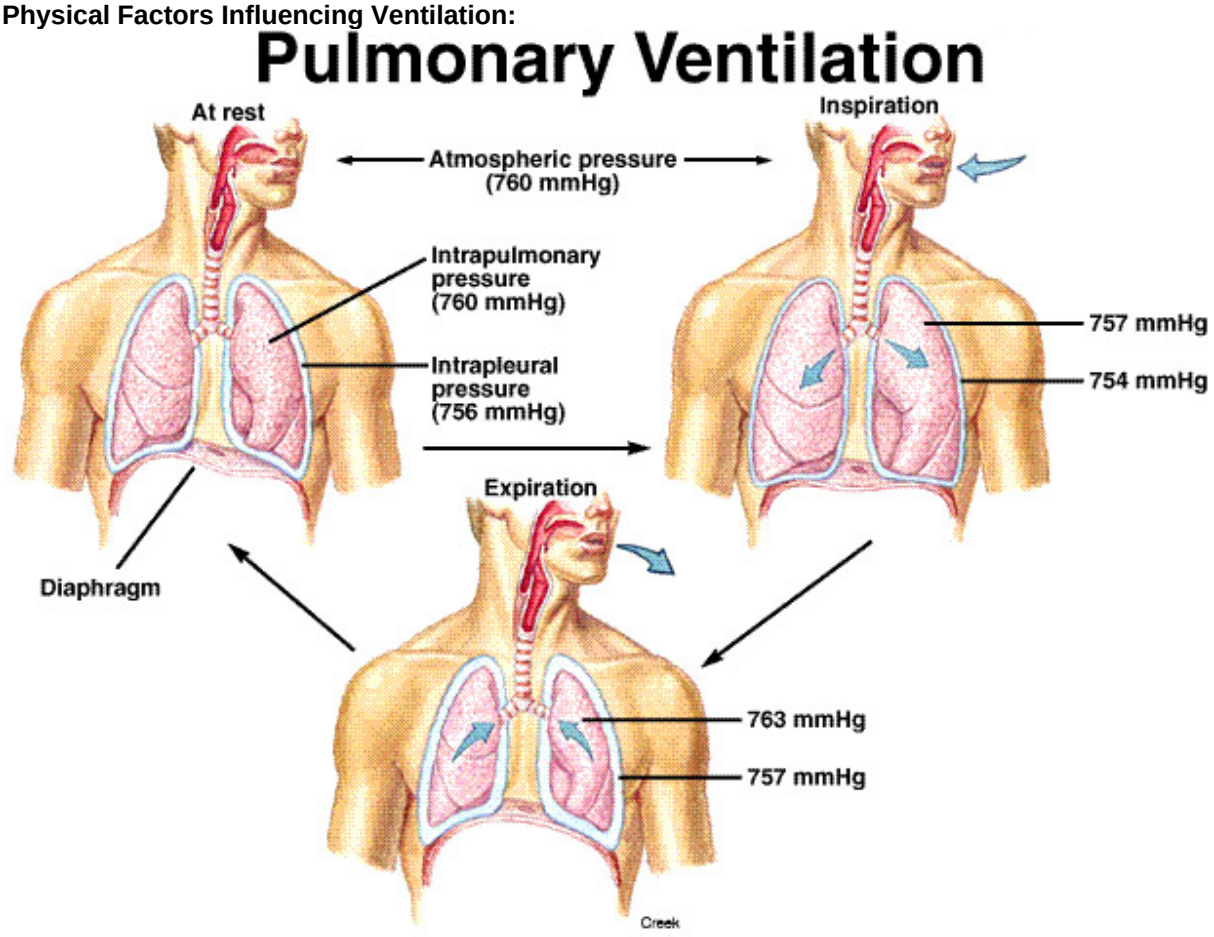
2. The **abdominals** are the main muscles of expiration. Contraction of these muscles opposes the action of the diaphragm, that is, tending to push the diaphragm upward.

3. The **internal intercostals** oppose action on the external intercostals. They are oriented so that contraction tends to pull the rib cage down and decreases the anterior-posterior thickness of the thorax.



Pulmonary Pressures

Physical Factors Influencing Ventilation:



Airway Resistance

- Friction is the major nonelastic source of resistance to airflow
- The relationship between flow (F), pressure (P), and resistance (R) is:

- The amount of gas flowing into and out of the alveoli is directly proportional to ΔP, the pressure gradient between the atmosphere and the alveoli
- Gas flow is inversely proportional to resistance with the greatest resistance being in the medium-sized bronchi
- As airway resistance rises, breathing movements become more strenuous
- Severely constricted or obstructed bronchioles:
  - Can prevent life-sustaining ventilation
  - Can occur during acute asthma attacks which stops ventilation
- Epinephrine release via the sympathetic nervous system dilates bronchioles and reduces air resistance

. Airway Resistance

A. The **rate of airflow** for a given driving pressure depends on **airway resistance:**

$$V = \frac{P_A}{R},$$

where

V = flow rate (L/s)

*P*A = alveolar pressure (mm Hg)

R = airway resistance (R units)

The more negative the intrapleural pressure (eg, during inspiration), the lower the

airway resistance.

B. According to Poiseuille's equation,

$$resistance \propto \frac{I}{r^4},$$

where

r = radius of the airway

Thus, a strong relationship exists between resistance and the radius of the airway.

The following factors influence airway resistance:

1. **Stimulation of parasympathetic nerves** produces **bronchoconstriction.**

2. Stimulation of sympathetic nerves or circulating catecholamine produces **bronchodilation.**

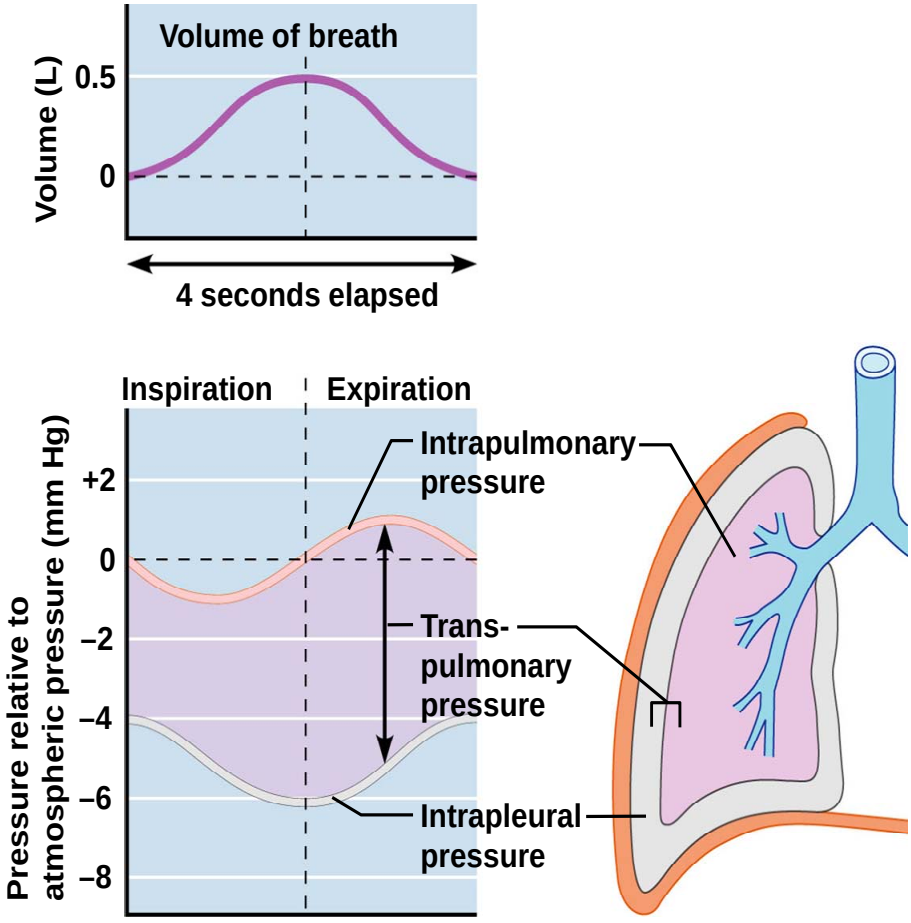
3. Low lung volumes are associated with **increased airway resistance,** whereas **high lung volumes** are associated with **decreased resistance.**

4. Breathing a **high-density gas increases resistance** to airflow, whereas breathing a low-density gas decreases resistance to airflow.

5. The first and second (ie, medium-sized) bronchi represent most of the airway resistance

Resistance in Repiratory Passageways

Changes in intrapulmonary and intrapleural pressures during inspiration and expiration,



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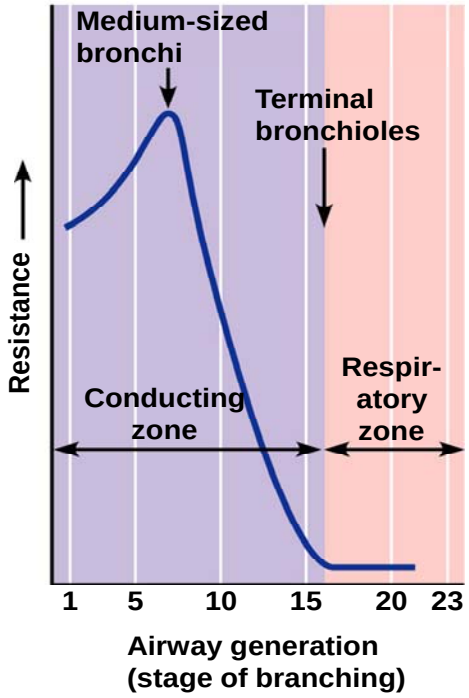
Resistance in respiratory passageways



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Alveolar Surface Tension

- Surface tension – the attraction of liquid molecules to one another at a liquid-gas interface
- The liquid coating the alveolar surface is always acting to reduce the alveoli to the smallest possible size
- Surfactant, a detergent-like complex, reduces surface tension and helps keep the alveoli from collapsing

Lung Compliance

- The ease with which lungs can be expanded
- Specifically, the measure of the change in lung volume that occurs with a given change in transpulmonary pressure
- Determined by two main factors
  - Distensibility of the lung tissue and surrounding thoracic cage
  - Surface tension of the alveoli

Compliance (CL) is the stretching of the lungs and is calculated as follows

$$C_L = \frac{\Delta V}{P_{TP}},$$

where

Δ*V* = change in lung volume

*P*TP = transpulmonary pressure

B. Compliance is the change in lung volume per unit change in airway pressure.

For example,

$$C_L = \frac{\Delta V}{\Delta_{P_{TP}}} = \frac{1000\ mL}{5\ cm\ H_2O} = 200\ mL/cm\ H_2O$$

C. High CL means more air will flow for a given change in pressure.

D. Low CL means less air will flow for a given change in pressure.

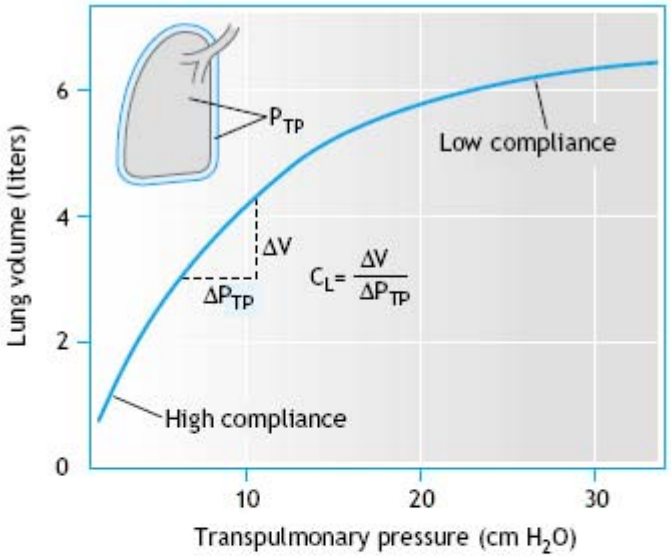


Figure 3–3. Transpulmonary pressure (P_{TP}) is determined by subtracting intrapleural pressure (P_{PL}) from alveolar pressure (P_A). Thus, P_{TP} is greater in the upper regions of the lung, where P_{PL} is more negative and holds the lungs in a more expanded position. The upper regions of the lungs also have greater volumes than the lower regions. Further increases in volume per unit increase in P_{TP} are smaller in the upper than lower regions of the lungs because the upper expanded lung is stiffer (ie, less compliant).

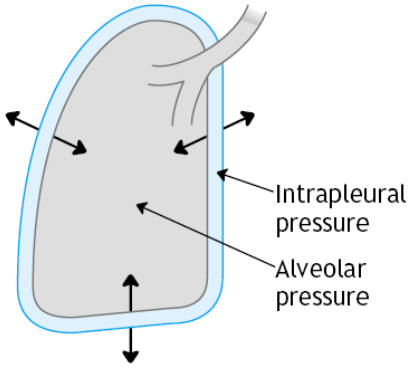


Figure 3–2. Alveolar and intrapleural pressures during normal breathing. Intrapleural pressure remains negative during inspiration and expiration. Alveolar pressure is negative during inspiration and positive during expiration.

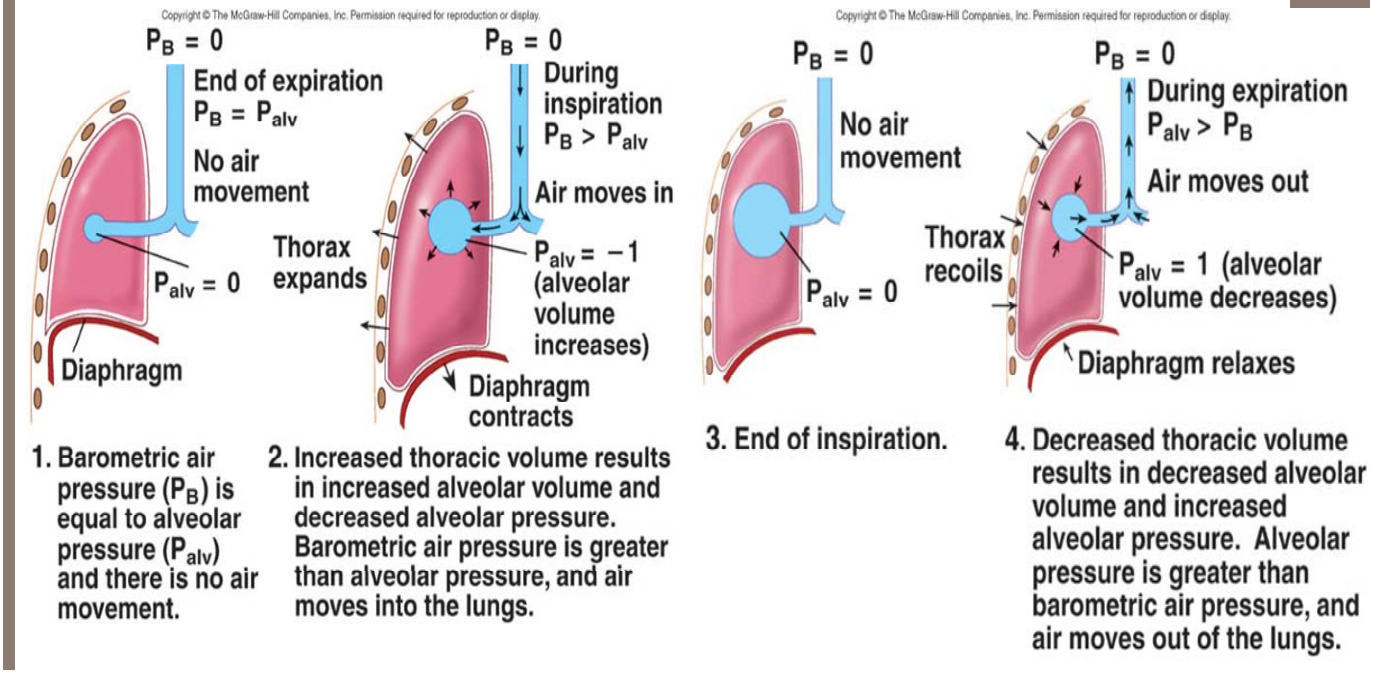
E. If PTP becomes more negative, more air will flow into the system, and if PTP becomes more positive more air will flow out of the system.

F. CL is an indicator of the effort required to expand the lungs to overcome recoil.

G. **Compliant lungs** have low recoil, whereas stiff lungs have a large recoil force

H. The **pressure-volume curve** is not the same for inspiration and expiration; this difference is called **hysteresis,** which is due primarily to the effects of airway resistance.

Alveolar Pressure Changes



Factors That Diminish Lung Compliance

- Scar tissue or fibrosis that reduces the natural resilience of the lungs
- Blockage of the smaller respiratory passages with mucus or fluid
- Reduced production of surfactant
- Decreased flexibility of the thoracic cage or its decreased ability to expand
- Examples include:
  - Deformities of thorax
  - Ossification of the costal cartilage
  - Paralysis of intercostal muscles

Components of Lung Recoil

A. The **collagen and elastic fibers** of the lung tissue provide elastance, which is the reciprocal of compliance.

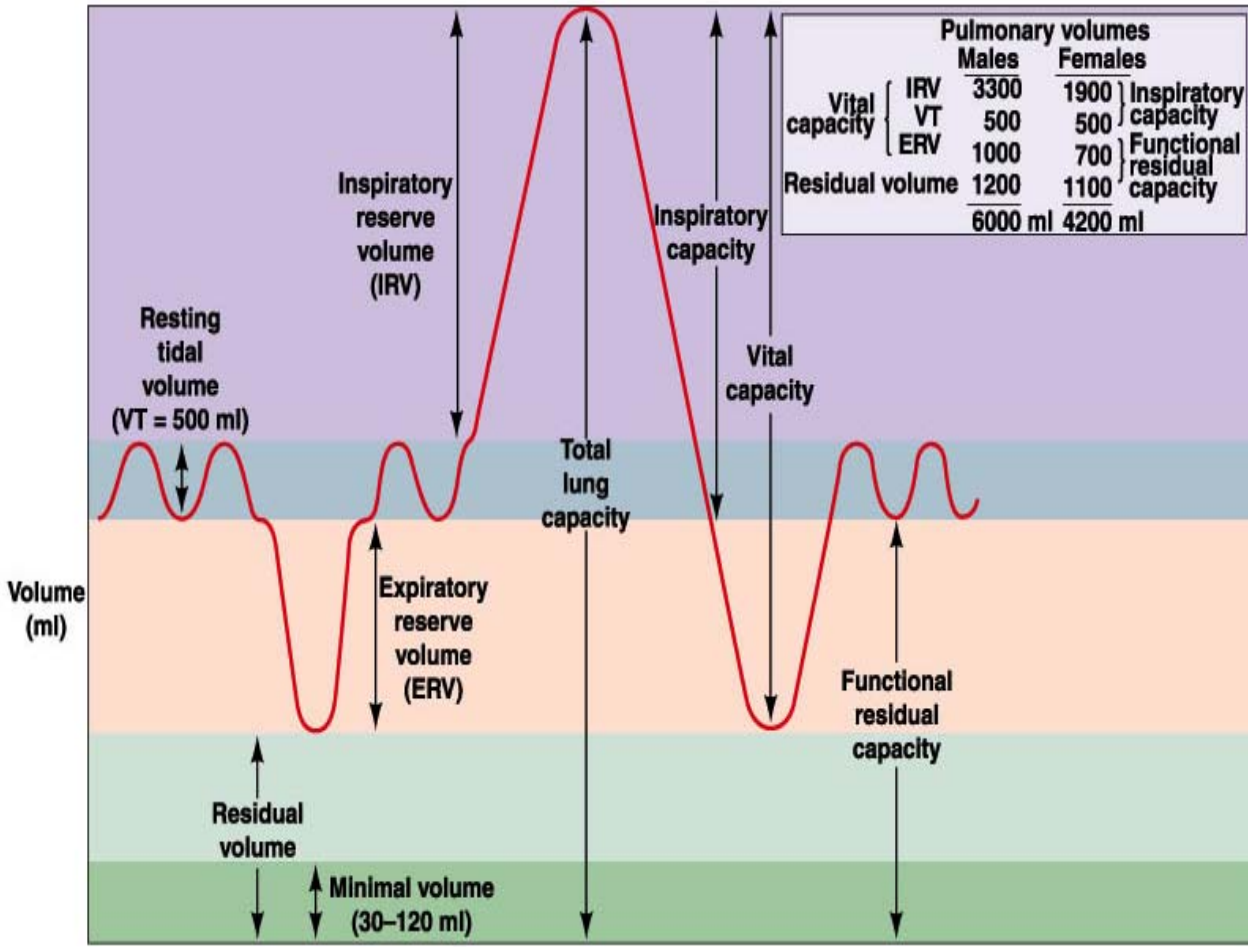
B. **Surface tension forces** created whenever a liquid-air interface is present in the fluid lining the alveoli act to collapse the alveoli and contribute to lung recoil.

1. The fluid lining the alveoli contains **surfactant,** a surface-tension–lowering agent.
2. Surfactant has three main functions.

a. It **lowers surface tension forces** in the alveoli, which reduces lung recoil and increases compliance.

b. The reduction in surface tension forces in small alveoli **decreases their tendency to collapse.**

c. It also **reduces capillary filtration forces,** which decreases the risk of pulmonary edema.



	Measurement	Adult male average value	Adult female average value	Description
Respiratory volumes	Tidal volume (TV)	500 ml	500 ml	Amount of air inhaled or exhaled with each breath under resting conditions
	Inspiratory reserve volume (IRV)	3100 ml	1900 ml	Amount of air that can be forcefully inhaled after a normal tidal volume inhalation
	Expiratory reserve volume (ERV)	1200 ml	700 ml	Amount of air that can be forcefully exhaled after a normal tidal volume exhalation
	Residual volume (RV)	1200 ml	1100 ml	Amount of air remaining in the lungs after a forced exhalation
Respiratory capacities	Total lung capacity (TLC)	6000 ml	4200 ml	Maximum amount of air contained in lungs after a maximum inspiratory effort: TLC = TV + IRV + ERV + RV
	Vital capacity (VC)	4800 ml	3100 ml	Maximum amount of air that can be expired after a maximum inspiratory effort: VC = TV + IRV + ERV (should be 80% TLC)
	Inspiratory capacity (IC)	3600 ml	2400 ml	Maximum amount of air that can be inspired after a normal expiration: IC = TV + IRV
	Functional residual capacity (FRC)	2400 ml	1800 ml	Volume of air remaining in the lungs after a normal tidal volume expiration: FRC = ERV + RV

(b) Summary of respiratory volumes and capacities for males and females

Respiratory Volumes

- Tidal volume (TV) – air that moves into and out of the lungs with each breath (approximately 500 ml)
- Inspiratory reserve volume (IRV) – air that can be inspired forcibly beyond the tidal volume (2100–3200 ml)
- Expiratory reserve volume (ERV) – air that can be evacuated from the lungs after a tidal expiration (1000–1200 ml)
- Residual volume (RV) – air left in the lungs after strenuous expiration (1200 ml)

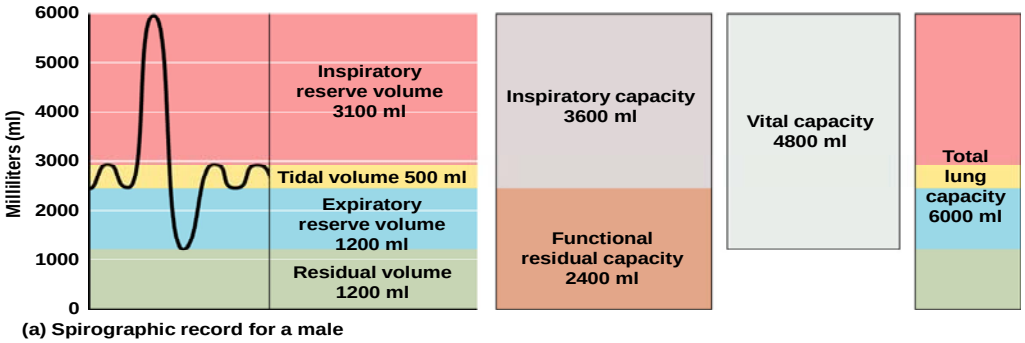
Respiratory Capacities

- Inspiratory capacity (IC) – total amount of air that can be inspired after a tidal expiration (IRV + TV)
- Functional residual capacity (FRC) – amount of air remaining in the lungs after a tidal expiration (RV + ERV)
- Vital capacity (VC) – the total amount of exchangeable air (TV + IRV + ERV)
- Total lung capacity (TLC) – sum of all lung volumes (approximately 6000 ml in males)

Dead Space

- Anatomical dead space – volume of the conducting respiratory passages (150 ml)
- Alveolar dead space – alveoli that cease to act in gas exchange due to collapse or obstruction
- Total dead space – sum of alveolar and anatomical dead spaces

Figure 22.16a: Respiratory volumes and capacities, p. 852.



(a) Spirographic record for a male

Human Anatomy and Physiology, 7e
by Elaine Marieb & Katja Hoehn

Pulmonary Function Tests

- Spirometer – an instrument consisting of a hollow bell inverted over water, used to evaluate respiratory function
- Spirometry can distinguish between:
  - Obstructive pulmonary disease – increased airway resistance
  - Restrictive disorders – reduction in total lung capacity from structural or functional lung changes
- Total ventilation – total amount of gas flow into or out of the respiratory tract in one minute
- Forced vital capacity (FVC) – gas forcibly expelled after taking a deep breath
- Forced expiratory volume (FEV) – the amount of gas expelled during specific time intervals of the FVC
- Increases in TLC, FRC, and RV may occur as a result of obstructive disease
- Reduction in VC, TLC, FRC, and RV result from restrictive disease

	Measurement	Adult male average value	Adult female average value	Description
Respiratory volumes	Tidal volume (TV)	500 ml	500 ml	Amount of air inhaled or exhaled with each breath under resting conditions
	Inspiratory reserve volume (IRV)	3100 ml	1900 ml	Amount of air that can be forcefully inhaled after a normal tidal volume inhalation
	Expiratory reserve volume (ERV)	1200 ml	700 ml	Amount of air that can be forcefully exhaled after a normal tidal volume exhalation
	Residual volume (RV)	1200 ml	1100 ml	Amount of air remaining in the lungs after a forced exhalation
Respiratory capacities	Total lung capacity (TLC)	6000 ml	4200 ml	Maximum amount of air contained in lungs after a maximum inspiratory effort: TLC = TV + IRV + ERV + RV
	Vital capacity (VC)	4800 ml	3100 ml	Maximum amount of air that can be expired after a maximum inspiratory effort: VC = TV + IRV + ERV (should be 80% TLC)
	Inspiratory capacity (IC)	3600 ml	2400 ml	Maximum amount of air that can be inspired after a normal expiration: IC = TV + IRV
	Functional residual capacity (FRC)	2400 ml	1800 ml	Volume of air remaining in the lungs after a normal tidal volume expiration: FRC = ERV + RV

(b) Summary of respiratory volumes and capacities for males and females

Alveolar Ventilation

- Alveolar ventilation rate (AVR) – measures the flow of fresh gases into and out of the alveoli during a particular time
- Slow, deep breathing increases AVR and rapid, shallow breathing decreases AVR

Respiratory Air Volumes

Respirometer Tracings of Lung Volumes and Capacities

- **Tidal Volume**--Volume of air moved in or out of the lungs during quiet breathing--about 500 mL.
- **Inspiratory Reserve Volume**--Volume that can be inhaled during forced breathing in addition to tidal volume--3000mL.
- **Expiratory Reserve Volume**--Volume that can be exhaled during forced breathing in addition to tidal volume--1100 mL.
- **Vital Capacity**--Maximum volume that can be exhaled after taking the deepest breath. **VC = TV + IRV + ERV**
- **Residual Volume**--Volume that remains in the lungs at all times--1200 mL.
- **Total Lung Capacity**--Total volume of air that the lungs can hold.**TLC = VC + RV**

Nonrespiratory Air Movements

- Most result from reflex action
- Examples include: coughing, sneezing, crying, laughing, hiccupping, and yawning

Nonrespiratory Air Movements

Air movements that occur in addition to breathing are called **nonrespiratory air movements**.

- **Cough**
  - Involves taking a deep breath, closing the glottis, and forcing air upward from the lungs against the closure.
  - Then the glottis is suddenly opened and a blast of air is forced upward from the lower respiratory tract.
- **Sneezing**
  - Is much like a cough, but it clears the upper respiratory tract rather than the lower.
  - Is a reflex act that is usually initiated by a mild irritation in the lining of the nasal cavity and, in response, a blast of air is forced up through the glottis.
- **Laughing**
  - Involves taking a breath and releasing it in a series of short expirations.
- **Crying**
  - Consists of movements similar to laughing.
- **Hiccup**
  - Caused by a sudden inspiration due to a spasmodic contraction of the diaphragm while the glottis is closed.
  - Sound of a hiccup is created by air striking the vocal cords.
- **Yawning**
  - Thought to aid respiration by providing an occasional deep breath.
  - Believed to be caused by lower than usual oxygenated blood.

Basic Properties of Gases:

Dalton's Law of Partial Pressures

- Total pressure exerted by a mixture of gases is the sum of the pressures exerted independently by each gas in the mixture
- The partial pressure of each gas is directly proportional to its percentage in the mixture

Basic Properties of Gases: Henry's Law

- When a mixture of gases is in contact with a liquid, each gas will dissolve in the liquid in proportion to its partial pressure
- The amount of gas that will dissolve in a liquid also depends upon its solubility:
  - Carbon dioxide is the most soluble
  - Oxygen is $1/20^{th}$ as soluble as carbon dioxide
  - Nitrogen is practically insoluble in plasma

Composition of Alveolar Gas

- The atmosphere is mostly oxygen and nitrogen, while alveoli contain more carbon dioxide and water vapor
- These differences result from:
  - Gas exchanges in the lungs – oxygen diffuses from the alveoli and carbon dioxide diffuses into the alveoli
  - Humidification of air by conducting passages
  - The mixing of alveolar gas that occurs with each breath

Partial Pressures of O2 and CO2 in the body (normal, resting conditions):

- Alveoli
  - PO2 = 100 mm Hg
  - PCO2 = 40 mm Hg
- Alveolar capillaries
  - Entering the alveolar capillaries
    - PO2 = 40 mm Hg (relatively low because this blood has just returned from the systemic circulation & has lost much of its oxygen)
    - PCO2 = 45 mm Hg (relatively high because the blood returning from the systemic circulation has picked up carbon dioxide)

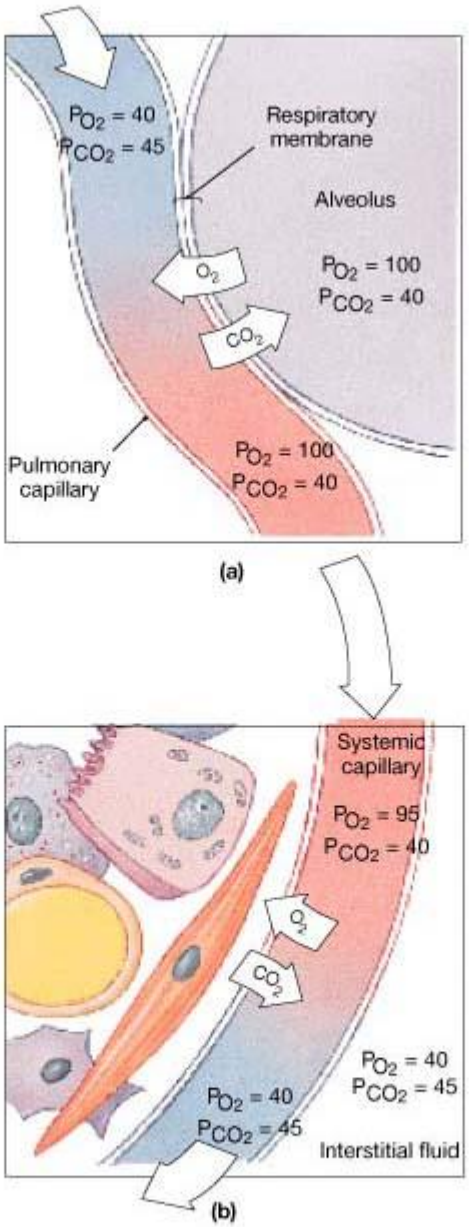
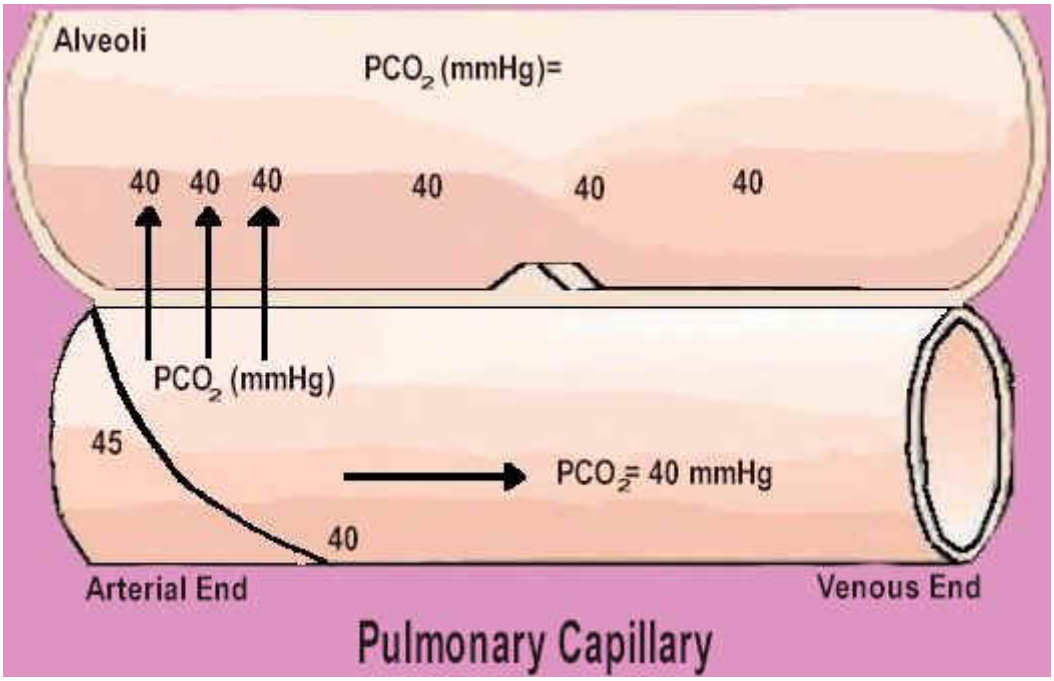


FIGURE 23-20 An Overview of Respiratory Processes and Partial Pressures in Respiration. **(a)** Partial pressures and diffusion at the respiratory membrane. **(b)** Partial pressures and diffusion in other tissues.



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
  - PO2 = 100 mm Hg
  - PCO2 = 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
  - PO2 = 100 mm Hg
  - PCO2 = 40 mm Hg
- Body cells (resting conditions)
  - PO2 = 40 mm Hg
  - PCO2 = 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
  - PO2 = 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.

External Respiration: Pulmonary Gas Exchange

- Factors influencing the movement of oxygen and carbon dioxide across the respiratory membrane
  - Partial pressure gradients and gas solubilities
  - Matching of alveolar ventilation and pulmonary blood perfusion
  - Structural characteristics of the respiratory membrane

Partial Pressure Gradients and Gas Solubilities

- The partial pressure oxygen (PO_2) of venous blood is 40 mm Hg; the partial pressure in the alveoli is 104 mm Hg
  - This steep gradient allows oxygen partial pressures to rapidly reach equilibrium (in 0.25 seconds), and thus blood can move three times as quickly (0.75 seconds) through the pulmonary capillary and still be adequately oxygenated
- Although carbon dioxide has a lower partial pressure gradient:
  - It is 20 times more soluble in plasma than oxygen
  - It diffuses in equal amounts with oxygen

Oxygenation of Blood

Ventilation-Perfusion Coupling

- Ventilation – the amount of gas reaching the alveoli
- Perfusion – the blood flow reaching the alveoli
- Ventilation and perfusion must be tightly regulated for efficient gas exchange
- Changes in P_{CO2} in the alveoli cause changes in the diameters of the bronchioles
  - Passageways servicing areas where alveolar carbon dioxide is high dilate
  - Those serving areas where alveolar carbon dioxide is low constrict

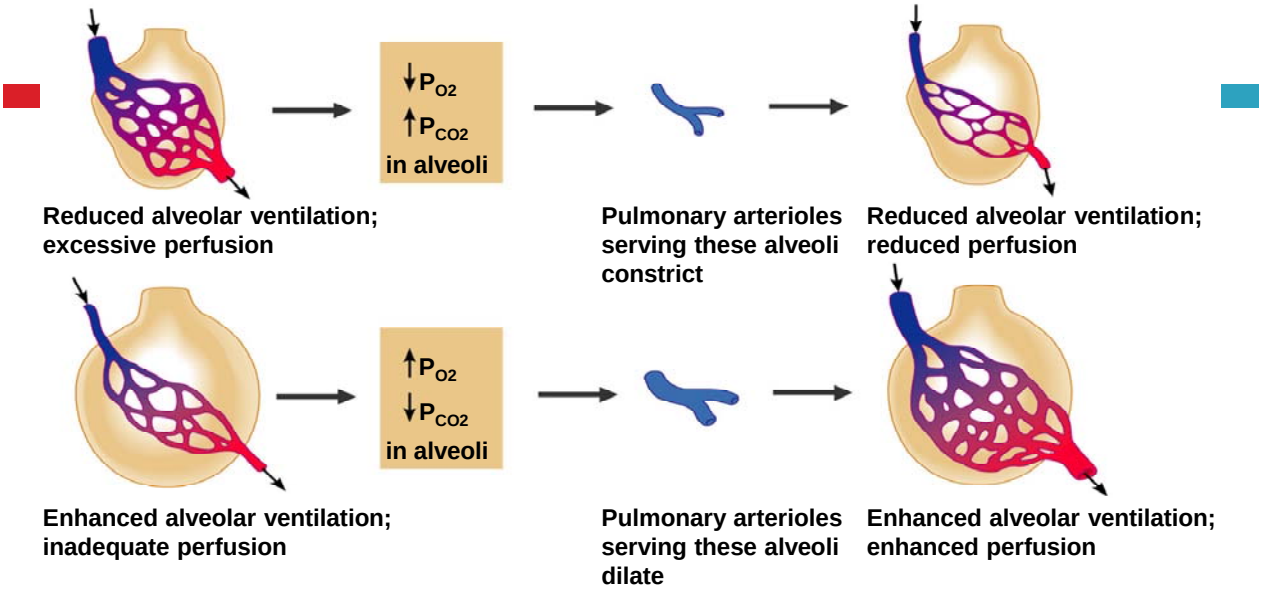


Figure 22.19

Surface Area and Thickness of the Respiratory Membrane

- Respiratory membranes:
  - Are only 0.5 to 1 μm thick, allowing for efficient gas exchange

- Have a total surface area (in males) of about 60 m^2 (40 times that of one's skin)
- Thicken if lungs become waterlogged and edematous, whereby gas exchange is inadequate and oxygen deprivation results
- Decrease in surface area with emphysema, when walls of adjacent alveoli break through

Internal Respiration

- The factors promoting gas exchange between systemic capillaries and tissue cells are the same as those acting in the lungs
  - The partial pressures and diffusion gradients are reversed
  - P_{O2} in tissue is always lower than in systemic arterial blood
  - P_{O2} of venous blood draining tissues is 40 mm Hg and P_{CO2} is 45 mm Hg

Oxygen Transport

- Molecular oxygen is carried in the blood:
  - Bound to hemoglobin (Hb) within red blood cells
  - Dissolved in plasma

Oxygen Transport: Role of Hemoglobin

- Each Hb molecule binds four oxygen atoms in a rapid and reversible process
- The hemoglobin-oxygen combination is called oxyhemoglobin (HbO_2)
- Hemoglobin that has released oxygen is called reduced hemoglobin (HHb)

Oxygen Transport: Role of Hemoglobin

- Each Hb molecule binds four oxygen atoms in a rapid and reversible process
- The hemoglobin-oxygen combination is called oxyhemoglobin (HbO_2)
- Hemoglobin that has released oxygen is called reduced hemoglobin (HHb)

$$HHb + O_2 \underset{\text{Tissues}}{\overset{\text{Lungs}}{\longleftrightarrow}} HbO_2 + H^+$$

How are oxygen & carbon dioxide transported in the blood?

- Oxygen is carried in blood:

  1 - bound to hemoglobin (98.5% of all oxygen in the blood)

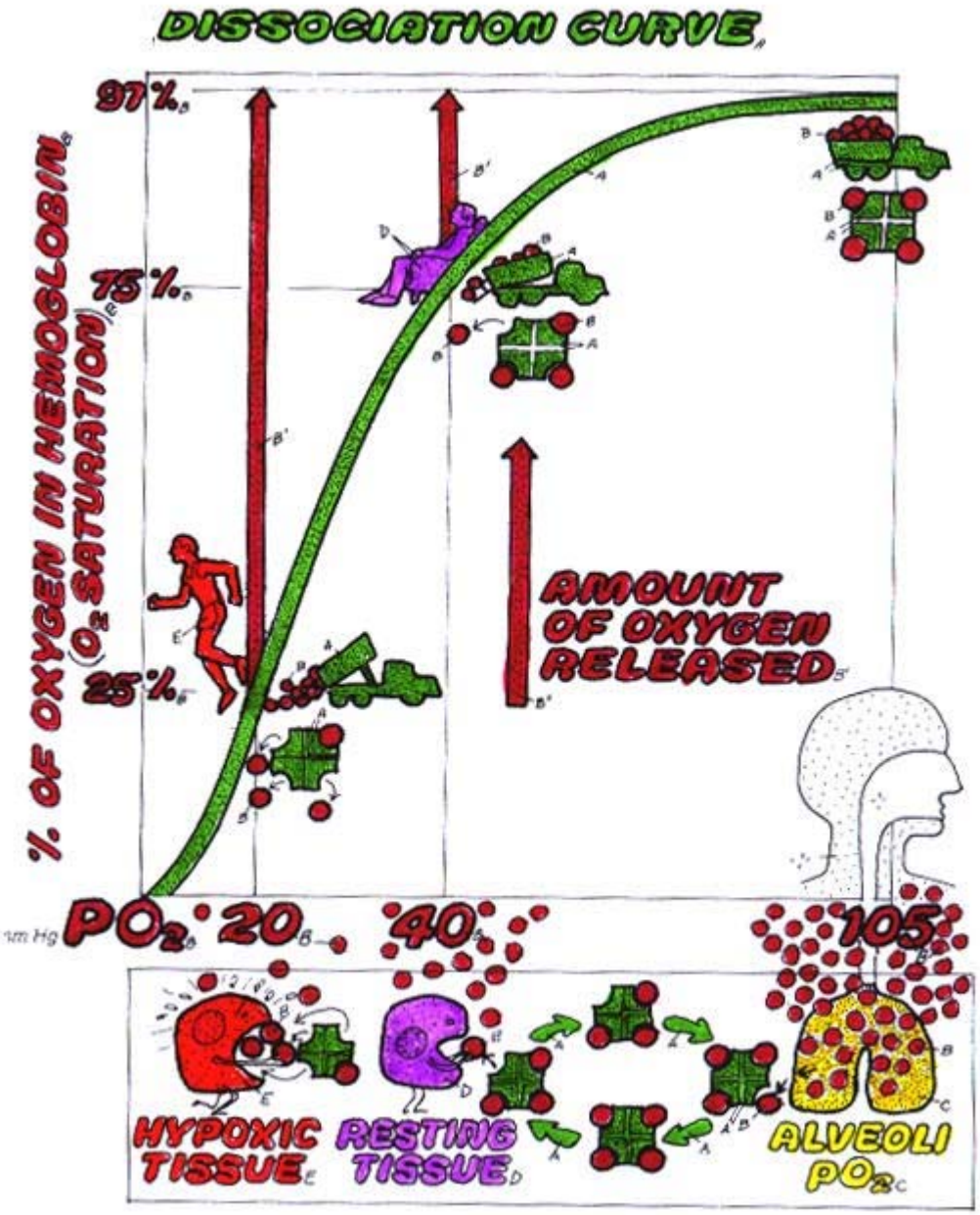
  2 - dissolved in the plasma (1.5%)

Because almost all oxygen in the blood is transported by hemoglobin, the relationship between the concentration

(partial pressure) of oxygen and hemoglobin saturation (the % of hemoglobin molecules carrying oxygen) is an important one.

Hemoglobin saturation:

- extent to which the hemoglobin in blood is combined with O2
- depends on PO2 of the blood:

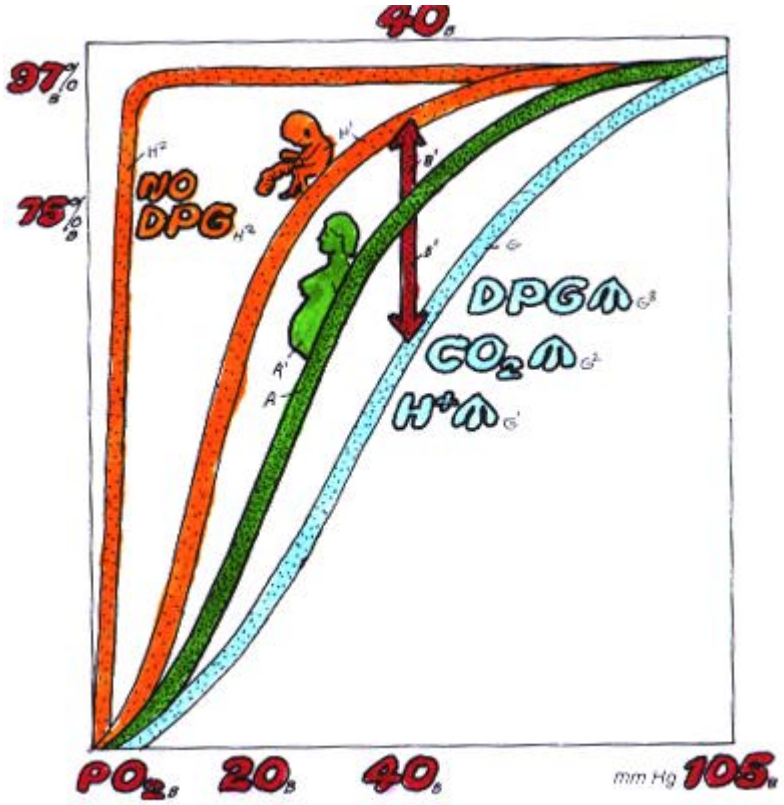


The relationship between oxygen levels and hemoglobin saturation is indicated by the **oxygen-hemoglobin dissociation (saturation) curve** (in the graph above). You can see that at high partial pressures of O2 (above about 40 mm Hg), hemoglobin saturation remains rather high (typically about 75 - 80%). This rather flat section

of the oxygen-hemoglobin dissociation curve is called the 'plateau.'

Recall that 40 mm Hg is the typical partial pressure of oxygen in the cells of the body. Examination of the oxygen-hemoglobin dissociation curve reveals that, under resting conditions, only about 20 - 25% of hemoglobin molecules give up oxygen in the systemic capillaries. This is significant (in other words, the 'plateau' is significant) because it means that you have a substantial reserve of oxygen. In other words, if you become more active, & your cells need more oxygen, the blood (hemoglobin molecules) has lots of oxygen to provide

When you do become more active, partial pressures of oxygen in your (active) cells may drop well below 40 mm Hg. A look at the oxygen-hemoglobin dissociation curve reveals that as oxygen levels decline, hemoglobin saturation also declines - and declines precipitously. This means that the blood (hemoglobin) 'unloads' lots of oxygen to active cells - cells that, of course, need more oxygen.



Factors that affect the Oxygen-Hemoglobin Dissociation Curve:

The oxygen-hemoglobin dissociation curve 'shifts' under certain conditions. These factors can cause such a shift:

- lower pH
- increased temperature
- more 2,3-diphosphoglycerate
- increased levels of CO2

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 (CO2). Making more ATP means releasing more heat; so the temperature in active tissues increases. More CO2 translates into a lower pH. That is so because this reaction occurs when CO2 is released:

$$CO2 + H20 \text{ -----> } H2CO3 \text{ -----> } HCO3^- + H^+$$

& more hydrogen ions = a lower (more acidic) pH. So, in active tissues, there are higher levels of CO2, a lower pH, and higher temperatures. In addition, at lower PO2 levels, red blood cells increase production of a substance called 2,3-diphosphoglycerate. These changing conditions (more CO2, 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. Another way of saying this is that the oxygen-hemoglobin dissociation curve 'shifts to the right' (as shown with the light blue curve in the graph below). This means that at a given partial pressure of oxygen, the percent saturation for hemoglobin with be lower. For example, in the graph below, extrapolate up to the 'normal' curve (green curve) from a PO2 of 40, then over, & the hemoglobin saturation is about 75%. Then, extrapolate up to the 'right-shifted' (light blue) curve from a PO2 of 40, then over, & the hemoglobin saturation is about 60%. So, a 'shift to the right' in the oxygen-hemoglobin dissociation curve (shown above) means that more oxygen is being released by hemoglobin - just what's needed by the cells in an active tissue!

Carbon dioxide - transported from the body cells back to the lungs as:

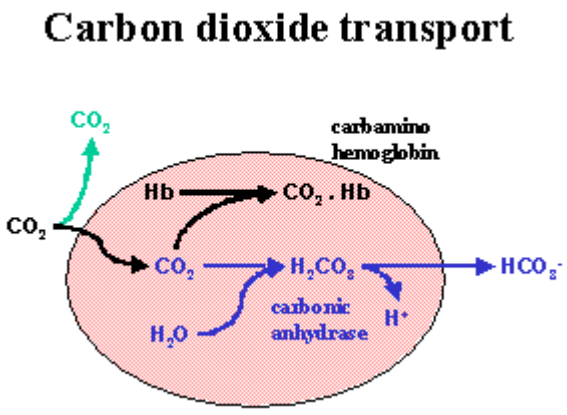
1 - bicarbonate (HCO3) - 60%

- formed when CO2 (released by cells making ATP) combines with H2O (due to the enzyme in red blood cells called carbonic anhydrase) as shown in the diagram below

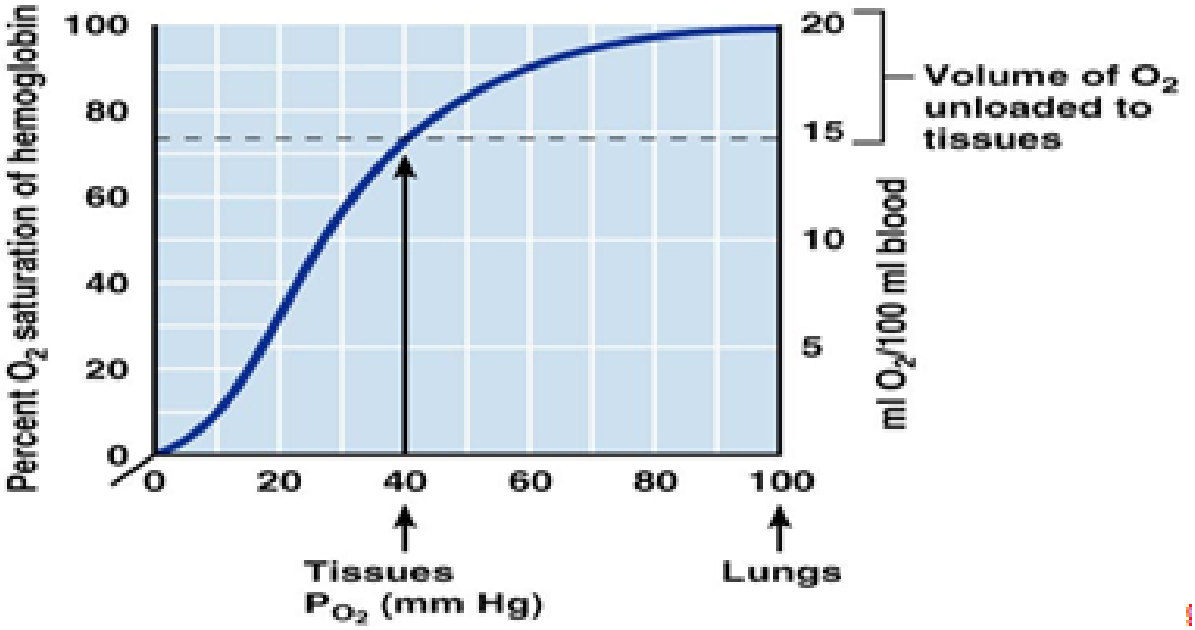
2 - carbaminohemoglobin - 30%

- formed when CO2 combines with hemoglobin (hemoglobin molecules that have given up their oxygen)

3 - dissolved in the plasma - 10%



Hemoglobin Saturation Curve



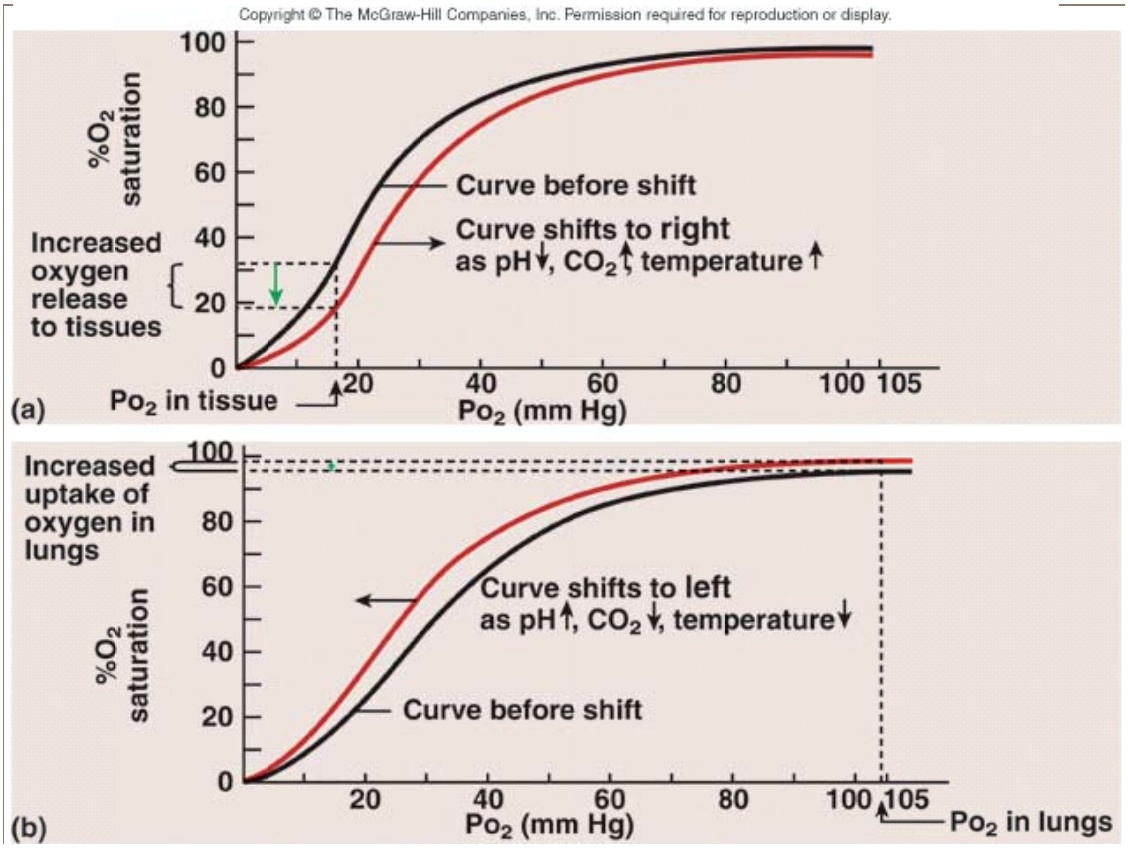
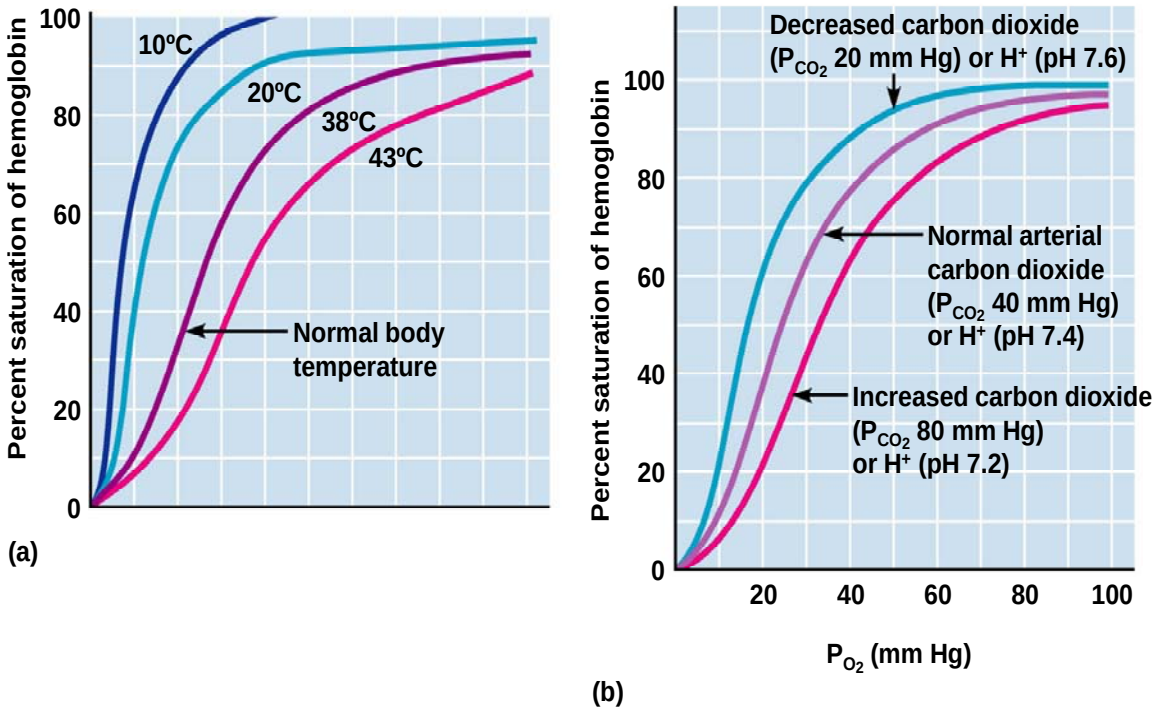


Figure 22.21: Effect of temperature, P_{CO_2}, and blood pH on the oxygen-hemoglobin dissociation curve, p. 860.



Human Anatomy and Physiology, 7e
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Gas Exchange and Oxygen Transport

A. Partial pressure equals the total pressure times the fractional gas concentration.

B. Assuming that total pressure is atmospheric (760 mm Hg) and the fractional concentration of O2 is 0.21, then

Po2 = 0.21 × 760 = 160 mm Hg

C. The **partial pressure** of humidified inspired air is calculated as follows:

$$PI\ \text{gas} = F\ \text{gas}\ (P\text{atm} - P\text{H2O}),$$

where

*P*atm = atmospheric pressure

PI gas = partial pressure of inspired gas

*P*H2O = partial pressure of H2O vapor

F gas = concentration of gas

The partial pressure of H2O at 37° is 47 mm Hg. Thus,

$$P_{I}o2 = 0.21\ (760 - 47) = 150 \text{ mm Hg}$$

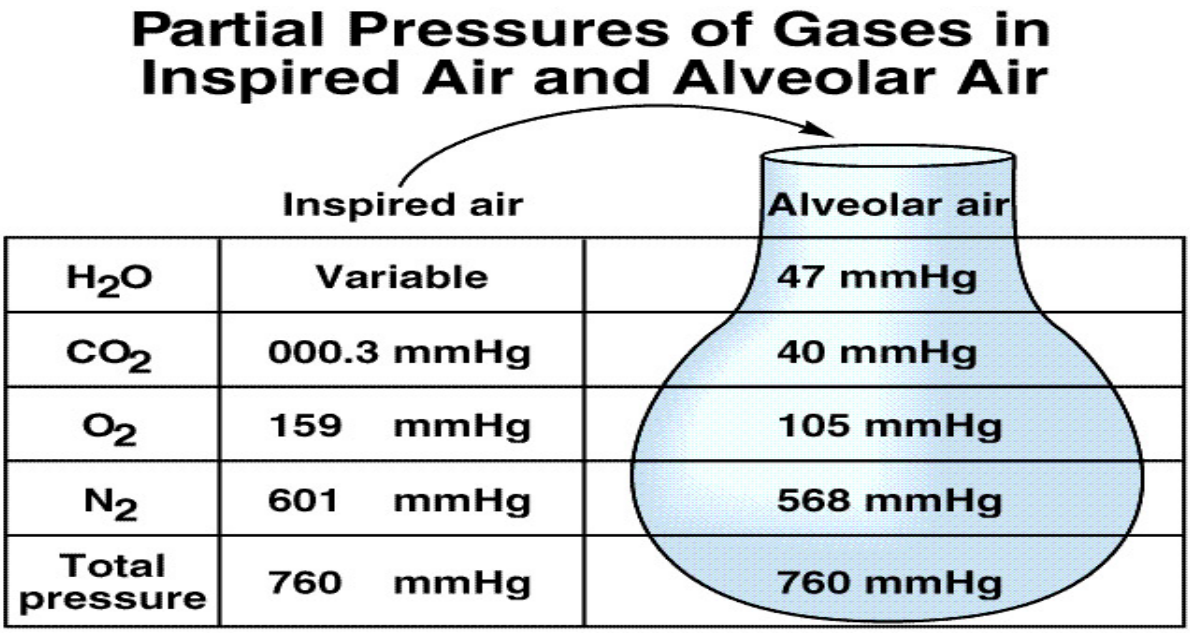
D. Because 2% of cardiac output bypasses the pulmonary circulation via a **physiologic shunt,** the PO2 of arterial blood is lower than that of alveolar air.

E. Physically dissolved oxygen (**O2**) consists of free O2 molecules in solution. O2 is also carried in blood bound to **hemoglobin** (**Hb**).

F. The amount of physically dissolved O2 is directly proportional to the **PO2.**

The units of concentration for a dissolved gas are mL gas per 100 mL blood.

G. At body temperature, blood equilibrated with a normal PO2 (~ 100 mm Hg) contains only 0.3 mL O2/100 mL blood (0.3 vol%), which is not enough to supply the needs of the tissues.



H. Saturation is the percentage of Hb-binding sites occupied by O2.

1. Each gram of Hb has an oxygen capacity of 1.34 mL O2, and because 100 mL of blood contains 15 g Hb, completely oxygenated blood contains approximately 20 mL O2 (1.34 mL O2 × 15 g Hb/100 mL).

2. Thus, the oxygen capacity of Hb in blood is approximately 20 mL O2/100 mL of blood or 20 vol%.

3. Each Hb molecule contains four subunits: two have α chains and two have β chains.

I. Physiologic implications of the **oxyhemoglobin dissociation curve** include the following

1. Hb combines rapidly and reversibly **with O2 to form oxyhemoglobin.**

2. The saturation curve has a sigmoid shape because oxygenation of the first heme group of the Hb molecule increases the affinity of O2 for the other heme group

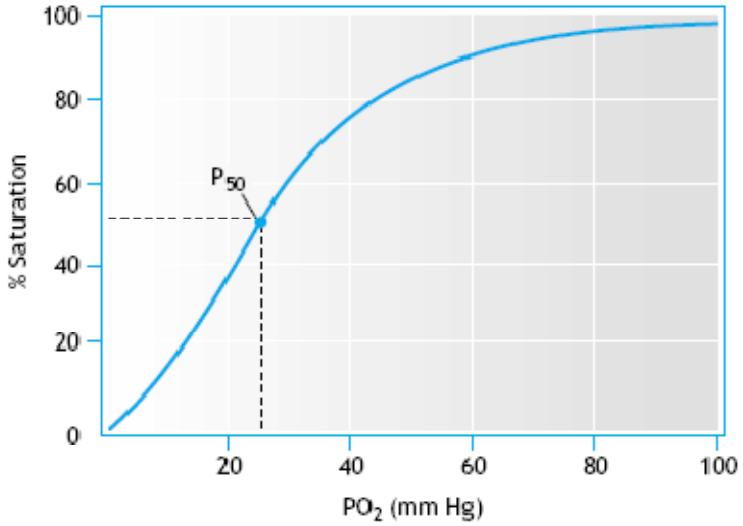


Figure 3–5. Saturation versus partial pressure. Each saturation curve has a single P_{50}, which is the P_{O_2} that gives 50% saturation. Normal P_{50} = 26 mm Hg.

Gas Exchange
In a mixture of different gases, each gas contributes to the total pressure of the mixture. The contribution of each gas, called the partial pressure, is equal to the pressure that the gas would have if it were alone in the enclosure. **Dalton's law** states that the sum of the partial pressures of each gas in a mixture is equal to the total pressure of the mixture.
The following factors determine the degree to which a gas will dissolve in a liquid:
• *The partial pressure of the gas.* According to **Henry's law,** the greater the partial pressure of a gas, the greater the diffusion of the gas into the liquid. • *The solubility of the gas.* The ability of a gas to dissolve in a liquid varies with the kind of gas and the liquid. • *The temperature of the liquid.* Solubility decreases with increasing temperature. Gas exchange occurs in the lungs between alveoli and blood plasma and throughout the body between plasma and interstitial fluids. The following factors facilitate diffusion of O_2 and CO_2 at these sites: • *Partial pressures and solubilities.* Poor solubility can be offset by a high partial pressure (or vice versa). Compare the following characteristics of O_2 and CO_2: o Oxygen. The partial pressure of O_2 in the lungs is high (air is 21% O_2), but is solubility poor. o Carbon dioxide. The partial pressure of CO_2 in air is extremely low (air is only 0.04% CO_2),

but its solubility in plasma is about 24 times that of O_2.

- *Partial pressure gradients.* A gradient is a change in some quantity from one region to another. Diffusion of a gas into a liquid (or the reverse) occurs down a partial pressure gradient-that is, from a region of higher partial pressure to a region of lower partial pressure. For example, the strong partial pressure gradient for O_2 (pO_2) from alveoli to deoxygenated blood (105 mm Hg in alveoli versus 40 mm Hg in blood) facilitates rapid diffusion.
- *Surface area for gas exchange.* The expansive surface area of the lungs promotes extensive diffusion.
- *Diffusion distance.* Thin alveolar and capillary walls increase the rate of diffusion.

Gas Transport

Oxygen is transported in the blood in two ways:

- A small amount of O_2 (1.5 percent) is carried in the plasma as a dissolved gas.
- Most oxygen (98.5 percent) carried in the blood is bound to the protein hemoglobin in red blood cells. A fully saturated oxyhemoglobin (HbO_2) has four O_2 molecules attached. Without oxygen, the molecule is referred to as deoxygemoglobin (Hb).

The ability of hemoglobin to bind to O_2 is influenced by the partial pressure of oxygen. The greater the partial pressure of oxygen in the blood, the more readily oxygen binds to Hb. The oxygen-hemoglobin dissociation curve, shown in Figure 1 , shows that as pO_2 increases toward 100 mm Hg, Hb saturation approaches 100%. The following four factors decrease the affinity, or strength of attraction, of Hb for O_2 and result in a shift of the O_2-Hb dissociation curve to the right:

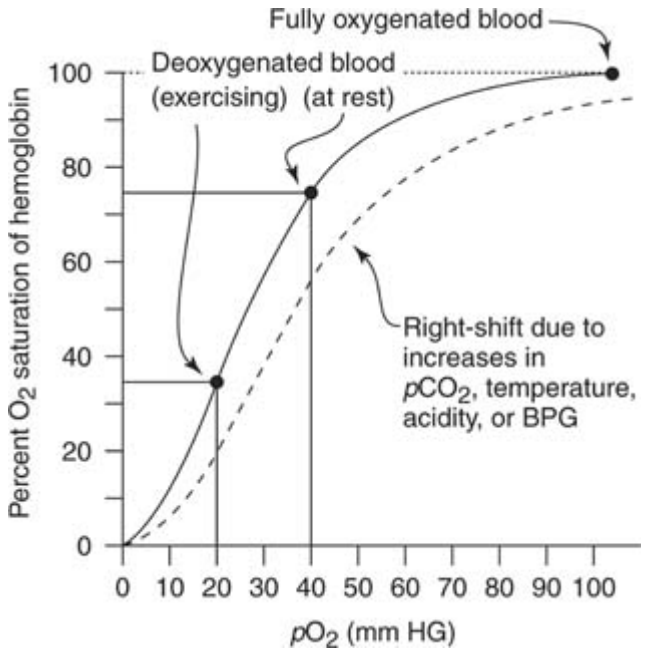


Figure 1 The oxygen-hemoglobin dissociation curve.

- Increase in temperature.
- Increase in partial pressure of CO_2 (pCO_2).
- Increase in acidity (decrease in pH). The decrease in affinity of Hb for O_2, called the Bohr effect,

results when H+ binds to Hb.
- Increase in BPG in red blood cells. BPG (bisphosphoglycerate) is generated in red blood cells when they produce energy from glucose.

Carbon dioxide is transported in the blood in the following ways.

- A small amount of CO_2 (8 percent) is carried in the plasma as a dissolved gas.
- Some CO_2 (25 percent) binds to Hb in red blood cells forming carbaminohemoglobin ($HbCO_2$). (The CO_2 binds to a place different from that of O_2.)
- Most CO_2 (65 percent) is transported as dissolved bicarbonate ions (HCO_3-) in the plasma. The formation of HCO_3-, however, occurs in the red blood cells, where the formation of carbonic acid (H_2CO_3-) is catalyzed by the enzyme carbonic anhydrase, as follows.

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

Following their formation in the red blood cells, most H+ bind to hemoglobin molecules(causing the Bohr effect) while the remaining H+ diffuse back into the plasma, slightly decreasing the pH of the plasma. The HCO_3- ions diffuse back into the plasma as well. To balance the overall increase in negative charges entering the plasma, chloride ions diffuse in the opposite direction, from the plasma to the red blood cells (chloride shift).

Control of Respiration

Respiration is controlled by these areas of the brain that stimulate the contraction of the diaphragm and the intercostal muscles. These areas, collectively called respiratory centers, are summarized here:

- The medullary inspiratory center, located in the medullar oblongata, generates rhythmic nerve impulses that stimulate contraction of the inspiratory muscles (diaphragm and external intercostal muscles). Normally, expiration occurs when these muscles relax, but when breathing is rapid, the inspiratory center facilitates expiration by stimulating the expiratory muscles (internal intercostal muscles and abdominal muscles).
- The pheumotaxic area, located in the pons, inhibits the inspiratory center, limiting the contraction of the inspiratory muscles, and preventing the lungs from overinflating.
- The apneustic area, also located in the pons, stimulates the inspiratory center, prolonging the contraction of inspiratory muscles.

The respiratory centers are influenced by stimuli received from the following three groups of sensory neurons:

- Central chemoreceptors (nerves of the central nervous system), located in the medulla oblongata, monitor the chemistry of cerebrospinal fluid. When CO_2 from the plasma enters the cerebrospinal fluid, it forms HCO_3- and H+, and the pH of the fluid drops (becomes more acidic). In response to the decrease in pH, the central chemoreceptors stimulate the respiratory center to increase the inspiratory rate.
- Peripheral chemoreceptors (nerves of the peripheral nervous system), located in aortic bodies in the wall of the aortic arch and in carotid bodies in the walls of the carotid arteries, monitor the chemistry of the blood. An increase in pH or pCO_2, or decrease in pO_2, causes these receptors to stimulate the respiratory center.
- Stretch receptors in the walls of bronchi and bronchioles are activated when the lungs expand to their physical limit. These receptors signal the respiratory center to discontinue stimulation of the inspiratory muscles, allowing expiration to begin. This response is called the inflation (Hering-Breur) reflex.

3. The **O2 capacity** is the maximum amount of O2 that can be bound to Hb and is determined by the Hb concentration in blood.

4. The **O2 content** is the total amount of O2 carried in the blood whether bound or dissolved in solution.

5. Figure 3–6 shows the **dissociation curve** as a function of partial pressure for two different amounts of Hb. The Hb concentration in normal blood is about 15 g/100 mL. The maximal amount of O2/100 mL (98% saturation) in combination with Hb is 20.1 mL O2/100 mL (1.34 mL × 15). The

amount of dissolved O2 is a linear function of the PO2 (0.003 mL/100 mL blood/mm Hg PO2).

a. In curve A, the total amount of O2 bound to Hb at 98% saturation is 19.7 mL O2/100 mL blood. With the 0.3 mL/100 mL of dissolved O2 added, the total O2 content is approximately 20 mL O2/100 mL of blood.

b. In curve B, the Hb is also 98% saturated, but this blood contains only 7.5 g Hb/100 mL blood. The total amount of O2 bound to Hb is only 10 mL O2/100 mL blood. Because of the lower amount of Hb, the amount of O2 is about half that of normal blood.

J. Several factors influence the oxyhemoglobin dissociation curve

1. Shifts to the right occur when the affinity of Hb-binding sites for O2 is decreased and it is easier for tissues to extract oxygen.

a. Causes of this shift include increased CO2 (Bohr effect), increased H+ (decreased pH), increased temperature, and increased 2,3-diphosphoglycerate (2,3-DPG).

b. Anemia is characterized by a reduced Hb concentration in blood and decreased arterial oxygen content.

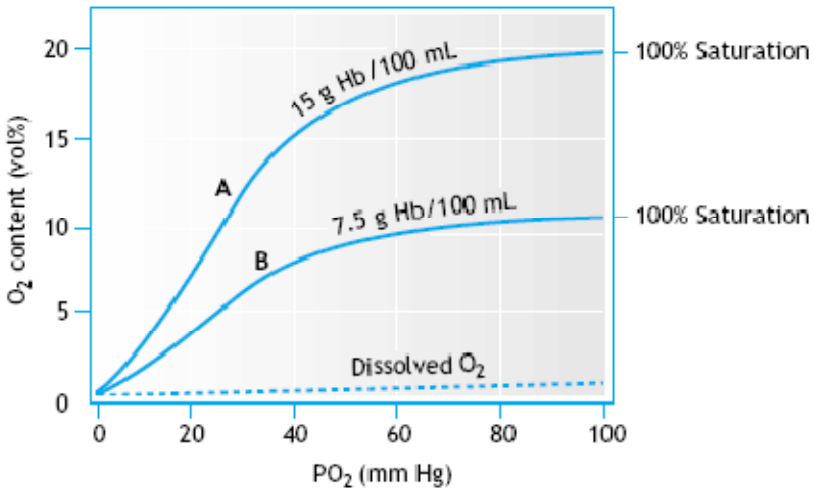


Figure 3–6. O_2 content versus partial pressure for two different hemoglobin (Hb) concentrations. Curve A represents normal Hb levels in blood (15 g/100 mL). Curve B represents a reduced concentration of Hb in blood (7.5 g/100 mL). The main effect of the lower Hb concentration is a reduced carrying capacity of the blood. Thus, in curve B, the total amount of O_2/100 mL of blood is around 10 mL O_2/100 mL, instead of the normal 20 mL O_2/100 mL.

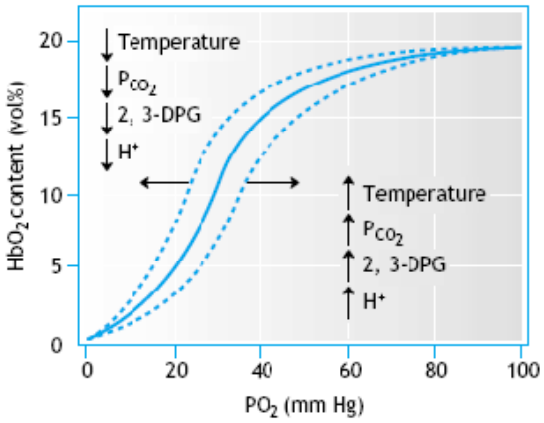


Figure 3–7. Changes in affinity of hemoglobin (Hb) for O_2 (oxyhemoglobin dissociation curve).

2. Shifts to the left occur when there is increased affinity of Hb for O2 and it is

more difficult for tissues to extract oxygen.

a. Causes of this shift include decreased temperature, decreased PCO2, decreased H+ (increased pH), and decreased 2,3-DPG.

b. Stored blood loses 2,3-DPG and fetal Hb, and both decreases **shift the curve to the left.**

c. Polycythemia (increased number of red blood cells in blood) is characterized by a higher than normal concentration of Hb in the blood, a shift to the left in the oxyhemoglobin dissociation curve, and increased arterial oxygen content.

Carbon Dioxide Transport

A. CO_2 is an important end product of aerobic cellular metabolism and is, therefore, continuously produced by body tissues.

B. After formation, CO_2 diffuses into the venous plasma, where it is 24 times more soluble than O_2 and then passes immediately into red blood cells.

C. CO_2 is carried in the plasma in three forms:

1. Five percent is dissolved CO_2, which is free in solution.

2. Five percent is in the form of carbaminohemoglobin, which is CO_2 bound to hemoglobin.

3. Ninety percent is in the form of bicarbonate from reaction with H_2O to form carbonic acid in the red blood cells, which dissociates into hydrogen and bicarbonate.

D. Bicarbonate leaves the red blood cells in exchange for chloride (called a **chloride shift**) to maintain electrical neutrality and is transported to the lungs

E. Inside the red blood cell, deoxyhemoglobin is a better buffer for H^+, and H^+ binding by deoxygenated Hb occurs in peripheral tissues where CO_2 is high.

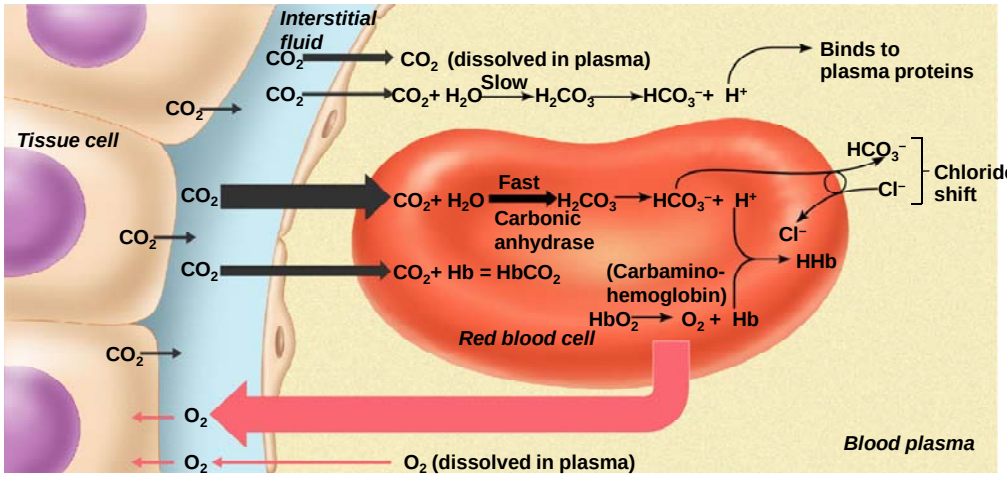
F. The enhancement of CO_2 binding to deoxygenated Hb at the venous end of capillaries leads to the formation of bicarbonate in red blood cells.

G. In the lung, the reaction in the pulmonary capillaries is in the opposite direction:

- O_2 is taken up by the red blood cells, CO_2 is released to the alveolus for expiration, and HCO_3^- enters the red blood cells in exchange for Cl^- and combines with H^+ to form H_2CO_3.

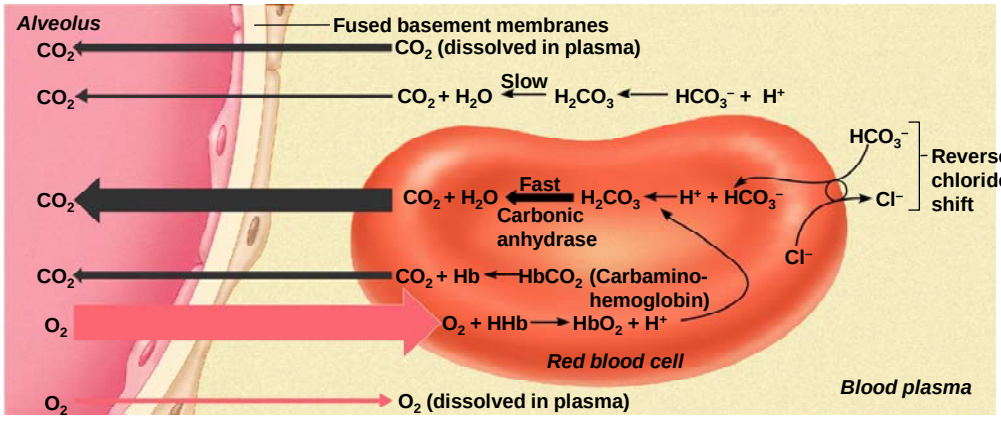
H. In summary, CO_2 entering the red blood cells causes a decreased pH that facilitates O_2 release. In lungs, O_2 binding to Hb lowers the CO_2 capacity of blood by lowering the amount of H^+ bound to Hb.

Figure 22.22a: Transport and exchange of CO_2 and O_2, p. 862.

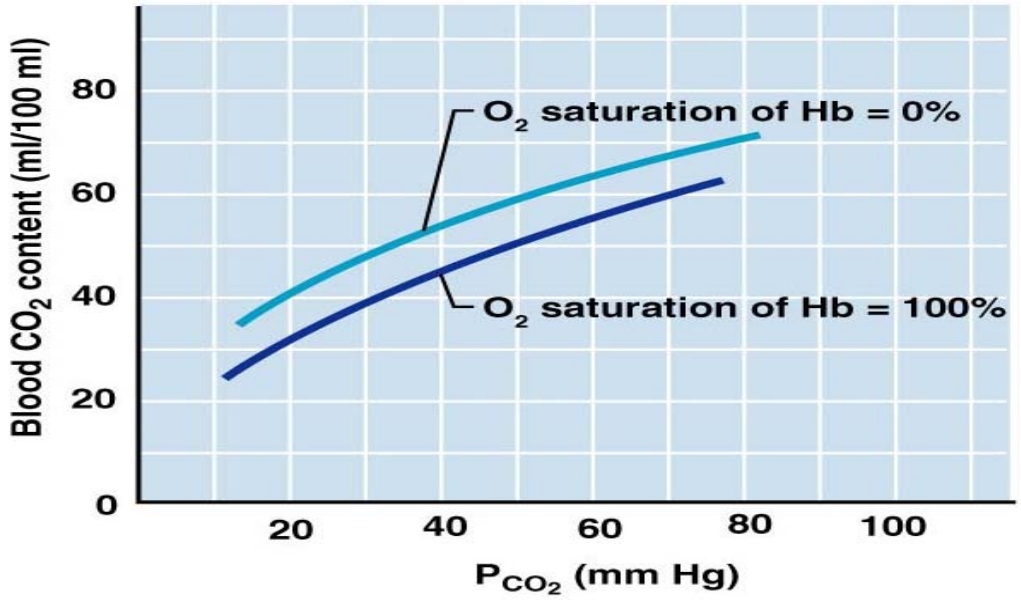


(a) Oxygen release and carbon dioxide pickup at the tissues

Figure 22.22b: Transport and exchange of CO_2 and O_2, p. 862.



(b) Oxygen pickup and carbon dioxide release in the lungs



Hemoglobin (Hb)

- Saturated hemoglobin – when all four hemes of the molecule are bound to oxygen
- Partially saturated hemoglobin – when one to three hemes are bound to oxygen
- The rate that hemoglobin binds and releases oxygen is regulated by:
  - P_{O2}, temperature, blood pH, P_{CO2}, and the concentration of BPG (an organic chemical)
    - These factors ensure adequate delivery of oxygen to tissue cells

Influence of P_{O2} on Hemoglobin Saturation

- Hemoglobin saturation plotted against P_{O2} produces a oxygen-hemoglobin dissociation curve
- 98% saturated arterial blood contains 20 ml oxygen per 100 ml blood (20 vol %)
- As arterial blood flows through capillaries, 5 ml oxygen are released
- The saturation of hemoglobin in arterial blood explains why breathing deeply increases the P_{O2} but has little effect on oxygen saturation in hemoglobin

Hemoglobin Saturation Curve

- Hemoglobin is almost completely saturated at a P_{O2} of 70 mm Hg
- Further increases in P_{O2} produce only small increases in oxygen binding
- Oxygen loading and delivery to tissue is adequate when P_{O2} is below normal levels
- Only 20–25% of bound oxygen is unloaded during one systemic circulation
- If oxygen levels in tissues drop:
  - More oxygen dissociates from hemoglobin and is used by cells
  - Respiratory rate or cardiac output need not increase

Other Factors Influencing Hemoglobin Saturation

- Temperature, H^+, P_{CO2}, and BPG
  - Modify the structure of hemoglobin and alter its affinity for oxygen
  - Increases of these factors:
    - Decrease hemoglobin's affinity for oxygen
    - Enhance oxygen unloading from the blood
  - Decreases act in the opposite manner
- These parameters are all high in systemic capillaries where oxygen unloading is the goal

Factors That Increase Release of Oxygen by Hemoglobin

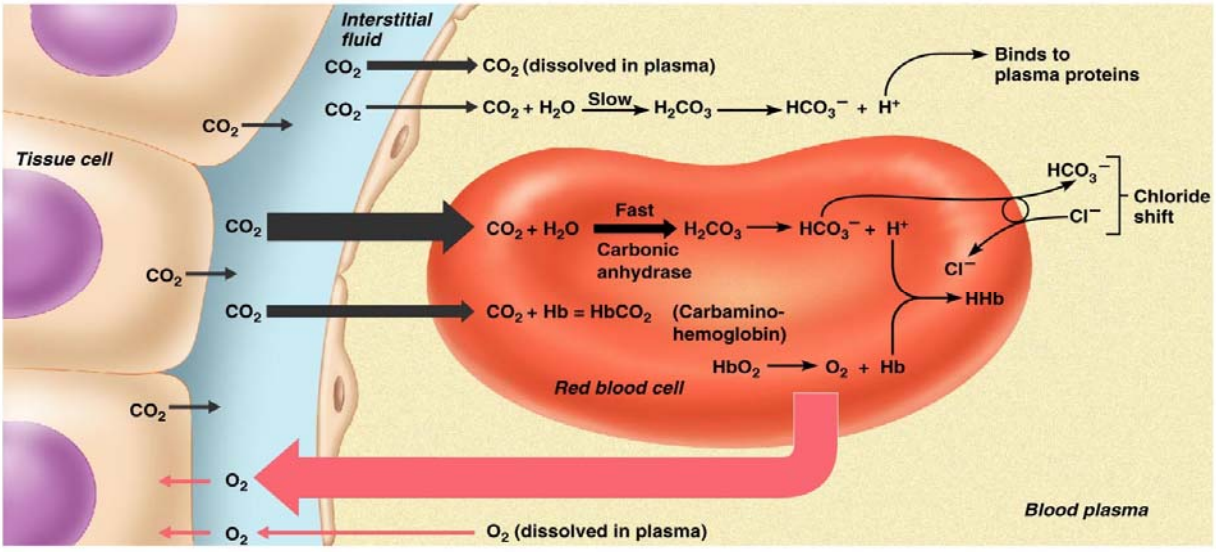
- As cells metabolize glucose, carbon dioxide is released into the blood causing:
  - Increases in P_{CO2} and H^+ concentration in capillary blood
  - Declining pH (acidosis), which weakens the hemoglobin-oxygen bond (Bohr effect)
- Metabolizing cells have heat as a byproduct and the rise in temperature increases BPG synthesis
- All these factors ensure oxygen unloading in the vicinity of working tissue cells

Hemoglobin-Nitric Oxide Partnership

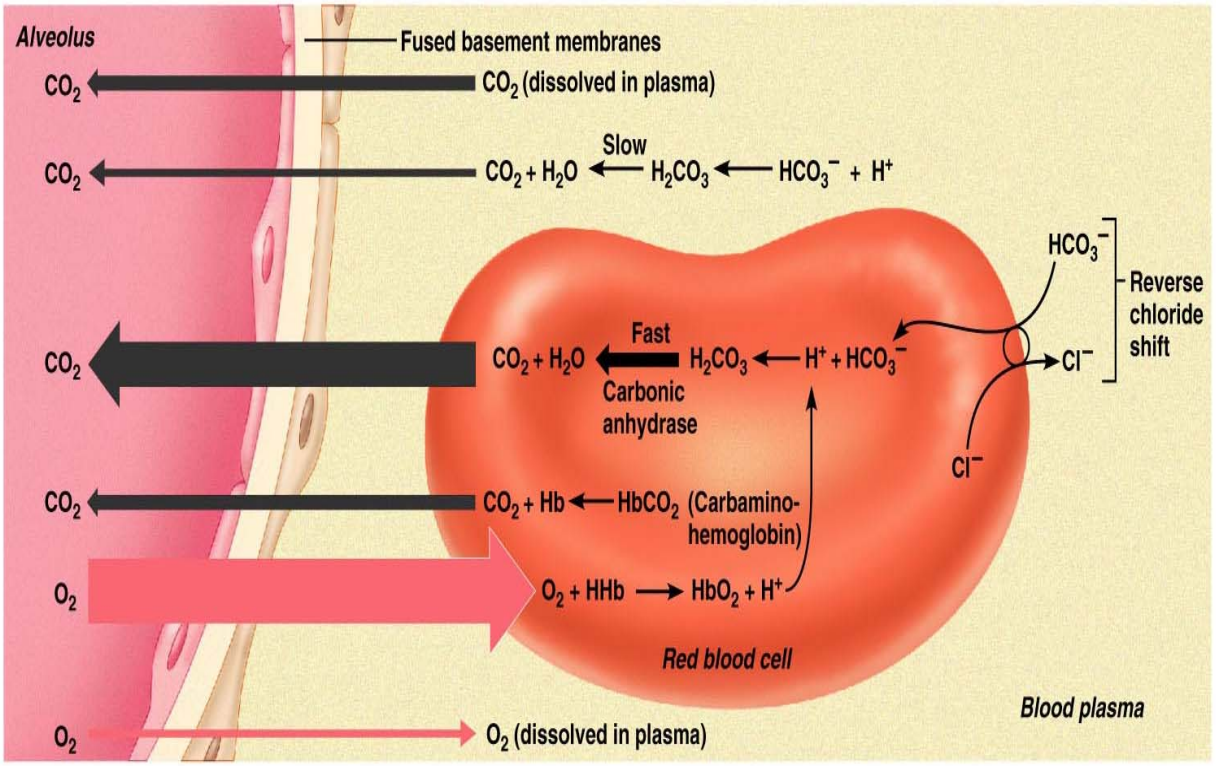
- Nitric oxide (NO) is a vasodilator that plays a role in blood pressure regulation
- Hemoglobin is a vasoconstrictor and a nitric oxide scavenger (heme destroys NO)
- However, as oxygen binds to hemoglobin:
  - Nitric oxide binds to a cysteine amino acid on hemoglobin
  - Bound nitric oxide is protected from degradation by hemoglobin's iron
- The hemoglobin is released as oxygen is unloaded, causing vasodilation
- As deoxygenated hemoglobin picks up carbon dioxide, it also binds nitric oxide and carries these gases to the lungs for unloading

Carbon Dioxide Transport

- Carbon dioxide is transported in the blood in three forms
  - Dissolved in plasma – 7 to 10%
  - Chemically bound to hemoglobin – 20% is carried in RBCs as carbaminohemoglobin
  - Bicarbonate ion in plasma – 70% is transported as bicarbonate (HCO_3^-)



(a) Oxygen release and carbon dioxide pickup at the tissues

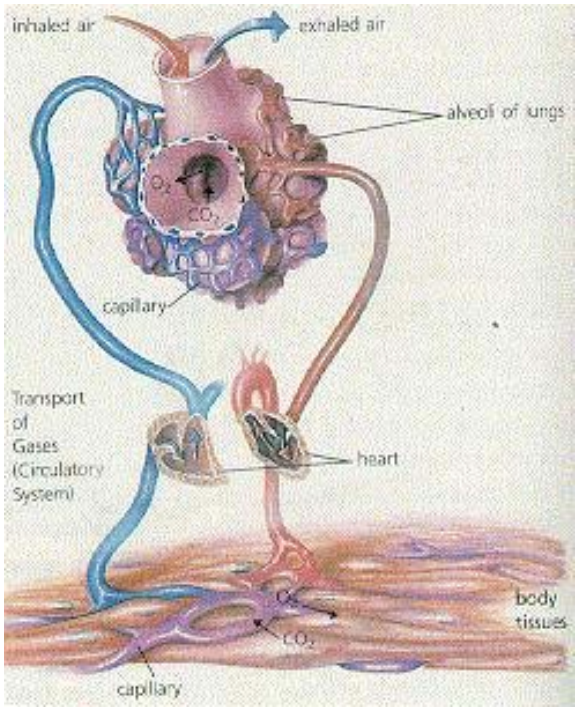


(b) Oxygen pickup and carbon dioxide release in the lungs

Carbon Dioxide Diffusion Gradients

- CO_2 is continually produced as a byproduct of cellular respiration and a diffusion gradient is established from tissue cells to the blood within the tissue capillaries.
    - Intracellular pCO_2 is about 46 mm Hg whereas that in the interstitial fluid is about 45 mm Hg.
    - At the arteriolar end of the tissue capillaries the pCO_2 is close to 40 mm Hg.

- After blood leaves the venous end of the capillaries, it is transported to the lungs



Transport and Exchange of Gases--Hemoglobin and Its Function *Hemoglobin*

- Oxygen is relatively insoluble in blood plasma; only about 0.3 mL of O_2 will dissolve in 100 mL of plasma. at normal atmospheric pressure.
- Hemoglobin is the respiratory pigment of humans.
- Hemoglobin is made up of four (4) subunits each of which comprises a heme unit and a polypeptide chain.
- The heme unit consists of a porphyrin ring with one atom of iron (Fe) at its center.
    - The Fe in each heme unit can unite with one molecule of O_2, thus each hemoglobin molecule can carry four molecules of O_2.
    - The O_2 molecules are added one at a time:
        - $Hb_4 + O_2 \; Hb_4O_2$
        - $Hb_4O_2 + O_2 \; Hb_4O_4$
        - $Hb_4O_4 + O_2 \; Hb_4O_6$
        - $Hb_4O_6 + O_2 \; Hb_4O_8$
    - The combination of the first subunit of Hb with O_2 increases the affinity of the second and oxygenation of the second increases the affinity of the third, etc.
- Whether O_2 combines with hemoglobin or is released from it depends on the pO_2 in the surrounding blood plasma.
- O_2 diffuses from the air into the alveolar capillaries.
    - In the capillaries where the pO_2 is high, most of the hemoglobin is combined with O_2.
    - In the tissues where the pO_2 is lower, O_2 is released from the hemoglobin molecules and diffuses into the tissues.
    - The system compensates automatically for the O_2 requirements of the tissues.
    - In adult humans: **OH-T110- O_2 and CO_2 Diffusion Gradients**
        - The pO_2 as the blood leaves the lungs is about 95 mm Hg.
            - At this pressure, the hemoglobin is saturated with O_2.

- As the hemoglobin molecules move through the tissue capillaries, the pO_2 drops, and as it drops the oxygen bound to the hemoglobin molecules is given up.

Transport and Exchange of Carbon Dioxide

- Carbon dioxide diffuses into RBCs and combines with water to form carbonic acid (H_2CO_3), which quickly dissociates into hydrogen ions and bicarbonate ions
- In RBCs, carbonic anhydrase reversibly catalyzes the conversion of carbon dioxide and water to carbonic acid
- At the tissues:
  - Bicarbonate quickly diffuses from RBCs into the plasma
  - The chloride shift – to counterbalance the outrush of negative bicarbonate ions from the RBCs, chloride ions (Cl^-) move from the plasma into the erythrocytes
- At the lungs, these processes are reversed
  - Bicarbonate ions move into the RBCs and bind with hydrogen ions to form carbonic acid
  - Carbonic acid is then split by carbonic anhydrase to release carbon dioxide and water
  - Carbon dioxide then diffuses from the blood into the alveoli

Transport of CO_2 *Chloride Shift*

- CO_2 is transports in the blood in three (3) major ways.
  - Approximately 8% is transports as CO_2 dissolved in plasma.
  - Approximately 20% is transported in combination with blood proteins (including hemoglobin).
  - 72% is transports as HCO_3.
- Blood proteins that bind to CO_2 are called **carbamino compounds**.
  - The most abundant protein to bind to CO_2 is hemoglobin and when CO_2 is bound to hemoglobin, the combination is called **carbaminohemoglobin**.
    - The CO_2 binds to globin and each globin molecule can combine with a single CO_2 molecule.
- Hemoglobin that has released its O_2 binds more readily to CO_2 than hemoglobin that has O_2 bound to it--**Haldane Effect**.
  - In tissues, after hemoglobin has released O_2, the hemoglobin has an increased ability to pick up CO_2.
  - In the lungs, as hemoglobin binds to O_2. the hemoglobin more readily releases CO_2.
- CO_2 diffuses into red blood cells where some of the CO_2 binds to hemoglobin, but most of the CO_2 reacts with H_2O to form H_2CO_3, a reaction that is catalyzed by **carbonic anhydrase** inside the red blood cell.
  - The H_2CO_3 ionizes to form H and HCO_3 ions.
- As a result of the above reactions, a higher concentration of HCO_3 is inside the cell than outside, and the HCO_3 readily diffuses out of the red blood cells into the plasma.
  - In response to this movement of negatively charged ions out of the red blood cells, negatively charged Cl ions move into the red blood cells from the plasma maintaining the electrical balance inside and outside the red blood cells.
- The exchange of Cl ions for HCO_3 ions across the cells' membranes is called the **chloride shift**.
- The H formed by the ionization of H_2CO_3 bind to the hemoglobin of the red blood cells.
  - This prevents the H ions from leaving the cells and increasing the [H] in the plasma.

Haldane Effect

- The amount of carbon dioxide transported is markedly affected by the P_{O2}
- Haldane effect – the lower the P_{O2} and hemoglobin saturation with oxygen, the more carbon dioxide can be carried in the blood
- At the tissues, as more carbon dioxide enters the blood:
  - More oxygen dissociates from hemoglobin (Bohr effect)
  - More carbon dioxide combines with hemoglobin, and more bicarbonate ions are formed
- This situation is reversed in pulmonary circulation

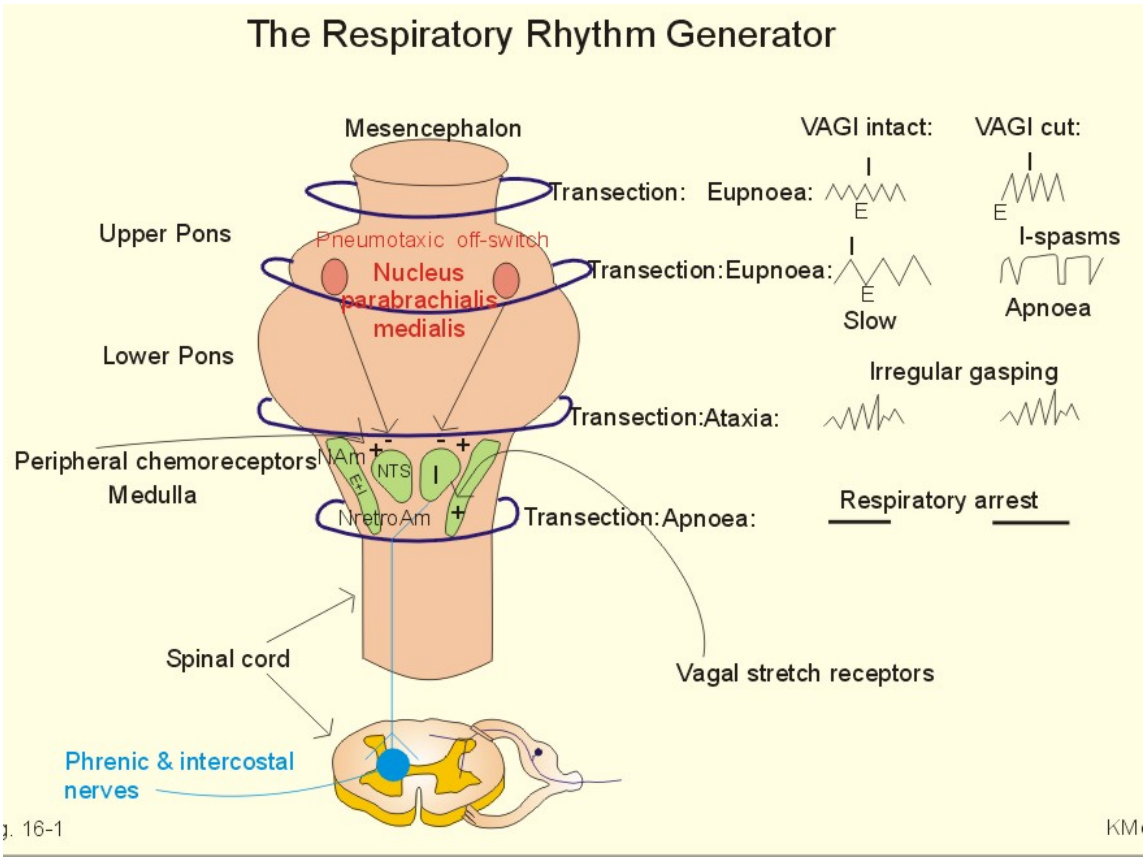
Influence of Carbon Dioxide on Blood pH

- The carbonic acid–bicarbonate buffer system resists blood pH changes
- If hydrogen ion concentrations in blood begin to rise, excess H^+ is removed by combining with HCO_3^-
- If hydrogen ion concentrations begin to drop, carbonic acid dissociates, releasing H^+
- Changes in respiratory rate can also:
  - Alter blood pH
  - Provide a fast-acting system to adjust pH when it is disturbed by metabolic factors

Control of Respiration:

Medullary Respiratory Centers

- The dorsal respiratory group (DRG), or inspiratory center:
  - Is located near the root of nerve IX
  - Appears to be the pacesetting respiratory center
  - Excites the inspiratory muscles and sets eupnea (12-15 breaths/minute)
  - Becomes dormant during expiration
- The ventral respiratory group (VRG) is involved in forced inspiration and expiration



Pons Respiratory Centers

- Pons centers:
  - Influence and modify activity of the medullary centers
  - Smooth out inspiration and expiration transitions and vice versa
- The pontine respiratory group (PRG) – continuously inhibits the inspiration center

Respiratory Rhythm

- A result of reciprocal inhibition of the interconnected neuronal networks in the medulla
- Other theories include
  - Inspiratory neurons are pacemakers and have intrinsic automaticity and rhythmicity
  - Stretch receptors in the lungs establish respiratory rhythm

Depth and Rate of Breathing

- Inspiratory depth is determined by how actively the respiratory center stimulates the respiratory muscles
- Rate of respiration is determined by how long the inspiratory center is active
- Respiratory centers in the pons and medulla are sensitive to both excitatory and inhibitory stimuli

Depth and Rate of Breathing: Reflexes

- Pulmonary irritant reflexes – irritants promote reflexive constriction of air passages
- Inflation reflex (Hering-Breuer) – stretch receptors in the lungs are stimulated by lung inflation
- Upon inflation, inhibitory signals are sent to the medullary inspiration center to end inhalation and allow expiration

Depth and Rate of Breathing: Higher Brain Centers

- Hypothalamic controls act through the limbic system to modify rate and depth of respiration
  - Example: breath holding that occurs in anger
- A rise in body temperature acts to increase respiratory rate
- Cortical controls are direct signals from the cerebral motor cortex that bypass medullary controls
  - Examples: voluntary breath holding, taking a deep breath

Depth and Rate of Breathing: P_{CO2}

- Changing P_{CO2} levels are monitored by chemoreceptors of the brain stem
- Carbon dioxide in the blood diffuses into the cerebrospinal fluid where it is hydrated
- Resulting carbonic acid dissociates, releasing hydrogen ions
- P_{CO2} levels rise (hypercapnia) resulting in increased depth and rate of breathing

- Hyperventilation – increased depth and rate of breathing that:
  - Quickly flushes carbon dioxide from the blood
  - Occurs in response to hypercapnia
- Though a rise CO_2 acts as the original stimulus, control of breathing at rest is regulated by the hydrogen ion concentration in the brain

- Hypoventilation – slow and shallow breathing due to abnormally low P_{CO2} levels
  - Apnea (breathing cessation) may occur until P_{CO2} levels rise
- Arterial oxygen levels are monitored by the aortic and carotid bodies
- Substantial drops in arterial P_{O2} (to 60 mm Hg) are needed before oxygen levels become a major stimulus for increased ventilation
- If carbon dioxide is not removed (e.g., as in emphysema and chronic bronchitis), chemoreceptors become unresponsive to P_{CO2} chemical stimuli
- In such cases, P_{O2} levels become the principal respiratory stimulus (hypoxic drive)

Depth and Rate of Breathing: Arterial pH

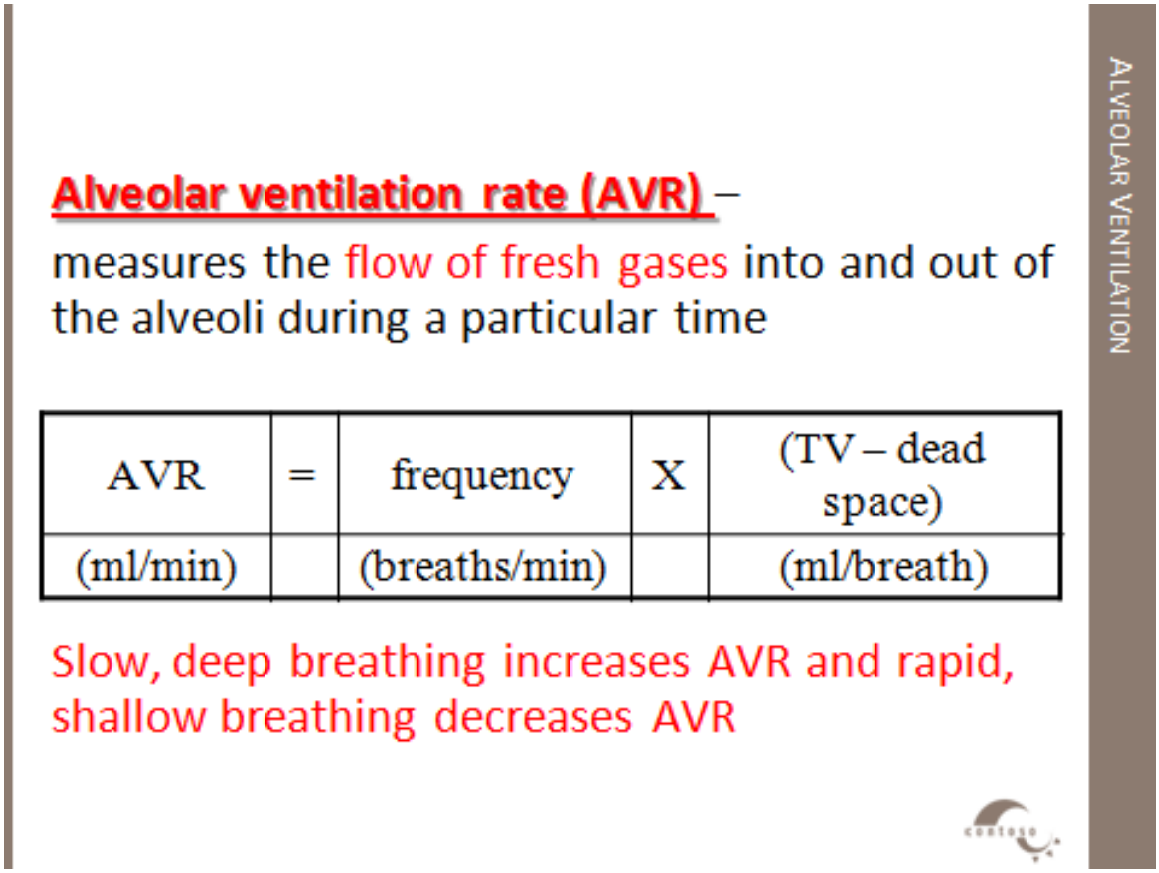
- Changes in arterial pH can modify respiratory rate even if carbon dioxide and oxygen levels are normal
- Increased ventilation in response to falling pH is mediated by peripheral chemoreceptors

Acidosis may reflect:
- Carbon dioxide retention
- Accumulation of lactic acid
- Excess fatty acids in patients with diabetes mellitus

- Respiratory system controls will attempt to raise the pH by increasing respiratory rate and depth

Respiratory Adjustments: Exercise

- Respiratory adjustments are geared to both the intensity and duration of exercise
- During vigorous exercise:
  - Ventilation can increase 20 fold
  - Breathing becomes deeper and more vigorous, but respiratory rate may not be significantly changed (hyperpnea)
- Exercise-enhanced breathing is not prompted by an increase in P_{CO2} or a decrease in P_{O2} or pH
  - These levels remain surprisingly constant during exercise
- As exercise begins:
  - Ventilation increases abruptly, rises slowly, and reaches a steady state
- When exercise stops:
  - Ventilation declines suddenly, then gradually decreases to normal



- Neural factors bring about the above changes, including:

- Psychic stimuli
- Cortical motor activation
- Excitatory impulses from proprioceptors in muscles

Respiratory Adjustments: High Altitude

- The body responds to quick movement to high altitude (above 8000 ft) with symptoms of acute mountain sickness – headache, shortness of breath, nausea, and dizziness
- Acclimatization – respiratory and hematopoietic adjustments to altitude include:
  - Increased ventilation – 2-3 L/min higher than at sea level
  - Chemoreceptors become more responsive to P_{CO2}
  - Substantial decline in P_{O2} stimulates peripheral chemoreceptors

Respiration Control

A. For **spontaneous breathing,** respiratory muscle activity **depends on neural input.**

1. Two main groups of respiratory neurons,

the dorsal respiratory group and the ventral respiratory group, are found in the medulla.

2. These groups comprise the **medullary respiratory center.**

a. The **dorsal respiratory group** is responsible for the inspiratory respiratory rhythm; input comes from the vagus and glossopharyngeal nerves and output is via the phrenic nerve to the diaphragm.

b. The **ventral respiratory group** innervates both inspiratory and expiratory muscles but is primarily responsible for expiration. It becomes active only during exercise.

B. The **apneustic center** in the lower pons has an intrinsic rhythm and when stimulated promotes prolonged inspirations.

C. Apneustic breathing is an abnormal breathing pattern characterized by prolonged inspirations alternating with short periods of expiration.

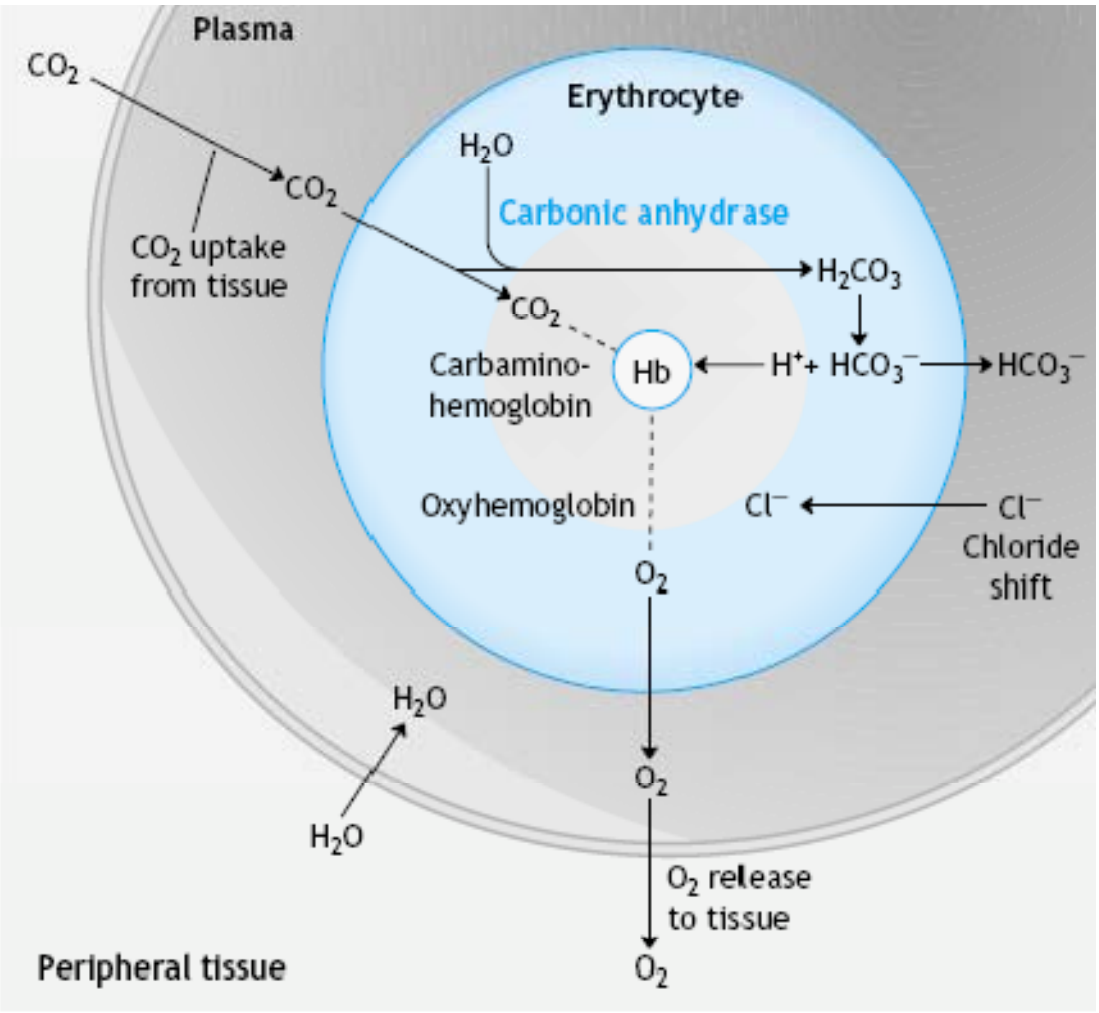


Figure 3–8. Chloride shift.

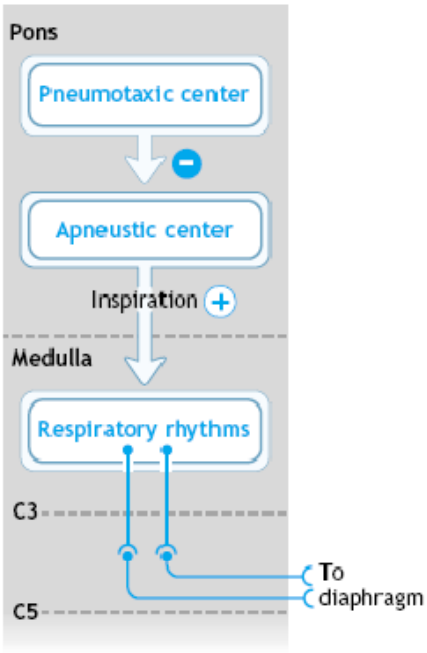
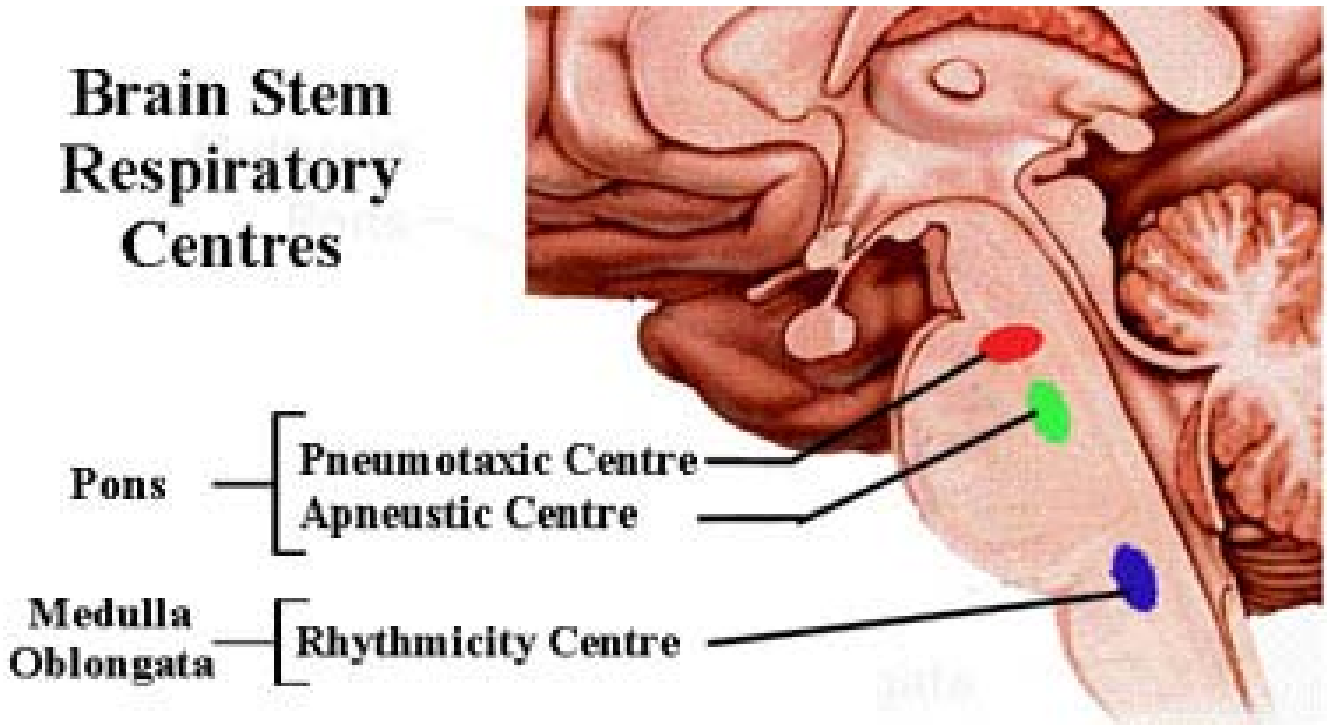


Figure 3–9. Neural control of respiration.

D. The **pneumotaxic center** is located in the upper pons and has an inhibitory influence on the **apneustic center. If the connection** between the pneumotaxic center and apneustic center **is cut, apneustic breathing occurs.**



E. **Central chemoreceptors** are located in the ventrolateral medulla and are the **most important chemoreceptors in the regulation of normal breathing.**

1. The **receptors are stimulated by cerebrospinal fluid** (**CSF**) **[H+] and CO2** because they are sensitive to CSF pH.

2. Because the blood-brain barrier is permeable to CO2, increases in PCO2 and [H+] stimulate breathing and decreases in PCO2 and [H+] inhibit breathing.

3. Therefore, the **primary drive for ventilation is CO2** (H+) on the central chemoreceptors.

F. **Peripheral chemoreceptors** are found in small bodies in two locations.

1. Carotid bodies (the more important of the two types) are found at the bifurcation of the common carotid arteries (ie, near the carotid sinus). **Aortic bodies** are found near the aortic arch.

2. These bodies have two different receptors:

a. **H+/CO2 receptors** monitor arterial PCO2, and increased PCO2 stimulates ventilation.

b. **PO2 receptors** monitor dissolved O2, and decreased arterial PO2 (> 60 mm Hg) stimulates breathing.

Brain Stem Respiratory Centres

Three areas within the Pons (two centres) and the medulla oblongata (one centre) control autonomic breathing.

Rhythmicity Centre	1	Situated in the Medulla oblongata
	2	**I neurons** stimulate spinal motor neurons that innervate the respiratory muscles producing **Inspiration**
	3	**E neurons** inhibit the I neurons and thus produce expiration by relaxation of the respiratory muscles
	4	I and E neuronal activity varies in a reciprocal way so that a rhythmic pattern is obtained
Apneustic Centre	1	Situated in the Pons
	2	Stimulate the I neurons in the Medulla Oblongata
	3	Result in Inspiration
	4	Provides a constant stimulus for inspiration
Pneumotaxic Centre	1	Situated in the Pons
	2	Seems to antagonise the apneustic centre
	3	Inhibits inspiration

CONTROL OF RESPIRATION

OVERVIEW OF RESPIRATORY CONTROL

The respiratory system has no intrinsic driving system like the heart. It is therefore absolutely dependent on an external neural drive.

Like all other control systems, the respiratory system has three parts.

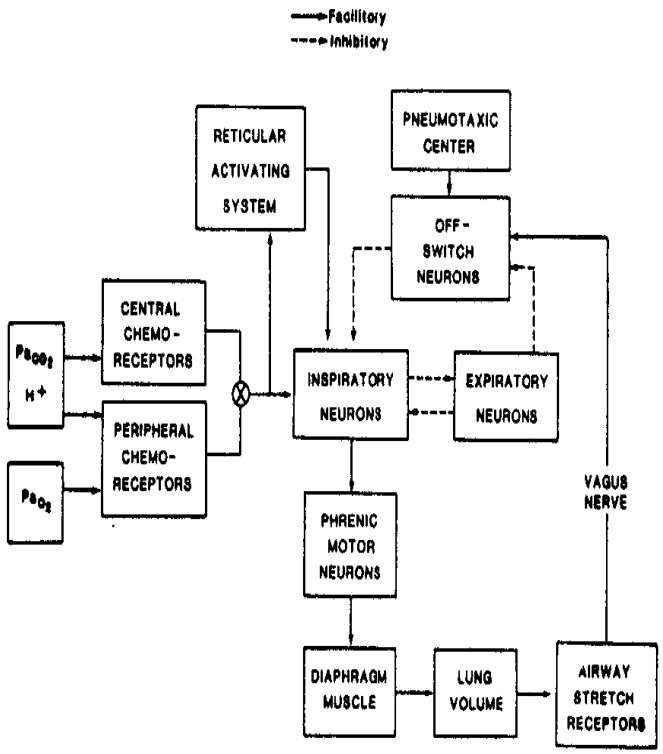


Figure 1. Block diagram showing major components of ventilatory control. Inspiratory neurons are facilitated by the reticular activating system and chemoreceptor output but inhibited by expiratory neurons throughout expiration and off-switch neurons late in inspiration. These off-switch neurons are facilitated by the pneumotaxic center and the vagal stretch receptor input. Note that the effects of the central and peripheral chemoreceptors are multiplicative (x), not additive.

Sensors and their afferents: Providing information on what the system is doing.

Central Controller: Compares intended operation with how the sensors say the system is actually working.

Efferents and Effectors: The respiratory muscles which actually carry out respiration.

Main goals of the respiratory control system

An alveolar ventilation sufficient to maintain normal blood gases.

Changes in alveolar ventilation rate sufficient to adapt to changing environments or metabolic needs (eg. exercise).

Adaptability to allow other activities such as talking or eating which share anatomical structures with the lung.

CHEMICAL CONTROL OF RESPIRATION

Two sets of chemoreceptors exist

Central Chemoreceptors: Responsive to arterial P_{CO_2} by way of hydrogen ion

concentration in cerebrospinal fluid (CSF).

Peripheral Chemoreceptors: Responsive to arterial P_{O_2}, P_{CO_2} and hydrogen ion concentration.

The most important single driver of ventilation is $P_{a_{CO_2}}$ acting on the central chemoreceptors by altering CSF [H^+]. Advantages of a $P_{a_{CO_2}}$ based control system are:

CO_2 production is related to oxygen consumption.

CO_2 production is related to pH.

P_{CO_2} is linearly related to content over the physiological range.

Central chemoreceptors increase ventilation in response to increased $P_{A_{CO_2}}$.

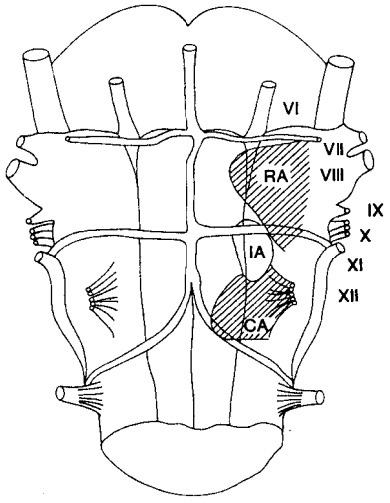


Figure 2. Central chemoreceptor area on the ventral surface of the medulla. Rostral (RA) and caudal (CA) areas (hatched) are sensitive to CO_2 tension and hydrogen ion, whereas the intermediate area (IA) appears to relay chemoreceptor signals. (Roman numerals indicate nerves.) (Redrawn from Loeschcke, H.H.: Central chemoreceptors. In Pallot, D.J. (ed.): *Control of Respiration*. New York: Oxford University Press, 1983, p. 57.)

Central chemosensitive cells are located on the ventral surface of medulla.

Chemosensitive cells are bathed in CSF which has a P_{CO_2} equilibrium with arterial P_{CO_2}.

CSF carbon dioxide combines with water to form carbonic acid which dissociates to form hydrogen ions and bicarbonate.

The CSF hydrogen ions diffuse into the tissue to stimulate medullary chemoreceptors.

Increased arterial H^+ may also stimulate central chemoreceptors slightly, but it does not diffuse into CSF as easily as CO_2. Its effect is likely due mainly to increasing

cerebral blood flow in the chemoreceptor region.

Chronic Adaptation of Central Chemoreceptors. Transport of HCO_{3^-} ions across the blood brain barrier buffers CSF hydrogen ion changes. This occurs in hours to days.

$P_{a_{CO_2}}$ enters CSF during hypercapnia.

$P_{a_{CO_2}}$ leaves CSF during hypocapnia.

$P_{a_{CO_2}}$ is exchanged for Cl^- via a specific anion carrier.

Chronic CO_2 retention. $P_{a_{CO_2}}$ movement into CSF is responsible for the decreased ventilatory drive via central chemoreceptors in chronic CO_2 retention of obstructive disease. The only remaining drive to breath is stimulation of peripheral chemoreceptors by low P_{O_2}.

Peripheral chemoreceptors increase ventilation in response to decreased $P_{a_{O_2}}$.

Location: Carotid bodies at bifurcation of common carotid. Aortic bodies found between ascending aorta and pulmonary artery.

Carotid bodies are sensitive to $P_{a_{O_2}}$, $P_{a_{CO_2}}$, and pH. Afferents in glossopharyngeal nerve.

Aortic bodies are sensitive to $P_{a_{O_2}}$ and $P_{a_{CO_2}}$, but not pH. Afferents in vagus nerve.

Carotid Body Function

Carotid bodies have one of the highest flows per unit weight in body. (2 L/min/100 g)

Carotid body oxygen consumption is (8 ml O_2/min/100g). This is above average for the body, but low in proportion to carotid body flow. Therefore, carotid bodies have a tiny arterial-venous O_2 difference, and the receptor cells are exposed mainly to arterial P_{O_2} levels.

Neural impulses from the carotid body increase as $P_{a_{O_2}}$ falls below about 60 mmHg. This responsiveness is potentiated by acidosis and hypercapnia. The responsiveness is blunted by alkalosis and hypocapnia.

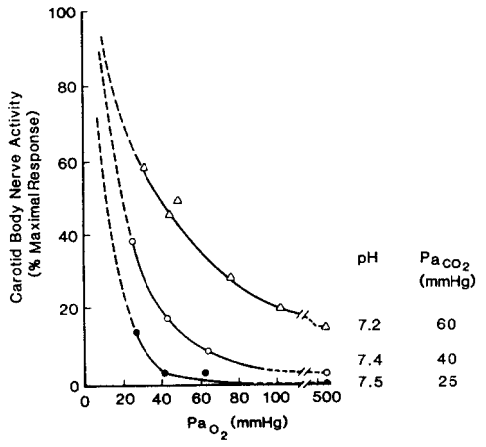


Figure 3. Carotid body nerve activity (per cent of maximal) as a function of P_aO_2. The enhanced response to hypoxia as arterial pH decreases from 7.5 to 7.2 and PCO_2 increases from 25 to 60 is shown. (Redrawn from Hornbein, T.P.: The relation between stimulus to chemoreceptors and their response. In: Torrance, R.W. (ed.): *The Proceedings of the Wates Foundation Symposium on Arterial Chemoreceptors*. Oxford: Blackwell, 1968, pp. 65-76.)

Aortic Body Function

Respond more weakly than carotid bodies $P_{a_{O_2}}$ decreases. Also less sensitive to $P_{a_{CO_2}}$ changes.

The aortic bodies seem to respond somewhat to changes in oxygen content such as are seen in anemia. This is due to the fact that the arterial-venous oxygen difference is greater for these cells than for the carotid bodies. Thus, the receptor cells see a lower average oxygen when content is reduced.

Summary of Ventilatory Response to $P_{a_{CO_2}}$ and pH

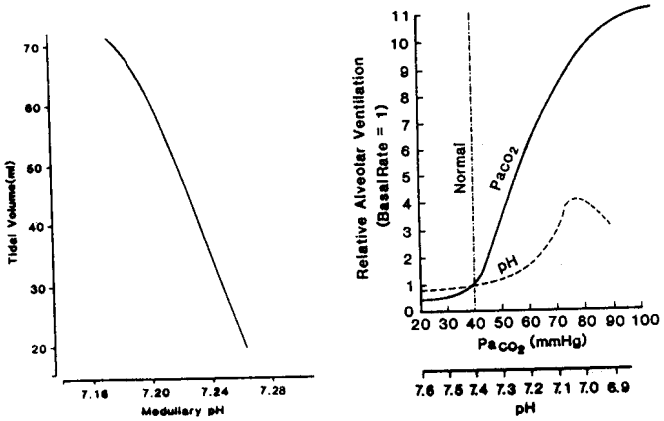


Figure 4. Stimulation of alveolar ventilation by decreased arterial pH or increased P_aCO_2. (Redrawn from

Guyton, A.C.: *Textbook of Medical Physiology*. 4th ed. Philadelphia: W.B. Saunders, 1971, p. 500.)

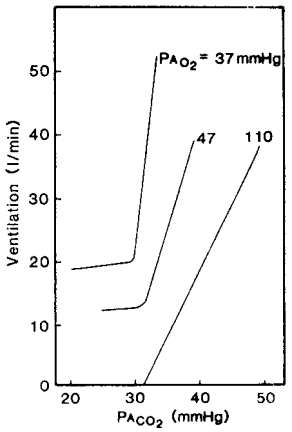


Figure 5. Ventilatory response to changes in P_ACO_2 at various fixed P_AO_2 values. The slopes progressively increased as P_AO_2 was decreased, but the slope of the curve as unchanged when P_AO_2 exceeded 110 mmHg. (Redrawn from Nielson, M., and Smith, H.: Studies on the regulation of respiration in acute hypoxia with an appendix on respiratory control during prolonged hypoxia. *Acta. Physiol. Scand. 24*:293-313, 1952.)

Increase CSF hydrogen ion concentration (decreased pH) leads to increased ventilation. Such an increase in CSF $[H^+]$ is mainly secondary to a $P_{a_{CO_2}}$ increase.

Metabolic acidosis decreases arterial pH. The pH stimulates peripheral chemoreceptors to stimulate ventilation. This in turn reduces $P_{a_{CO_2}}$ and CSF P_{CO_2}. The reduced P_{CO_2} reduces CSF $[H^+]$ and blunts the central drive to breath. The overall response to pH changes is less than the overall response to P_{CO_2} changes.

Hypoxia potentiates the ventilatory response to an increase in $P_{A_{CO_2}}$. Increased ventilation represents the integrated response of central and peripheral chemoreceptor stimulation. As $P_{a_{O_2}}$ falls ventilation is greater at any given $P_{a_{CO_2}}$ and rises more rapidly with any increase in $P_{a_{CO_2}}$.

OTHER PULMONARY RECEPTORS

Hering-Breuer Reflex. Slowly adapting stretch receptors (SARs) in bronchial airways send afferent information to respiratory centers through vagus.

Stimulation of SARs helps terminate inspiration. This is the Hering-Breuer Response. By affecting the timing of inspiratory termination they affect respiratory frequency.

Stronger sustained stimulation of SARs causes activation of expiratory neurons as well.

At normal tidal volumes in adults these receptors don't appear to be activated at end inspiration and are probably not important. They may help terminate inspiration in infants.

Hering-Breuer reflex is important in adults during moderate and strenuous exercise when tidal volume is increased.

Chronic lung diseases which increase lung compliance augment distension and influence ventilation by stimulating these receptors.

Rapidly adapting stretch receptors (irritant receptors). Respond to mechanical and chemical irritation. These are the receptors involved in reflexes causing coughing, sneezing, bronchoconstriction, and increased airway secretions. Mainly located in epithelium of carinal region.

J-Receptor Reflexes. (Juxtapulmonary Receptors). Respond to increased interstitial volume.

Thought to mediate the hyperpnea associated with increases in left atrial pressure as in vascular congestion and pulmonary edema of other causes.

May mediate apnea of pulmonary embolism when arterial end of capillary is blocked.

Peripheral receptors. Stimulation causes increased inspiration.

Pain receptors in muscles and skin.

Proprioceptors in muscles tendons and joints.

Muscle spindles of diaphragm and intercostal muscles.

Cortical override. We can override the involuntary system on a short term basis for such activities as speaking. This override can not continue indefinitely because the involuntary system eventually asserts itself.

BRAINSTEM SECTION WITH AND WITHOUT VAGAL AFFERENT FEEDBACK

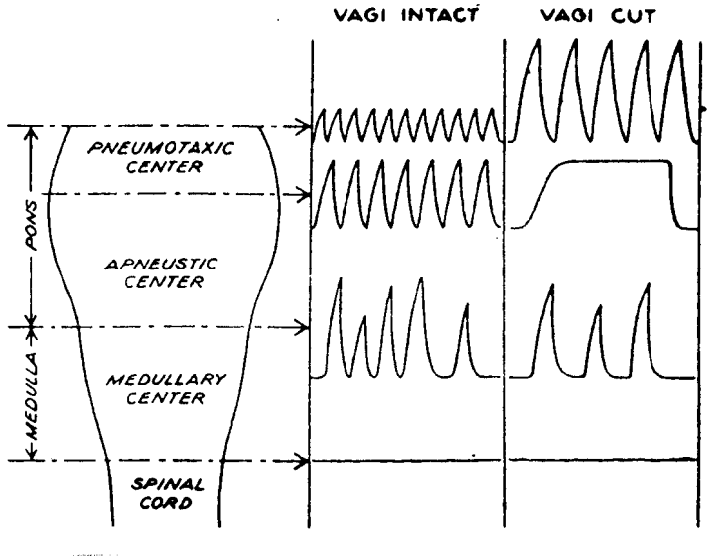


Figure 6

Section above the pons causes no significant alteration of normal respiratory rhythm. Vagotomy removes afferent input from stretch receptors. Inspiration is enhanced because the

Hering-Breuer Response is abolished.

Section at midpontine level increases the depth of breathing because signals from the pneumotaxic center in upper pons normally terminate inspiration. When vagotomy is added, apneuses (sustained inspiratory effort) results. Both central and peripheral inhibition of inspiration have been eliminated.

Section between medulla and pons. Respiration is rhythmic if somewhat irregular. Vagotomy has little effect. This shows that basic respiratory rhythm generator is at medullary levels or below.

Section between spinal cord and medulla. Basic respiratory rhythm disappears suggesting that the respiratory rhythm generator is at medullary levels.

RESPIRATORY CENTERS

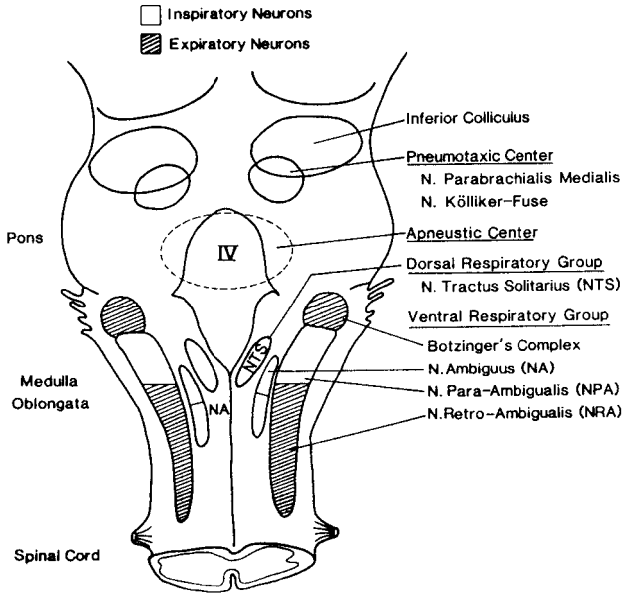


Figure 7. Dorsal view of the brainstem showing the major groups of respiratory-related neurons. IV refers to the fourth ventricle. Inspiratory and expiratory neurons are shown by open and hatched regions, respectively.

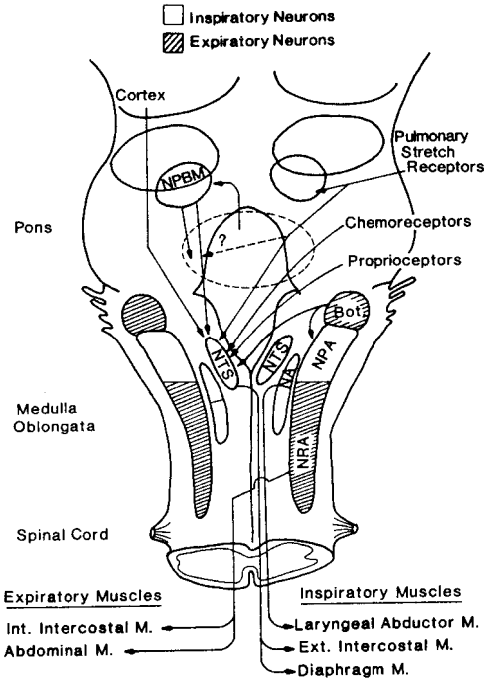


Figure 8. Dorsal view of the brainstem showing facilitory and inhibitory inputs to the nucleus tractus solitarius (NTS) and outflow pathways to inspiratory and expiratory muscle groups. Structures shown include the nucleus parabrachialis medialis (NPSM), nucleus ambiguus (NA), nucleus para-ambigualis (NPA), nucleus retro-ambigualis (NRA), and Botzinger's complex (Bot.)

Areas involved

Pontine Areas: Pneumotaxic Center; apneustic center.

Medullary Areas: Ventral Respiratory Group; Dorsal Respiratory Group.

Pneumotaxic Center: Act as "off-switch" neurons for inspiration. Stimulation of this area causes earlier termination of inspiration. This in turn causes higher respiratory frequency and reduced tidal volumes.

Apneustic Center. Anatomically this area is poorly defined. Stimulation causes apneuses. This area is thought to be an area where inspiratory cutoff information from the pneumotaxic center and vagus are integrated before projecting caudally to the dorsal respiratory group (DRG).

Dorsal Respiratory Group (DRG). Located in NTS. The "upper motor neurons" of inspiration. They also drive ventral respiratory group. Input from virtually all peripheral afferents impinge on the DRG.

Ventral Respiratory Group (VRG). Contains both inspiratory and expiratory neurons.

Inspiratory neurons mainly project to accessory muscles of inspiration and external intercostal.

Expiratory neurons project to internal intercostals and abdominal muscles. These neurons are quiescent during normal breathing but may become active during

exercise.

IX. Pulmonary Blood Flow

A. Pressures Within the Pulmonary Circuit

1. The **most important difference** between the pulmonary and systemic circulations **is the low blood pressure** in the pulmonary arteries. The pulmonary arterial systolic pressure is approximately 22 mm Hg, whereas the left ventricular systolic pressure is around 120 mm Hg.

2. The pulmonary circulation is a low-resistance circuit that must accommodate the entire cardiac output at rest and during exercise.

3. When pulmonary arterial pressure increases, vascular resistance decreases for two reasons:

a. Increased pressure increases the caliber (**distention**) of the arteries.

b. Increased pressure causes more capillaries to open (**recruitment**).

B. Effects of Gravity on Blood Flow

1. Because of the low blood pressures in the pulmonary circulation, **gravity has**

a large effect on blood flow to different parts of the lung

a. In an upright subject, the effect of gravity causes blood flow to be larger at the base than at the apex. Ventilation is also larger at the base than at the apex.

b. Although the **base receives the greatest ventilation,** it does not match the $\frac{\dot{V}_A}{\dot{Q}}$ very high blood flow. Thus, the base is an underventilated region, in which the ratio is less than 0.8.

c. Even though the **apex receives the lowest ventilation,** it is too high for the low blood flow. Therefore, the apex can be considered an overventilated region, in which the $\frac{\dot{V}_A}{\dot{Q}}$ ratio is greater than 0.8.

d. An overventilated lung unit acts like dead space, whereas an underventilated lung unit acts like a pulmonary shunt.

2. Regional blood flow in the lungs has been separated into three zones

C. Hypoxic Vasoconstriction

1. A decrease in alveolar PO2 produces a local vasoconstriction of pulmonary arterioles, thereby lowering blood flow to that part of the lung.

2. In other systemic organs, hypoxia results in vasodilation of arterioles.

D. Pulmonary Edema

1. For normal respiratory function, it is crucial that the alveoli do not accumulate fluid.

2. A small amount of fluid moves into peribronchial and perivascular spaces each day but is removed by lymphatic vessels.

3. If net fluid movement out of the pulmonary capillaries exceeds the ability of the lymphatic system to remove it, a net fluid accumulation, or edema, occurs.

4. Severe alveolar edema occurs when accumulated fluid in alveoli impairs normal gas exchange.

5. The two **causes of pulmonary edema** are

a. Increased capillary permeability

b. Increased pulmonary blood pressure due to hypoxic vasoconstriction, left heart failure, or loss of surfactant

E. Shunts

1. In **an absolute right-to-left shunt,** venous blood is delivered to the left side of the heart without contacting ventilated alveoli; this shunt produces **hypoxemia**

a. The shunt **results in a decrease in arterial PO2 and widening of the PO2 systemic alveolar-arterial (A-a) difference.**

b. With a significant pulmonary shunt (such as occurs in regional atelectasis), breathing 100% O2 does not result in a significant increase in systemic arterial PO2, leading to a diagnosis of a pulmonary right-to-left shunt.

c. Thus, **overventilating** part of the lung does not compensate for the shunt because the empty Hb-binding sites in the shunted blood will bind the dissolved O2 from the ventilated part of the lung, only slightly increasing PO2 levels.

d. A **physiologic shunt** is the amount of absolute shunt that would cause the observed A-a difference.

2. In a **left-to-right shunt,** the pressures are higher in the left side of the heart; therefore, **hypoxemia is absent.** This type of shunt can be **due to arterial or ventricular septal defects** or **patent ductus arteriosis**

X. Ventilation-Perfusion Differences (Figure 3–12)

A. The relative difference between alveolar ventilation (**VA**) **and blood flow** (**Q**) is known as the $\frac{\dot{V}_A}{\dot{Q}}$ **ratio.**

B. Thus, the **local alveolar gas composition** is not determined by ventilation alone or by blood flow (ie, perfusion) alone but by the ratio between ventilation and perfusion. In the normal lung, the $\frac{\dot{V}_A}{\dot{Q}}$ ratio is approximately 0.8.

C. Physiologic dead space is defined as anatomic dead space plus the volume of all airways that behave as if they have received no blood flow.

1. In health, anatomic dead space and physiologic dead space are essentially equal.

2. In **ventilation-perfusion mismatch,** the amount of physiologic dead space is much greater than the amount of anatomic dead space.

a. Some regions of the lung may have **a high** $\frac{\dot{V}_A}{\dot{Q}}$ **,** and **PO2** in these alveoli **is below average.**

b. The **Bohr method** measures the volume of all airways in which no CO2 has been added from the blood; this is the physiologic dead space.

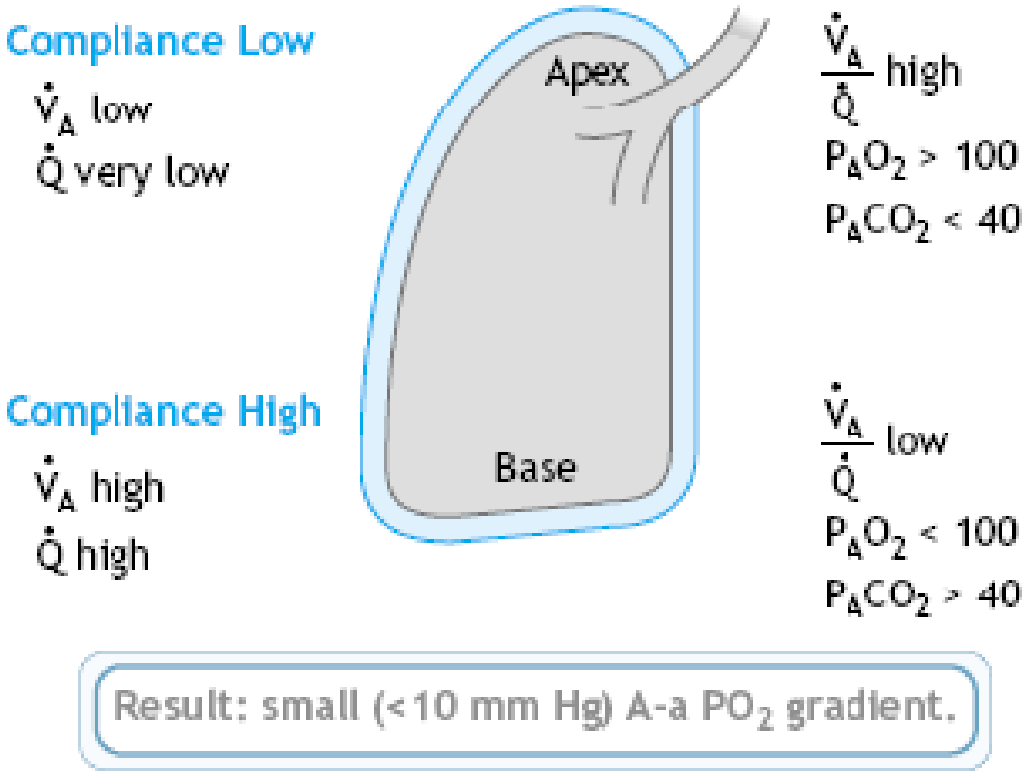


Figure 3–12. Ventilation-perfusion difference.

c. In many pulmonary diseases, the physiologic shunt and the physiologic dead space will be increased.

d. The consequence of increased physiologic dead space is wasted ventilation.

D. Hypoventilation is associated with equal decreases in PO2 in the alveolar, pulmonary end capillary, and systemic arterial compartments. **Supplemental oxygen or increased alveolar ventilation will return arterial PO2 to normal.**

E. Diffusion impairment refers to a lung structural problem (eg, increased thickness of lung membrane).

1. With significant diffusion impairment, the **A-a gradient** widens.

2. Supplemental oxygen will increase the gradient across the alveolar membranes and **return arterial PO2 toward normal.**

F. Exercise increases ventilation and pulmonary blood flow. During exercise, the alveolar $\frac{\dot{V}_A}{\dot{Q}}$ ratio is greater than 0.8, ventilation increases more than cardiac output, and base-to-apex flows become more equal.

XI. Special Environments

A. High Altitude

1. At high altitude, atmospheric pressure is reduced from 760 mm Hg, **resulting in** decreased alveolar and arterial PO2 (**hypoxemia**).

2. Low PO2 stimulates peripheral chemoreceptors, inducing hyperventilation, a decrease in alveolar and

arterial PCO2, and respiratory alkalosis.

3. Hypoxemia stimulates erythropoietin, a hormone produced by the kidney that increases red blood cell production and **can lead to polycythemia.**

The increased Hb production increases O2 content of the blood.

4. 2,3-DPG levels increase, shifting the oxyhemoglobin dissociation curve to the right and facilitating O2 extraction by the tissues.

5. Hypoxemia also **results in hypoxic vasoconstriction** (ie, pulmonary vasoconstriction), resulting eventually in hypertrophy of the right ventricle due to increased work of the right heart.

B. Hyperbaric Chamber

1. Breathing room air (21% O2; 79% N2) in a hyperbaric environment increases the partial pressure of O2 and N2 in alveoli and arterial blood. Elevated PO2 can produce oxygen toxicity, and the high PN2 can lead to the **bends** (also known as caisson disease).

2. Sudden decompression causes bubbles of nitrogen to accumulate in the blood and tissues. Treatment is recompression and gradual decompression.

References :

Road map physiology for the USMLE