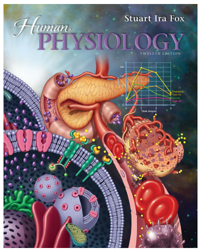
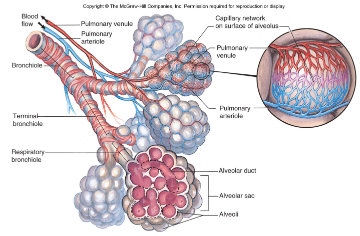


Chapter 16

Respiratory Physiology

Lecture PowerPoint

I. The Respiratory System



Respiratory System

- Divided into:
  - Respiratory zone: site of gas exchange
  - Conduction zone: gets air to the respiratory zone

Respiration

- Includes:
  - Ventilation (breathing)
  - Gas exchange between blood and lungs and between blood and tissues
  - Oxygen utilization by tissues to make ATP
- Ventilation and gas exchange in lungs = external respiration
- Oxygen utilization and gas exchange in tissues = internal respiration

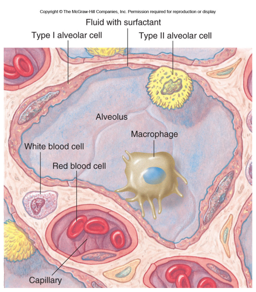
Gas Exchange in Lungs

- Occurs via diffusion
- O_2 concentration is higher in the lungs than in the blood, so O_2 diffuses into blood.
- CO_2 concentration in the blood is higher than in the lungs, so CO_2 diffuses out of blood.

Alveoli

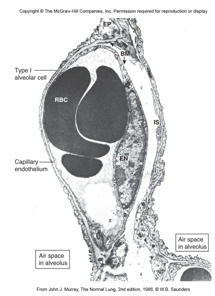
- Air sacs in the lungs where gas exchange occurs
- 300 million of them
  - Provide large surface area (760 square feet) to increase diffusion rate

Alveoli

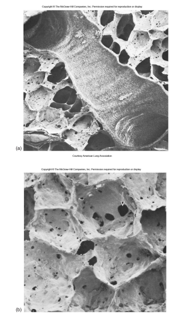


Alveoli

Capillary within alveolar wall



Bronchiole and alveoli



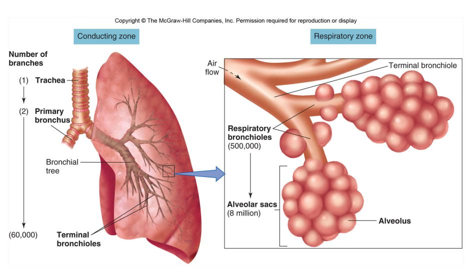
Alveolar Cells

- Type I: 95−97% total surface area where gas exchange occurs
- Type II: secrete pulmonary surfactant and reabsorb sodium and water, preventing fluid buildup

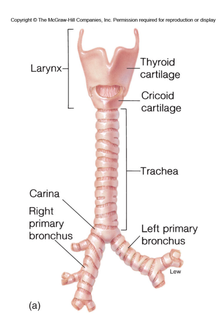
Conducting Zone

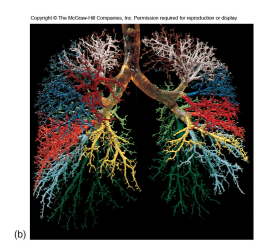
- Air travels down the nasal cavity →
  Pharynx →
  Larynx →
  Trachea →
  Right and left primary bronchi →
  Secondary bronchi →
  Tertiary bronchi → (more branching) →
  Terminal bronchioles →
  Respiratory zone (respiratory bronchioles →
  Terminal alveolar sacs

Respiratory Structures



Trachea and Respiratory Bronchi

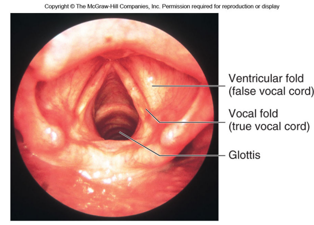




Functions of Conducting Zone

- Transports air to the lungs
- Warms, humidifies, filters, and cleans the air
  - Mucus traps small particles, and cilia move it away from the lungs.
- Voice production in the larynx as air passes over the vocal folds

Functions of Conducting Zone



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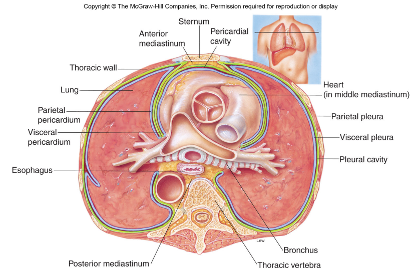
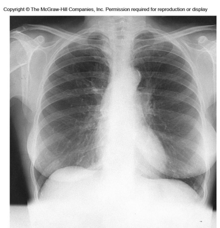
Thoracic Cavity

- Contains the heart, trachea, esophagus, and thymus within the central mediastinum
- The lungs fill the rest of the cavity.
  - The parietal pleura lines the thoracic wall.
  - The visceral pleura covers the lungs.
  - The parietal and visceral pleura are normally pushed together, with a potential space between called the intrapleural space.

Thoracic Cavity Cross Section

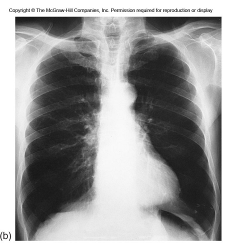


X-ray of the Lungs



(a)

Courtesy of Edward C. Vasquez, R.T.C.R.T., Dept of Radiologic Technology, Los Angeles City College



(b)

Courtesy of Edward C. Vasquez, R.T.C.R.T., Dept of Radiologic Technology, Los Angeles City College

II. Physical Aspects of Ventilation

Ventilation

- Air moves from higher to lower pressure.
  - Pressure differences between the two ends of the conducting zone occur due to changing lung volumes.
  - Compliance, elasticity, and surface tension are important physical properties of the lungs.

Pressure

- Atmospheric pressure: pressure of air outside the body
- Intrapulmonary pressure: pressure in the lungs
- Intrapleural pressure: pressure within the intrapleural space (between parietal and visceral pleura)

Pressure Differences When Breathing

- Inhalation: Intrapulmonary pressure is lower than atmospheric pressure.
  - Pressure below that of the atmosphere is called subatmospheric or negative pressure
- Exhalation: Intrapulmonary pressure is greater than atmospheric pressure.

Pressure Differences When Breathing

Table 16.1 | Pressure Changes in Normal, Quiet Breathing

	Inspiration	Expiration
Intrapulmonary pressure (mmHg)	−3	+3
Intrapleural pressure (mmHg)	−6	−3
Transpulmonary pressure (mmHg)	+3	+6

Note: Pressures indicate mmHg below or above atmospheric pressure.

Intrapleural Pressure

- Lower than intrapulmonary and atmospheric pressure in both inhalation and exhalation
  - The difference between intrapulmonary and intrapleural pressure is called the transpulmonary pressure.
  - Keeps the lungs against the thoracic wall

Boyle's Law

- States that the pressure of a gas is inversely proportional to its volume
  - An increase in lung volume during inspiration decreases intrapulmonary pressure to subatmospheric levels.
    - Air goes in.
  - A decrease in lung volume during exhalation increases intrapulmonary pressure above atmospheric levels.
    - Air goes out.

Lung Compliance

- Lungs can expand when stretched.
- Defined as the change in lung volume per change in transpulmonary pressure:
  $\Delta V/\Delta P$
- Reduced by infiltration of connective tissue proteins in pulmonary fibrosis

Elasticity

- Lungs return to initial size after being stretched.
  - Lungs have lots of elastin fibers.
  - Because the lungs are stuck to the thoracic wall, they are always under elastic tension.

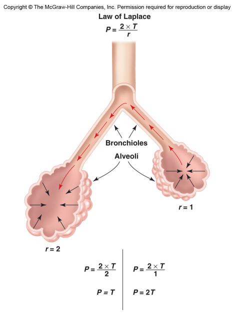
Surface Tension

- Resists distension
- Exerted by fluid secreted in the alveoli
- Raises the pressure of the alveolar air as it acts to collapse the alveolus

Law of Laplace

- Pressure is directly proportional to surface tension and inversely proportional to radius of alveolus.
  - Small alveoli would be at greater risk of collapse without surfactant.

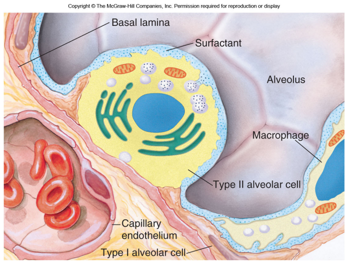
Law of Laplace



Surfactant

- Secreted by type II alveolar cells
- Consists of hydrophobic protein and phospholipids
- Reduces surface tension between water molecules
- More concentrated in smaller alveoli
- Prevents collapse

Surfactant



Surfactant

- Production begins late in fetal life, so premature babies may be born with a high risk for alveolar collapse called respiratory distress syndrome (RDS).

III. Mechanics of Breathing

Breathing

- Also called pulmonary ventilation
  - Inspiration: breathe in
  - Expiration: breathe out
- Accomplished by changing thoracic cavity/ lung volume

Breathing

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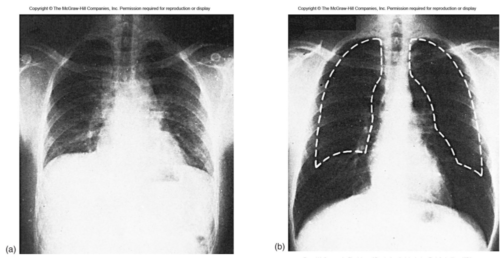

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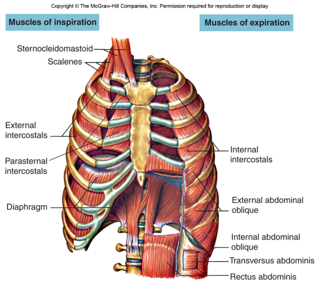
Muscles Involved in Breathing

- Diaphragm most important.
  - Contracts in inspiration
  - Relaxes in expiration
- Inspiration: external intercostals
- Expiration: internal intercostals, abs

Muscles Involved in Breathing



Mechanisms of Breathing

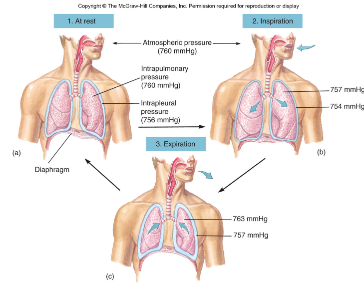
- Inspiration: Volume of thoracic cavity (and lungs) increases vertically when diaphragm contracts (flattens) and horizontally when parasternal and external intercostals raise the ribs.
- Expiration: Volume of thoracic cavity (and lungs) decreases vertically when diaphragm relaxes (dome) and horizontally when internal intercostals lower the ribs in forced expiration.

Normal vs. Forced Breathing

Table 16.2 | Mechanisms Involved in Normal, Quiet Ventilation and Forced Ventilation

	Inspiration	Expiration
Normal, Quiet Breathing	Contraction of the diaphragm and external intercostal muscles increases the thoracic and lung volume, decreasing intrapulmonary pressure to about −3 mmHg.	Relaxation of the diaphragm and external intercostals, plus elastic recoil of lungs, decreases lung volume and increases intrapulmonary pressure to about +3 mmHg.
Forced Ventilation	Inspiration, aided by contraction of accessory muscles such as the scalenes and sternocleidomastoid, decreases intrapulmonary pressure to −20 mmHg or lower.	Expiration, aided by contraction of abdominal muscles and internal intercostal muscles, increases intrapulmonary pressure to +30 mmHg or higher.

Mechanisms of Breathing



Pulmonary Function Tests

- Spirometry: Subject breathes into and out of a device that records volume and frequency of air movement on a spirogram.
- Measures lung volumes and capacities
- Can diagnose restrictive and disruptive lung disorders

Lung Volume Measurements

- Tidal volume: amount of air expired or inspired in quiet breathing
- Expiratory reserve volume: amount of air that can be forced out after tidal volume
- Inspiratory reserve volume: amount of air that can be forced in after tidal volume
- Residual volume: amount of air left in lungs after maximum expiration

Lung Capacity Measurements

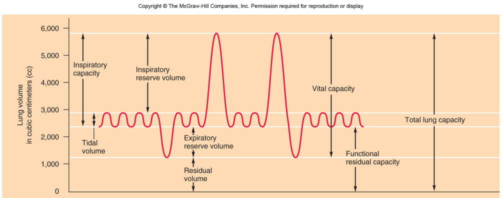
- Vital capacity: maximum amount of air that can be forcefully exhaled after a maximum inhalation
- Total lung capacity: amount of gas in the lungs after a maximum inspiration
- Inspiratory capacity: amount of gas that can be inspired after a normal expiration
- Functional residual capacity: amount of gas left in lungs after a normal expiration

Lung Volume and Capacity

- Relationships between these:
  - Vital capacity = inspiratory reserve volume + expiratory reserve volume + tidal volume
  - Functional residual capacity = residual volume + expiratory reserve volume
  - Total minute volume = tidal volume X breaths per minute

Lung Volume and Capacity

Spirogram:

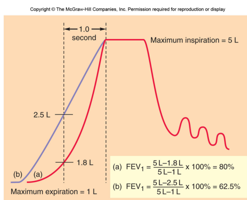


Restrictive and Obstructive Disorders

- Restrictive: Lung tissue is damaged. Vital capacity is reduced, but forced expiration is normal.
  - Examples: pulmonary fibrosis and emphysema
- Obstructive: Lung tissue is normal. Vital capacity is normal, but forced expiration is reduced.
  - Example: asthma

Forced Expiratory Volume (FEV) Test

- Obstructive lung disorders are usually diagnosed by doing forced expiratory volume tests.



Asthma

- Symptoms: dyspnea (shortness of breath) and wheezing
- Caused by inflammation, mucus secretion, and constriction of bronchioles
- Often called airway hyperresponsiveness

Asthma

- Allergic asthma: triggered by allergens stimulating T lymphocytes to secrete cytokines and recruit eosinophils and mast cells, which contribute to inflammation
- Can also be triggered by cold or dry air
- Reversible with bronchodilator
  - Albuterol

Chronic Obstructive Pulmonary Disease (COPD)

- Chronic inflammation, narrowing of the airways, and alveolar destruction
  - Includes emphysema and chronic obstructive bronchiolitis
- Accelerated decline in FEV
- Inflammation involves macrophages, neutrophils, and cytotoxic T cells

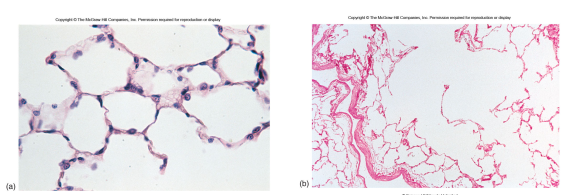
Chronic Obstructive Pulmonary Disease (COPD)

- Excessive mucus production and inflammation triggered by smoking
- Most people with COPD smoke.
  - Smoking also promotes the infiltration of obstructing fibrous tissue and muscle in the airways and remodeling of blood vessels in the lungs, leading to pulmonary hypertension.
- There is no cure.
- 5th leading cause of death

Emphysema

- Destruction of alveoli
- Reduces surface area for gas exchange
- With fewer alveoli to put pressure on bronchioles, they collapse during expiration.
- Smoking is the most common cause. It triggers inflammation and destruction of alveoli by immune cells

Emphysema



Pulmonary Fibrosis

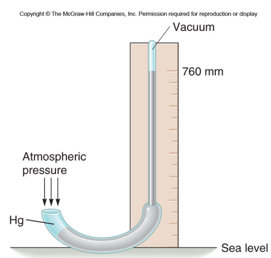
- Some people accumulate fibrous tissues in the lungs when alveoli are damaged.
  - May be due to inhalation of small particles
  - Example: black lung in miners

IV. Gas Exchange in the Lungs

Atmospheric Pressure

- Can be measured using a barometer
- At sea level, the atmospheric pressure is 760 mmHg.

Atmospheric Pressure



Dalton's Law

- The total pressure of a gas mixture is equal to the sum of the pressures of each gas in it.
- Partial pressure: the pressure of an individual gas; can be measured by multiplying the % of that gas by the total pressure
  - O_2 makes up 21% of the atmosphere, so partial pressure of O_2 = 760 X 20% = 159 mmHg.

Total Pressure

- Nitrogen makes up 78% of the atmosphere, O_2 21%, and CO_2 1%.

  $P_{dry} = P_{N_2} + P_{O_2} + P_{CO_2} = 760$ mmHg

- When air gets to our lungs, it is humid, so the calculation changes to:

  $P_{wet} = P_{N_2} + P_{O_2} + P_{CO_2} + P_{H_2O} = 760$ mmHg

Partial Pressure

- Addition of water vapor also takes away from the total atmospheric pressure when calculating partial pressure O_2.
  - Pressure of water is a constant 47 mmHg.
  - Partial pressure O_2 at sea level:

    $.21(760 - 47) = 150$ mmHg

Role of Gas Exchange

- In the alveoli, the percentage of oxygen decreases and CO_2 increases, changing the partial pressure of each.

Role of Gas Exchange

	Inspired air	Alveolar air
H_2O	Variable	47 mmHg
CO_2	000.3 mmHg	40 mmHg
O_2	159 mmHg	105 mmHg
N_2	601 mmHg	568 mmHg
Total pressure	760 mmHg	760 mmHg

Partial Pressure Oxygen

- Changes with altitude and location

Table 16.5 | Effect of Altitude on Partial Oxygen Pressure (P_{O_2})

Altitude (Feet Above Sea Level)*	Atmospheric Pressure (mmHg)	P_{O_2} in Air (mmHg)	P_{O_2} in Alveoli (mmHg)	P_{O_2} in Arterial Blood (mmHg)
0	760	159	105	100
2,000	707	148	97	92
4,000	656	137	90	85
6,000	609	127	84	79
8,000	564	118	79	74
10,000	523	109	74	69
20,000	349	73	40	35
30,000	226	47	21	19

*For reference, Pike's Peak (Colorado) is 14,110 feet; Mt. Whitney (California) is 14,505 feet; Mt. Logan (Canada) is 19,524 feet; Mt. McKinley (Alaska) is 20,320 feet; and Mt. Everest (Nepal and Tibet), the tallest mountain in the world, is 29,029 feet.

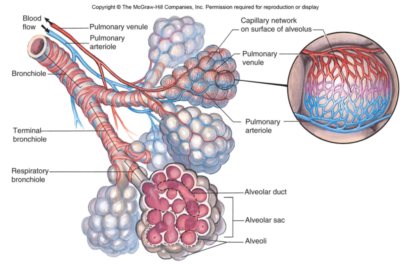
Partial Pressure in Blood

- Alveoli and blood capillaries quickly reach equilibrium for O_2 and CO_2.
  - This helps maximize the amount of gas dissolved in fluid.
  - Henry's Law predicts this.

Henry's Law

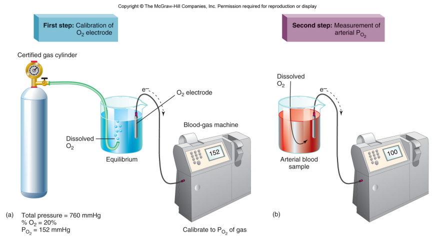
- The amount of gas that can dissolve in liquid depends on:
  - Solubility of the gas in the liquid (constant)
  - Temperature of the fluid (more gas can dissolve in cold liquid); doesn't change for blood
  - Partial pressure of the gases, the determining factor

Relationship Between Alveoli and Capillaries



Blood Gas Measurement

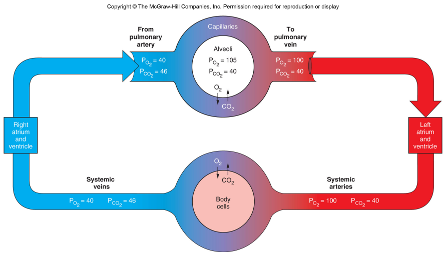
- Uses an oxygen electrode



Blood Gas Measurement

- Only measures oxygen dissolved in the blood plasma. It will not measure oxygen in red blood cells.
- It does provide a good measurement of lung function.
  - If partial pressure oxygen in blood is more than 5 mmHg below that of lungs, gas exchange is impaired.

Partial Pressure of Gas in Blood



Pulmonary Circulation

- The rate of blood flow through the lungs is equal to that through the systemic circuit (5.5 L/minute cardiac output).
- The pressure difference between the left atrium and the pulmonary artery is only 10 mmHg.
- Vascular resistance must be very low.
  - Low pressure/low resistance pathway
  - Reduces possibility of pulmonary edema

Pulmonary Circulation

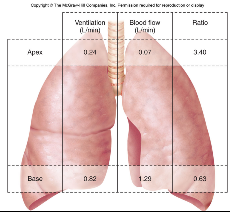
- Pulmonary arterioles constrict when alveolar partial pressure O_2 is low and dilate when partial pressure O_2 is high.
  - Blood flow to alveoli is increased when they are full of oxygen and decreased when not.
  - Opposite of systemic arterioles that constrict when partial pressure O_2 in tissues is high. This ensures that only tissues that need oxygen are sent blood.

Arteriole Response to O_2

- Low oxygen depolarizes smooth muscle cells of the arteriole wall by inhibiting outward flow of K^+.
- This opens voltage-gated Ca^{2+} channels, which stimulate contraction.

Ventilation/Perfusion Ratios

- The response of pulmonary arterioles to low oxygen levels makes sure that ventilation (O_2 into lungs) matches perfusion (blood flow).



Disorders Caused by High Partial Pressure of Gases

- Problems for deep-sea divers
  - Oxygen toxicity: 100% oxygen is dangerous at 2.5 atmospheres.
    - Due to oxidation of enzymes
  - Nitrogen narcosis: occurs if nitrogen is inhaled under pressure; results in dizziness and drowsiness

Disorders Caused by High Partial Pressure of Gases

- Problems for deep-sea divers
  - Decompression sickness: When a diver comes to the surface too fast, nitrogen bubbles can form in the blood and block small vessels.
  - Can also happen if an airplane suddenly loses pressure

V. Regulation of Breathing

Two Tracts to Control Breathing

- Contraction and relaxation of breathing muscles is controlled by motor neurons from two areas of the brain.
- Voluntary breathing: from cerebral cortex
- Involuntary breathing: from respiratory control centers of the medulla oblongata and pons

Motor Neurons

- Those that innervate the diaphragm form the phrenic nerve and arise from the cervical region of the spinal cord.
- Those that innervate the other breathing muscles arise from the thoracolumbar region of the spinal cord.
- Regulated by descending neurons from the brain.

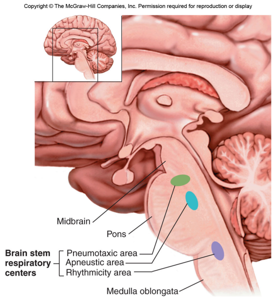
Medulla Oblongata

- Rhythmicity center: four types of neurons identified for different stages of breathing
  - Dorsal respiratory group: made up of inspiratory neurons that stimulate neurons of the phrenic nerve
  - Ventral respiratory group: made up of inspiratory neurons that stimulate spinal respiratory neurons and expiratory neurons that inhibit the phrenic nerve

Pons

- Influences medulla activity
- Apneustic center: promotes inspiration
- Pneumotaxic center: inhibits inspiration

Pons



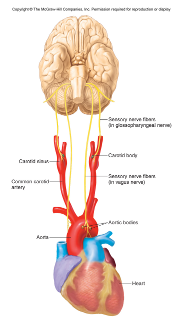
Chemoreceptors

- Automatic control of breathing is influenced by feedback from chemoreceptors, which monitor pH of fluids in the brain and pH, P_{CO2} and P_{O2} of the blood.
  - Central chemoreceptors in medulla
  - Peripheral chemoreceptors in carotid and aorta arteries

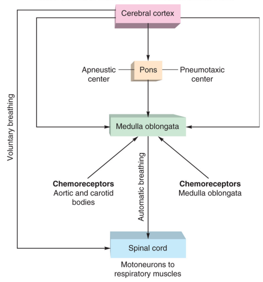
Aortic and Carotid Bodies

- Aortic body sends feedback to medulla along vagus nerve.
- Carotid body sends feedback to medulla along glossopharyngeal nerve.

Aortic and Carotid Bodies



Regulation of Ventilation

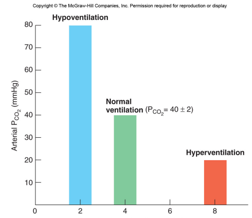


Effects of pH and P_{CO_2} on Ventilation

- When ventilation is inadequate, CO_2 levels rise and pH falls.
  - carbon dioxide + water = carbonic acid
- In hyperventilation, CO_2 levels fall and pH rises.
- Oxygen levels do not change as rapidly because of oxygen reserves in hemoglobin, so O_2 levels are not a good index for control of breathing.

Effects of P_{CO_2} on Ventilation

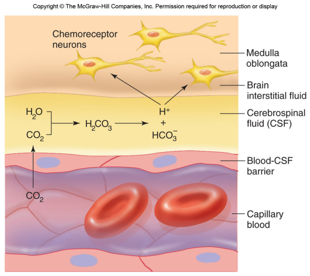
- Ventilation is controlled to maintain constant levels of CO_2 in the blood. Oxygen levels naturally follow.



Chemoreceptors in the Medulla

- When increased CO_2 in the fluids of the brain decrease pH, this is sensed by chemoreceptors in the medulla, and ventilation is increased.
  - Takes longer, but responsible for 70–80% of increased ventilation

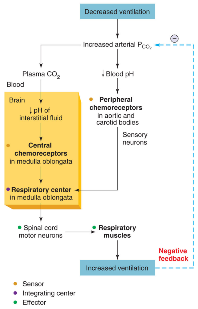
Chemoreceptors in the Medulla



Peripheral Chemoreceptors

- Aortic and carotid bodies respond to rise in H^+ due to increased CO_2 levels.
- Respond much quicker

Peripheral Chemoreceptors



Effect of Blood P_{O_2} on Ventilation

- Indirectly affects ventilation by affecting chemoreceptor sensitivity to P_{CO2}
  - Low blood O_2 makes the carotid bodies more sensitive to CO_2.

Effect of Blood P_{O_2} on Ventilation

Table 16.6 | Sensitivity of Chemoreceptors to Changes in Blood Gases and pH

Stimulus	Chemoreceptor	Comments
↑P_{CO_2}	Medullary chemoreceptors; aortic and carotid bodies	Medullary chemoreceptors are sensitive to the pH of cerebrospinal fluid (CSF). Diffusion of CO_2 from the blood into the CSF lowers the pH of CSF by forming carbonic acid. Similarly, the aortic and carotid bodies are stimulated by a fall in blood pH induced by increases in blood CO_2.
↓pH	Aortic and carotid bodies	Peripheral chemoreceptors are stimulated by decreased blood pH independent of the effect of blood CO_2. Chemoreceptors in the medulla are not affected by changes in blood pH because H^+ cannot cross the blood-brain barrier.
↓P_{O_2}	Carotid bodies	Low blood P_{O_2} (hypoxemia) augments the chemoreceptor response to increases in blood P_{CO_2} and can stimulate ventilation directly when the P_{O_2} falls below 50 mmHg.

Pulmonary Receptors and Ventilation

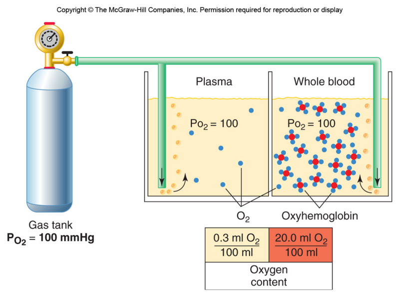
- Unmyelinated C fibers: affected by capsaicin; produce rapid shallow breathing when a person breathes in pepper spray
- Receptors that stimulate coughing:
  - Irritant receptors: in wall of larynx; respond to smoke, particulates, etc.
  - Rapidly adapting receptors: in lungs; respond to excess fluid

Pulmonary Receptors and Ventilation

- Hering-Breuer reflex: stimulated by pulmonary stretch receptors
- Inhibits respiratory centers as inhalation proceeds
- Makes sure you do not inhale too deeply

VI. Hemoglobin and Oxygen Transport

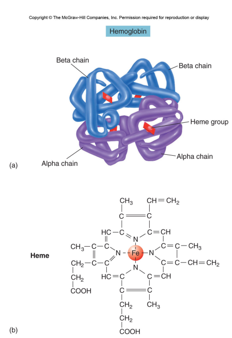
Oxygen Content of Blood



Hemoglobin

- Most of the oxygen in blood is bound to hemoglobin.
  - 4 polypeptide globins and 4 iron-containing hemes
  - Each hemoglobin can carry 4 molecules O_2.
  - 248 million hemoglobin/RBC

Hemoglobin



Forms of Hemoglobin

- Oxyhemoglobin/reduced hemoglobin: Iron is in reduced form (Fe^{2+}) and can bind with O_2.
- Methemoglobin: Oxidized iron (Fe^{3+}) can't bind to O_2.
  - Abnormal; some drugs cause this.
- Carboxyhemoglobin: Hemoglobin is bound with carbon monoxide.

% Oxyhemoglobin Saturation

- % oxyhemoglobin to total hemoglobin
- Measured to assess how well lungs have oxygenated the blood
- Normal is 97%
- Measured with a pulse oximeter or blood–gas machine

Hemoglobin Concentration

- Oxygen-carrying capacity of blood is measured by its hemoglobin concentration.
  - Anemia: below-normal hemoglobin levels
  - Polycythemia: above-normal hemoglobin levels; may occur due to high altitudes
- Erythropoietin made in the kidneys stimulates hemoglobin/RBC production when O_2 levels are low.

Loading and Unloading

- Loading: when hemoglobin binds to oxygen in the lungs
- Unloading: when oxyhemoglobin drops off oxygen in the tissues

deoxyhemoglobin + O_2 ⟷ oxyhemoglobin

- Direction of reaction depends on P_{O_2} of the environment and affinity for O_2.
  – High P_{O_2} favors loading.

Oxygen Unloading

- Systemic arteries have a P_{O_2} of 100 mmHg.
  – This makes enough oxygen bind to get 97% oxyhemoglobin.
  – 20 ml O_2/100 ml blood
- Systemic veins have a P_{O_2} of 40 mmHg.
  – This makes enough oxygen bind to get 75% oxyhemoglobin.
  – 15.5 ml O_2/100 ml blood
  – 22% oxygen is unloaded in tissues

P_{O_2} and % Oxyhemoglobin

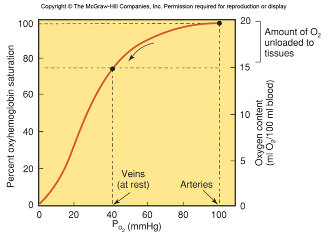
Table 16.7 | Relationship Between Percent Oxyhemoglobin Saturation and P_{O_2} (at pH of 7.40 and Temperature of 37° C)

P_{O_2} (mmHg)	100	80	61	45	40	36	30	26	23	21	19
Percent Oxyhemoglobin	97	95	90	80	75	70	60	50	40	35	30
	Arterial Blood				Venous Blood						

Oxygen Dissociation Curve

- Oxygen remaining in veins serves as an oxygen reserve.
- Oxygen unloading during exercise is even greater:
  – 22% at rest
  – 39% light exercise
  – 80% heavy exercise

Oxygen Dissociation Curve



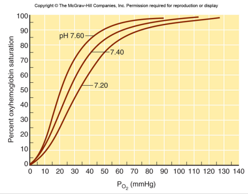
Effect of pH and Temperature on Oxygen Transport

- pH and temperature change the affinity of hemoglobin for O_2.
  – This ensures that muscles get more O_2 when exercising.
  – Affinity decreases at lower pH and increases at higher pH = Bohr effect.
  – More unloading occurs at lower pH.
  – Increased metabolism = more CO_2 = lower pH

Effect of pH and Temperature on Oxygen Transport

Table 16.8 | Effect of pH on Hemoglobin Affinity for Oxygen and Unloading of Oxygen to the Tissues

pH	Affinity	Arterial O_2 Content per 100 ml	Venous O_2 Content per 100 ml	O_2 Unloaded to Tissues per 100 ml
7.40	Normal	19.8 ml O_2	14.8 ml O_2	5.0 ml O_2
7.60	Increased	20.0 ml O_2	17.0 ml O_2	3.0 ml O_2
7.20	Decreased	19.2 ml O_2	12.6 ml O_2	6.6 ml O_2



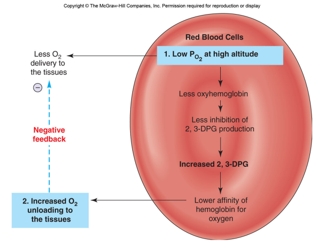
Effect of pH and Temperature on Oxygen Transport

- Hemoglobin affinity for O_2 is decreased at increased temperatures.
  - This further enhances the amount of O_2 unloaded to muscles during exercise.

Effect of 2,3-DPG on Oxygen Transport

- RBCs obtain energy from the anaerobic metabolism of glucose.
  - During this process, 2,3 diphosphoglyceric acid (2,3-DPG) is made.
  - Inhibited by oxyhemoglobin
  - 2,3-DPG is produced if a person is anemic or at high altitude.
  - This increases oxygen unloading.

Effect of 2,3-DPG on Oxygen Transport



Factors That Affect O_2 Transport

Table 16.9 | Factors That Affect the Affinity of Hemoglobin for Oxygen and the Position of the Oxyhemoglobin Dissociation Curve

Factor	Affinity	Position of Curve	Comments
↓pH	Decreased	Shift to the right	Called the Bohr effect; increases oxygen delivery during hypercapnia
↑Temperature	Decreased	Shift to the right	Increases oxygen unloading during exercise and fever
↑2,3-DPG	Decreased	Shift to the right	Increases oxygen unloading when there is a decrease in total hemoglobin or total oxygen content; an adaptation to anemia and high-altitude living

Fetal Hemoglobin

- Adult hemoglobin (hemoglobin A) can bind to 2,3-DPG, but fetal hemoglobin (hemoglobin F) cannot.
  - Fetal hemoglobin therefore has a higher affinity for O_2 than the mother, so oxygen is transferred to the fetus.

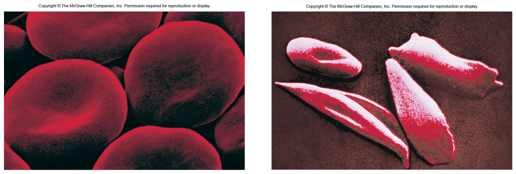
Inherited Hemoglobin Defects

- Sickle-cell anemia: found in 8−11% of African Americans
  - The affected person has hemoglobin S with a single amino acid difference.
  - Deoxygenated hemoglobin S polymerizes into long fibers, creating a sickle-shaped RBC.
  - This hinders flexibility and the ability to pass through small vessels.

Inherited Hemoglobin Defects

- Sickle-cell anemia:
  - Blood flow to organs is restricted, and RBCs hemolyse.
  - Treated with hydroxyurea; stimulates production of fetal hemoglobin without the defect

Inherited Hemoglobin Defects


(a) (b)

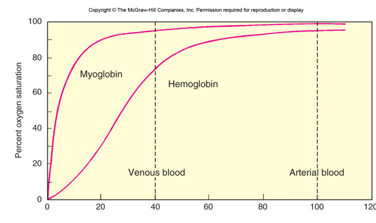
Inherited Hemoglobin Defects

- Thalassemia: found mainly in people of Mediterranean heritage
  - Production of either alpha or beta chains is defective.
  - Symptoms are similar to sickle-cell anemia.
- Both inherited hemoglobin defects carry resistance to malaria.

Myoglobin

- Red pigment found in skeletal and cardiac muscles
- Similar to hemoglobin, but with 1 heme, so it can only carry 1 oxygen molecule
- Higher affinity to oxygen; oxygen is only released when P_{O2} is very low
- Stores oxygen and serves as go-between in transferring oxygen from blood to mitochondria

Myoglobin and Hemoglobin Dissociation Curves



VII. Carbon Dioxide Transport

Carbon Dioxide in the Blood

- Carried in the blood in three forms:
  - Dissolved in plasma
  - As carbaminohemoglobin attached to an amino acid in hemoglobin
  - As bicarbonate ions

Carbonic Anhydrase

- Enzyme that combines water with CO_2 to form carbonic acid at high P_{CO2}
- Occurs within RBCs in the capillaries of systemic circulation:

$$H_2O + CO_2 \longrightarrow H_2CO_3$$

Formation of Bicarbonate and H^+

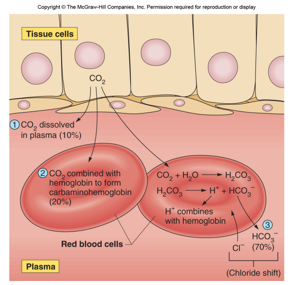
- Increases in carbonic acid favor dissociation into bicarbonate and hydrogen ions:

$$H_2CO_3 \longrightarrow H^+ + HCO_3^-$$

Chloride Shift

- H^+ in RBCs attach to hemoglobin and attract Cl^-.
- The exchange of bicarbonate out of and Cl^- into RBCs is called the chloride shift.

Chloride Shift



Bohr Effect

- Bonding of H^+ to hemoglobin lowers the affinity for O_2 and helps with unloading.
- This allows more H^+ to bind, which helps the blood carry more carbon dioxide.

Reverse Chloride Shift

- In pulmonary capillaries, increased P_{O2} favors the production of oxyhemoglobin.
- This makes H^+ dissociate from hemoglobin and recombine with bicarbonate to form carbonic acid:

$$H^+ + HCO_3^- \longrightarrow H_2CO_3$$

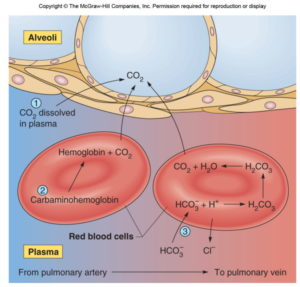
Reverse Chloride Shift

- In low P_{CO2}, carbonic anhydrase converts carbonic acid back into CO_2 + H_2O:

$$H_2CO_3 \longrightarrow CO_2 + H_2O$$

- CO_2 is exhaled.

Reverse Chloride Shift



VIII. Acid- Base Balance of the Blood

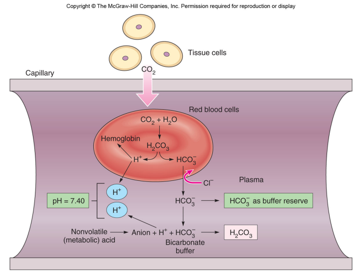
Acid-Base Balance

- Maintained within a constant range by the actions of the lungs and kidneys
  - pH ranges from 7.35 to 7.45.
  - Since carbonic acid can be converted into a gas and exhaled, it is considered a volatile acid.
  - Nonvolatile acids (lactic, fatty, ketones) are buffered by bicarbonate.

Bicarbonate as a Buffer

- Buffering cannot continue forever because bicarbonate will run out.
  - Kidneys help by releasing H^+ in the urine.

Bicarbonate as a Buffer



Blood pH: Acidosis

- Acidosis: when blood pH falls below 7.35
  - Respiratory acidosis: hypoventilation
  - Metabolic acidosis: excessive production of acids, loss of bicarbonate (diarrhea)

Blood pH: Alkalosis

- Alkalosis: when blood pH rises above 7.45
  - Respiratory alkalosis: hyperventilation
  - Metabolic alkalosis: inadequate production of acids or overproduction of bicarbonates, loss of digestive acids from vomiting
- Respiratory component of blood pH measured by plasma CO_2
- Metabolic component measured by bicarbonate

Acid Base Balance

Table 16.10 | Terms Used to Describe Acid-Base Balance

Term	Definition
Acidosis, respiratory	Increased CO_2 retention (due to hypoventilation), which can result in the accumulation of carbonic acid and thus a fall in blood pH to below normal
Acidosis, metabolic	Increased production of "nonvolatile" acids, such as lactic acid, fatty acids, and ketone bodies, or loss of blood bicarbonate (such as by diarrhea), resulting in a fall in blood pH to below normal
Alkalosis, respiratory	A rise in blood pH due to loss of CO_2 and carbonic acid (through hyperventilation)
Alkalosis, metabolic	A rise in blood pH produced by loss of nonvolatile acids (such as excessive vomiting) or by excessive accumulation of bicarbonate base
Compensated acidosis or alkalosis	Metabolic acidosis or alkalosis are partially compensated for by opposite changes in blood carbonic acid levels (through changes in ventilation) Respiratory acidosis or alkalosis are partially compensated for by increased retention or excretion of bicarbonate in the urine.

Table 16.11 | Classification of Metabolic and Respiratory Components of Acidosis and Alkalosis

Plasma CO_2	Plasma HCO_3^-	Condition	Causes
Normal	Low	Metabolic acidosis	Increased production of "nonvolatile" acids (lactic acids, ketone bodies, and others), or loss of HCO_3^- in diarrhea
Normal	High	Metabolic alkalosis	Vomiting of gastric acid; hypokalemia; excessive steroid administration
Low	Low	Respiratory alkalosis	Hyperventilation
High	High	Respiratory acidosis	Hypoventilation

Henderson-Hasselbalch Equation

- Normal blood pH is maintained when bicarbonate and CO_2 are at a ratio of 20:1.

$$pH = 6.1 + \log \frac{HCO_3^-}{0.03P_{CO2}}$$

Ventilation and Acid-Base Balance

- Ventilation controls the respiratory component of acid-base balance.
  - Hypoventilation: Ventilation is insufficient to "blow off" CO_2. P_{CO2} is high, carbonic acid is high, and respiratory acidosis occurs.
  - Hyperventilation: Rate of ventilation is faster than CO_2 production. Less carbonic acid forms, P_{CO2} is low, and respiratory alkalosis occurs.

Ventilation and Acid-Base Balance

- Ventilation can compensate for the metabolic component.
  - A person with metabolic acidosis will hyperventilate.
  - A person with metabolic alkalosis will hypoventilate.

Ventilation and Acid-Base Balance

Table 16.12 | Effect of Lung Function on Blood Acid-Base Balance

Condition	pH	P_{CO_2}	Ventilation	Cause or Compensation
Normal	7.35–7.45	39–41 mmHg	Normal	Not applicable
Respiratory acidosis	Low	High	Hypoventilation	Cause of the acidosis
Respiratory alkalosis	High	Low	Hyperventilation	Cause of the alkalosis
Metabolic acidosis	Low	Low	Hyperventilation	Compensation for acidosis
Metabolic alkalosis	High	High	Hypoventilation	Compensation for alkalosis

IX. Effect of Exercise and High Altitude on Respiratory Function

Ventilation During Exercise

- Exercise produces deeper, faster breathing to match oxygen utilization and CO_2 production.
  - Called hyperpnea
- Neurogenic and humoral mechanisms control this.

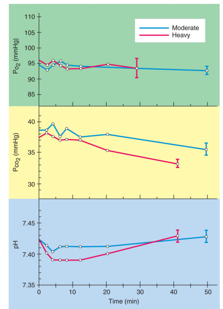
Proposed Neurogenic Mechanisms

- Sensory nerve activity from exercising muscles stimulates respiration via spinal reflexes or brain stem respiratory centers.
- Cerebral cortex stimulates respiratory centers.

Humoral Mechanisms

- Rapid and deep breathing continues after exercise is stopped due to humoral factors.
  - P_{CO2} and pH differences at sensors

Humoral Mechanisms



Lactate Threshold

- Ventilation does not deliver enough O_2 at the beginning of exercise.
  - Anaerobic respiration occurs at this time.
  - After a few minutes, muscles receive enough oxygen.
- If heavy exercise continues, lactic acid fermentation will be used again.
  - The lactate threshold is the maximum rate of oxygen consumption attained before lactic acid levels rise.

Lactate Threshold

- Occurs when 50−70% maximum oxygen uptake is reached
  - Due to aerobic limitations of the muscles, not the cardiovascular system
  - Endurance exercise training increases mitochondria and Krebs cycle enzymes in the muscles

Changes in Ventilation During Exercise

Table 16.13 | Changes in Respiratory Function During Exercise

Variable	Change	Comments
Ventilation	Increased	In moderate exercise, ventilation is matched to increased metabolic rate. Mechanisms responsible for increased ventilation are not well understood.
Blood gases	No change	Blood gas measurements during light and moderate exercise show little change because ventilation is increased to match increased muscle oxygen consumption and carbon dioxide production.
Oxygen delivery to muscles	Increased	Although the total oxygen content and P_{O_2} do not increase during exercise, there is an increased rate of blood flow to the exercising muscles.
Oxygen extraction by muscles	Increased	Increased oxygen consumption lowers the tissue P_{O_2} and lowers the affinity of hemoglobin for oxygen (due to the effect of increased temperature). More oxygen, as a result, is unloaded so that venous blood contains a lower oxyhemoglobin saturation than at rest. This effect is enhanced by endurance training.

Acclimation to High Altitude

- Adjustments must be made to compensate for lower atmospheric PO_2.
  - Changes in ventilation
  - Hemoglobin affinity for oxygen
  - Total hemoglobin concentration

Blood Gas Measurements at Different Altitudes

Table 16.14 | Blood Gas Measurements at Different Altitudes

Altitude	Arterial P_{O_2} (mmHg)	Percent Oxyhemoglobin Saturation	Arterial P_{CO_2} (mmHg)
Sea level	90–95	97%	40
1,524 m (5,000 ft)	75–81	95%	32–33
2,286 m (7,500 ft)	69–74	92%–93%	31–33
4,572 m (15,000 ft)	48–53	86%	25
6,096 m (20,000 ft)	37–45	76%	20
7,620 m (25,000 ft)	32–39	68%	13
8,848 m (29,029 ft)	26–33	58%	9.5–13.8

Source: From P. H. Hackett et al.,"High Altitude Medicine" in *Management of Wilderness and Environmental Emergencies,* 2d ed., edited by Paul S. Auerbach and Edward C. Geehr. Copyright © 1989 Mosby-Yearbook. Reprinted by permission.

Changes in Ventilation

- Hypoxic ventilatory response: Decreases in P_{O2} stimulate the carotid bodies to increase ventilation.
  - Hyperventilation lowers P_{CO2}, causing respiratory alkalosis.
  - Kidneys increase urinary excretion of bicarbonate to compensate.
  - Chronically apoxic people produce NO in the lungs, a vasodilator that increases blood flow.

Affinity of Hemoglobin for Oxygen

- Oxygen affinity decreases, so a higher proportion of oxygen is unloaded.
  - Occurs due to increased production of 2,3-DPG
  - At extreme high altitudes, effects of alkalosis will override this, and affinity for oxygen will increase.

Increased Hemoglobin Production

- Kidney cells sense decreased P_{O2} and produce erythropoietin.
  - This stimulates bone marrow to produce more hemoglobin and RBCs.
  - Increased RBCs can lead to polycythemia, which can produce pulmonary hypertension.

Changes at High Altitude

Table 16.15 | Changes in Respiratory Function During Acclimatization to High Altitude

Variable	Change	Comments
Partial pressure of oxygen	Decreased	Due to decreased total atmospheric pressure
Partial pressure of carbon dioxide	Decreased	Due to hyperventilation in response to low arterial P_{O_2}
Percent oxyhemoglobin saturation	Decreased	Due to lower P_{O_2} in pulmonary capillaries
Ventilation	Increased	Due to lower P_{O_2}
Total hemoglobin	Increased	Due to stimulation by erythropoietin; raises oxygen capacity of blood to partially or completely compensate for the reduced partial pressure
Oxyhemoglobin affinity	Decreased	Due to increased DPG within the red blood cells; results in a higher percent unloading of oxygen to the tissues

Respiratory Adaptations to High Altitude