RESPIRATORY PHYSIOLOGY

Based on the lecture and text material, you should be able to do the following:

→ describe the basic anatomy of the respiratory system
→ describe several protective mechanisms of the respiratory system
→ describe the structure of the respiratory membrane (the interface between the alveolar air and the capillary plasma) and relate structure to function
→ describe the pleural coverings of the lungs and the physiological mechanisms maintaining intrapleural pressure
→ describe the mechanical events associated with breathing
→ describe the physical factors influencing pulmonary ventilation
→ explain the relative roles of the respiratory muscles and lung elasticity in effecting volume changes that cause air to flow in and out of the lungs
→ describe the different respiratory volumes
→ describe gas exchange across the lungs
→ describe how oxygen is transported in the blood
→ describe how CO₂ is transported by the blood
→ describe how ventilation is controlled
→ compare and contrast the influences of the following factors on respiratory rate and depth of breathing: Lung reflexes, emotions, arterial pH, and partial pressures of O₂ and CO₂ in arterial blood
Pressure Relationships in the Thoracic Cavity

Respiratory pressures are always described in relation to atmospheric pressure (the pressure exerted by the gases surrounding the body), which is 760 mm Hg at sea level.

*Intrapulmonary pressure* is the pressure within the alveoli of the lungs. It fluctuates during the process of breathing but always equalizes itself with the atmospheric pressure.

*Intrapleural* pressure is the pressure within the pleural cavity. It fluctuates with breathing but is always about 4 mm Hg less than intrapulmonary pressure; therefore, it is always negative relative to intrapleural and atmospheric pressures.

**How do the lungs remain inflated/open?**

2 forces act to pull the visceral pleura away from the parietal pleura (hence collapsing the lungs):

% elasticity of the lungs gives them a natural tendency to recoil and assume their smallest possible size

% fluid film on in the alveoli create surface tension which acts to draw the alveoli in to their smallest possible dimension (this force is minimal due to surfactant, which is discussed later)

Λ These forces are **opposed** by the natural elasticity of the chest wall which tends to pull the thorax outward and enlarge the lungs

Λ a healthy person none of these forces overrides an other | the pleura secrete pleural fluid into the pleural cavity, creating a surface tension that secures the 2 pleural layers together and allow them to slide over one another | separating them requires great force

**How is the negative intrapleural pressure maintained?**

almost as quickly as the pleura secrete it, pleural fluid is pumped out of the pleural cavity into the lymphatic system | this ensures that only a minimal amount of pleural fluid remains in the pleural cavity

if the fluid is not adequately pumped out, and excessive pleural fluid accumulates in the pleural cavity, a positive pressure is created in the pleural cavity and the lung(s) will collapse (**atelectasis**)
Note: since each lung is in a separate pleural cavity, one lung can collapse while the other remains unaltered

*pneumothorax* refers to the presence of air in the intrapleural space

**Pulmonary Ventilation (Breathing)**

is a completely mechanical process that depends on volume changes in the thoracic cavity

**Boyle’s Law** states that when the temperature is constant, the pressure of gas varies inversely with its volume:

\[
P_2V_2 = P_1V_1
\]

(where \(P\) is the pressure of gas in millimeters of mercury [mm Hg] and \(V\) is the volume of gas in mm³)

- gases conform to the shape of their container (i.e. the lungs) and they always fill their container.

\%
- therefore, in a large volume, the gas molecules will be far apart and the pressure will be low
\%
- if the volume is reduced, the gas molecules will be compressed and the pressure will rise

**Inspiration**

results from the enlargement of the thoracic cavity by the actions of the **diaphragm** and the **external intercostals muscles**

when the diaphragm contracts, it moves inferiorly and flattens out, which increases the height of the thoracic cavity

when the external intercostals muscles contract, the rib cage is lifted and the sternum is pulled forward, which increases the width and depth of the thoracic cavity
the diaphragm plays a more important role in the volume changes that lead to *normal quiet respiration*, while the external intercostals play a prominent role in heavy deep breathing.

as the thoracic cavity enlarges, the intrapulmonary pressure decreases since gases always flow from areas of higher pressure to those of lower pressure, air then rushes into the thoracic cavity, hence inspiration.

as air rushes into the lungs, intrapulmonary pressure increases again when the intrapulmonary pressure atmospheric pressure are equal, inspiration ends.

**Expiration**

in healthy people, expiration is a passive process that depends on the natural elasticity of the lungs inspiratory muscles relax, lungs recoil, intrapulmonary pressure increases forcing air out of the lungs.

forced expiration is an active process generated by contraction of abdominal muscles, internal intercostals, the latissimus dorsi and others.

**Physical Factors Influencing Breathing**

energy is needed for inspiratory muscles to contract (thereby enlarging the thoracic cavity) and to overcome several physical obstacles to breathing which include:

- Airway resistance
- Alveolar surface tension forces
- Lung compliance

**Airway resistance**

the major source of non-elastic resistance to air flow friction in the respiratory passageways.

resistance in the respiratory tree is determined mostly by the diameters of the conducting tubules (i.e. trachea, bronchi, bronchioles, etc.)

generally, airway resistance is insignificant because:

- airways in the initial part of the respiratory tree have huge diameters
gas flow stops at the terminal bronchioles, where airways have small diameters, but this is not a problem because here diffusion takes over as the main force driving gas movements. Therefore, the greatest resistance to gas flow occurs in the medium-sized bronchi.

Smooth muscle in the walls of the bronchioles is extremely sensitive to neural and some chemical stimulation. I.e. parasympathetic reflexes activated by inhaled irritants, and chemicals such as histamine, cause a very powerful constriction of bronchioles and significant reduction in size of airways. During an acute asthma attack, airways may be so severely reduced in size that breathing may become impossible. Epinephrine must be administered immediately to dilate the bronchioles and reduce airway resistance.

**Alveolar surface tension forces**

Walls of alveoli are coated with a thin film of liquid composed mostly of water but also containing surfactant. At any gas-liquid interface, the molecules of liquid are more strongly attracted to each other than to the gas. This results in surface tension that:

- Draws the liquid molecules together, reducing their overall contact with the gas
- Resists any force that tends to increase the area of the liquid surface

Surfactant in the alveolar film is made up of lipid-protein complexes produced by the type II alveolar cells. It interferes with the cohesiveness of water molecules, reducing the surface tension of the alveolar fluid. As a result, less energy is required to overcome surface tension forces to expand the lungs and discourage alveolar collapse.

**Lung compliance**

Describes the ability of the lungs to stretch. The higher the compliance of the lungs, the easier it is to expand them at any given transpulmonary pressure.
lungs compliance is determined mainly by 2 factors:

% elasticity of lung tissue and the thoracic cage
% surface tension in the alveoli

the lungs of healthy people have high compliance - because lung tissue and thoracic elasticity are high and alveolar surface tension is low (due to surfactant) allowing for efficient ventilation

Gas Exchanges in the Body

**Dalton's Law of Partial Pressure** states that the total pressure exerted by a mixture of gases is the sum of the pressures exerted independently by each gas in the mixture.

the pressure exerted by each gas, or its *partial pressure*, is directly proportional to its percentage in the total gas mixture.

**Henry's Law** states that when a mixture of gases comes in contact with a liquid, each gas will dissolve in the liquid in proportion to its partial pressure. Therefore, the greater the concentration of a gas in the mixture, the more and faster it will go into a solution.

should the partial pressure of a gas become greater in the liquid than in the gas phase, some of the gas molecules will return to the gas phase. Therefore the direction and amount of gas movements are determined by the partial pressures of the gas in the two phases.

the volume of the gas that will dissolve in a liquid at any given partial pressure is proportional to the solubility of the gas in the liquid. Among the gases found in air, carbon dioxide is most soluble, oxygen is only 1/20 as soluble as CO₂, and nitrogen is practically insoluble in blood plasma.

the solubility of any gas in water (or plasma) decreases with increasing temperature

Composition of Alveolar Gases

air is composed of nitrogen (79%); oxygen (21%); carbon dioxide (0.04%)
the alveoli contain much more carbon dioxide (5%) and much less oxygen (14%)
these differences are largely due to the fact that:

- gas exchanges are occurring in the lungs. Oxygen is diffusing from the alveoli into the pulmonary blood and carbon dioxide is diffusing in the opposite direction.
- with each tidal inspiration, alveolar gas is actually a mixture of newly inspired air and air that remained in the respiratory pathway between breaths.

**Pulmonary Gas Exchange (External Respiration)**

- oxygen enters the blood in the lungs and carbon dioxide leaves.
- the movement of these gases is affected by partial pressure gradients and gas solubilities.
- there is a steep gradient of \( P_{O_2} \) across the respiratory membrane \( (P_{O_2} \) of venous blood in the pulmonary arteries is only 40 mm Hg compared to 104 mm Hg in the alveoli), as a result, oxygen diffuses rapidly from the alveoli into the lung capillaries.
- the partial pressure gradient for \( CO_2 \) is much less steep \( (45 \text{ mm Hg in the lung capillary blood vs. } 40 \text{ mm Hg in the alveoli}) \), however, because \( CO_2 \) is 20 times more soluble in plasma than oxygen is, it is exchanged at equal rates as oxygen.

**Capillary Gas Exchange in the Body Tissues (Internal Respiration)**

- the partial pressure and diffusion gradients are reversed in the body tissues.
- due to their metabolic activities, cells constantly use oxygen and produce equal amounts of carbon dioxide.
- the \( P_{O_2} \) in the tissues is always lower than in the systemic arterial blood \( (40 \text{ mm Hg to } 104 \text{ mm Hg, respectively}) \), therefore, oxygen rapidly diffuses from the blood into the tissues.
- \( CO_2 \) moves in the opposite direction \( (\text{from tissues into the blood}) \), along its own partial pressure gradient.
venous blood draining the capillary beds of the tissues and returning to the heart has a Po2 of 40 mm Hg and a PCO2 of 45 mm Hg

**Oxygen Transport**

oxygen is transported in blood in two ways:

% dissolved in plasma (only 1.5% because O2 is poorly soluble in plasma)
% bound to hemoglobin inside RBCs (98.5% is carried this way)

hemoglobin (Hb) is a protein composed of 4 polypeptide chain subunits

each subunit is bound to an iron-containing heme group

since iron ions serve as oxygen-binding sites, each hemoglobin can rapidly and reversibly bind 4 oxygen molecules

a hemoglobin molecule bound with oxygen is called *oxyhemoglobin (HbO2)*
a hemoglobin molecule that has released its oxygen is called *deoxyhemoglobin (HHb)*

when the first oxygen molecule binds the first iron molecule, the hemoglobin changes shape and the affinity for the other 3 oxygen molecules progressively increases

similarly, when the first oxygen is unloaded, the affinity for oxygen is decreased and it becomes progressively easier for the other 3 oxygen molecules to dissociate from the hemoglobin

hemoglobin is *fully saturated* when all four heme groups are bound to oxygen

if fewer than all four heme groups are bound, the hemoglobin is said to be *partially saturated*

**The Oxygen-Hemoglobin Dissociation Curve**

describes the relationship between percentage of hemoglobin saturation and Po2
it is a sigmoid-shaped (S-shaped) curve because changes in affinity of hemoglobin depend on oxygen saturation

the curve has a steep slope between 10-50 mm Hg \( P_{O_2} \) and a plateau between 70-100 mm Hg \( P_{O_2} \) (see figure 23.19)

under normal resting conditions, arterial blood has a \( P_{O_2} \) of 104 mm Hg and a saturation of 98%

100 ml of arterial blood contains about 20 ml of oxygen, therefore, the oxygen content can be written as 20 vol. % (volume percent)

as arterial blood flows through the systemic capillaries, about 5 ml \( O_2 \)/ 100 ml of blood is released into tissue \( \frac{this}{oxygen content} \) to 15 ml vol. %, \( hemoglobin saturation \) to 75%, and \( P_{O_2} \) to 40 mm Hg in the venous blood

a large decrease in \( P_{O_2} \) (104 \( | \) 40 mm Hg) is associated with a much smaller decrease in Hb saturation (98% \( | \) 75%) \textbf{How is this possible?}

\%
- the alveoli have a large surface area, as do the pulmonary capillaries
\%
- the respiratory membrane is extremely thin
\%
- the blood flow rate in capillaries is very slow

as a result, the amount of oxygen dissolved in plasma equals the amount of oxygen in the alveolar air \( P_{O_2} \) in alveoli and pulmonary capillaries is equal (104 mm Hg)

a significant amount of oxygen is still available in venous blood and can easily be unloaded from blood to tissues during, for example, vigorous exercise

since hemoglobin in arterial blood is 98% saturated, heavy breathing during exercise increases \( P_{O_2} \) above the normal 104 mm Hg, but causes very little change in % saturation

hemoglobin is almost completely saturated at any \( P_{O_2} \) above 70 mm Hg \( B \) this allows for normal oxygen delivery to tissues when \( P_{O_2} \) of inspired air is below normal (i.e. high altitudes)

other factors have a significant effect on the affinity of hemoglobin for oxygen by modifying its 3-dimensional shape:
temperature
pH (H+ concentration)
P<sub>CO2</sub>
BPG (biphosphoglycerate) is a unique compound produced by RBCs that binds reversibly with Hb

generally, an increase in any of these factors results in a decreased affinity for oxygen, while a decrease in any of these factors results in an increased affinity for oxygen.

this makes sense because these factors tend to be at their highest levels in the systemic capillaries where (as the Bohr effect states) oxygen unloading is most needed and therefore accelerated.

for example, heat is released by active tissues | active tissues require more oxygen than inactive ones | the rise in temperature decreases hemoglobin=s affinity for oxygen, thereby making more oxygen available for the active tissue.

similarly, active cells metabolize glucose and use oxygen while producing carbon dioxide | this increase the P<sub>CO2</sub> and H+ concentration | this in turn weakens the hemoglobin-oxygen bond and makes available more oxygen.

Impairments of Oxygen Transport

*hypoxia* refers to inadequate delivery of oxygen to body tissues.

The most common causes include:

- **anemic hypoxia**: too few RBCs or RBCs that have abnormal hemoglobin.

- **ischemic hypoxia**: impaired or blocked blood circulation.

- **histotoxic hypoxia**: body cells cannot use oxygen even though there is adequate supply to the tissues (caused by metabolic poisons such as cyanide).

- **hypoxemic hypoxia**: reduced arterial P<sub>O2</sub> due to pulmonary disease or any condition that interferes with ventilation (i.e. CO poisoning) or breathing air with low oxygen content (i.e. very high altitudes).
Carbon Dioxide Transport in Blood

- The human body produces about 200 ml of CO₂ each minute
- CO₂ is transported in the blood in 3 ways:
  - 10% dissolved in plasma
  - 20-30% forms carbamino compounds with NH₂ groups on proteins like hemoglobin
  - 60-70% is converted to HCO₃⁻ and transported in plasma

- Remember: CO₂ is 20 times more soluble in plasma than is oxygen.
- The loading and unloading of CO₂ to and from Hb depends on:
  - APCO₂
  - Hb saturation (with oxygen)
  - Remember that CO₂ is loaded in tissues where PCO₂ is high and PO₂ is low and unloaded in the lungs where the opposite is true, therefore, deoxygenated blood binds to CO₂ more easily than oxygenated blood.
  - This phenomenon is referred to as the Haldane effect.

Regulation of Gas Transfer and Respiration

- Is controlled in 2 ways:
  - Ventilation-perfusion coupling
  - Neural regulation

Ventilation-perfusion Coupling

- For efficient gas exchange to occur, the amount of gas reaching the alveoli (ventilation) must be coupled to the flow of blood in pulmonary capillaries (perfusion).
- Local autoregulatory mechanisms ensure that this is the case.
  - In alveoli where ventilation is inadequate, PO₂ is low. This results in constriction of pulmonary terminal arterioles and redirection of blood to areas of the lung with proper ventilation.
  - In alveoli where ventilation is maximal, pulmonary terminal arterioles dilate to increase blood flow into associated capillaries.
this mechanism is opposite to that discussed earlier in the autoregulation of blood flow in the systemic circulation

changes in $P_{CO_2}$ affect the diameter of the bronchioles: those leading to areas of the lungs with high $CO_2$ concentrations dilate, while those serving areas with low $CO_2$ concentration constrict

in summary, poor ventilation results in low $P_{O_2}$ and high $P_{CO_2}$ in the alveoli. this leads to constriction of pulmonary arteries and dilation of the bronchioles which creates equilibrium of air and blood flows

the opposite is true for high $P_{O_2}$ and low $P_{CO_2}$

**Neural Regulation**

provided by:

- medullary respiratory centers
- pons respiratory centers

**Medullary Respiratory Centers**

2 medullary centers play a role in respiration:

- *dorsal respiratory group (DRG)*
- *ventral respiratory group (VRG)*

the DRG is a cluster of neurons located near the root of cranial nerve IX and appears to be the pacesetting respiratory center

the DRG is therefore called the inspiratory center (since it is inspiration that is the active process, while expiration is a passive process)

when neurons in the DRG fire, impulses travel down the *phrenic* and *intercostal* nerves to stimulate the diaphragm and external intercostal muscles (respectively)

the thoracic cavity expands and air rushes in = inspiration

the DRG then becomes dormant, allowing the inspiratory muscles to relax and the passive process of expiration to take place
the rhythm of the DRG creates a respiratory rate of 12-15 breathes per
minute, with the inspiratory phase lasting about 2 seconds and the expiratory
phase lasting about 3 seconds

this normal resp. rate and rhythm is called eupnea

the VRG is a network of neurons that extend from the spinal cord (within the
ventral brain stem) to the pons-medullary border

the role of the VRG is unclear, but it is thought to be involved in forced
breathing, especially forced expiration

Pons Respiratory Centers

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Pons Respiratory Centers

these 2 centers influence and modify the activity in both the DRG and the
VRG:

% the pneumotaxic center (inhibits the medulla)
% the apneustic center (may have a stimulatory effect on DRG)

Factors Influencing the Rate and Depth of Breathing

Pulmonary irritant reflexes

are stimulated by activation of receptors that respond to irritants in the lungs
(i.e. accumulated mucus and inhaled smoke, dust, lint or noxious fumes)

these receptors send signals to the respiratory centers via afferent fibers of
the vagus nerve

if receptors in the bronchioles are stimulated, these airways constrict

if receptors in the trachea or bronchi are stimulated, coughing is induced

if receptors in the nasal cavity are stimulated, sneezing is induced

The inflation reflex (Hering-Breuer reflex)
baroreceptors (stretch receptors) in the visceral pleura and airways to the lungs are stimulated during inspiration

these receptors send action potentials to the medullary respiratory centers via afferent fibers of the vagus nerve

despite these signals inhibit inspiration and allow expiration to occur

as the lungs recoil, the baroreceptors stop firing and inspiration is initiated once again

despite this reflex protects the lungs from over-inflation and excessive stretching

The influence of higher brain centers

despite the hypothalamus and the cerebral cortex can both influence the rhythmic activity of the respiratory centers

strong emotions, pain, and changes in temperature all activate centers in the hypothalamus which in turn alters the resp. rate and rhythm:

\[
\begin{align*}
\text{anger} & \quad \text{increases resp. rate} \\
\text{excitation} & \quad \text{decrease in temp. can cause apnea} \\
\text{decrease in temp.} & \quad \text{increase in temp. causes an increase in resp. rate}
\end{align*}
\]

the cerebral motor cortex directly stimulates the motor neurons of the inspiratory muscles (bypassing the medullary centers) when we want to consciously control our breathing i.e. holding our breath or changing the depth of our breathing

however, our ability to hold our breath is limited the respiratory centers automatically reinitiate breathing when concentrations of CO₂ in the blood reach critical levels this is why drowning victims always have water in their lungs

Chemical factors

most important are CO₂, O₂ and H⁺ concentrations in arterial blood

despite these chemicals are monitored by chemoreceptors of two kinds:
central chemoreceptors (CCRs) found in the medulla

peripheral chemoreceptors (PCRs) found within the aortic arch and carotid arteries in the neck

**Effects of PCO₂**

- most important and most closely controlled
- concentration is monitored mainly by the CCRs (PCRs are weakly responsive to PCO₂)
- as CO₂ diffuses from the blood into the CSF, carbonic acid is formed and quickly dissociated into hydrogen ions and water; the CSF contains very few proteins and therefore has no ability to buffer these free ions (therefore, as PCO₂ levels rise, the pH of CSF rapidly decreases)
- the decrease pH leads to excitation of the CCRs which synapse directly with resp. regulatory centers in the midbrain
- resp. centers increase the depth and rate of breathing (hyperventilation), which flushes the CO₂ from the blood; the blood pH increases; CSF pH increases
- Note: CCRs respond directly to the rising H+ concentrations (decreasing pH) not to the CO₂ levels themselves
- when PCO₂ levels are abnormally low, breathing becomes slow and shallow (hypoventilation), or may stop completely, until the arterial CO₂ rises again and stimulates respiration

**Effects of PO₂**

- arterial oxygen levels are monitored by the PCRs in the aortic bodies of the aortic arch and the carotid bodies at the bifurcation of the common carotid arteries (the latter is the main oxygen sensor)
- PO₂ must drop to 60 mm Hg or less to have a significant effect on ventilation since there is a huge reservoir of oxygen bound to hemoglobin (Hb remains almost completely saturated as long as PO₂ stays above 60 mm Hg)
- when arterial oxygen levels do fall below this critical value, the CCRs suffer from oxygen starvation and become depressed; PCRs, however, become
excited and stimulate resp. centers to increase ventilation, thereby maintaining adequate resp. despite depression of brain centers due to hypoxia

Effects of arterial pH

<table>
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<tr>
<th>decreasing arterial pH can be a result of:</th>
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<tbody>
<tr>
<td>%  CO₂ buildup</td>
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<tr>
<td>%  accumulation of lactic acid during exercise</td>
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<tr>
<td>%  accumulation of fatty and ketone acids in patients with poorly controlled diabetes mellitus</td>
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<tr>
<td>%  other metabolic causes</td>
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| regardless of cause, declining pH induces the resp. system to increase both rate and depth of breathing, thereby eliminating carbon dioxide. |