# Respiratory system

I. Introduction

A. Respiration -- the sum of processes that accomplish passive movement of $O_2$ from atmosphere to tissues to support metabolism, as well as passive movement of $CO_2$ from tissues to the atmosphere

- internal respiration: occurs in mitochondria; use of cellular fuels (glucose, fatty acids) to produce ATP; $O_2$ is final electron acceptor and $CO_2$ produced as a metabolic waste product.

- external respiration: oxygen from the environment taken up and delivered to individual cells; carbon dioxide produced during cell metabolism excreted into environment

B. External and internal respiration

1. External respiration

- ventilation
- exchange of gases between air in alveoli and blood
- transport of gases
- exchange of gases between the blood and the tissues

2. Internal respiration.

C. Functional anatomy.

- nasal cavity, pharynx, larynx, trachea, bronchi, bronchioles, terminal bronchioles, respiratory bronchioles, alveolar ducts, alveolar sacs, alveoli.

1. two functional zones:

- conducting zone: includes passageways which serve as conduits for air to reach site of gas exchange; cleanse, humidify, warm incoming air.

- respiratory zone: actual site of gas exchange.

2. respiratory tract

a. nasal cavity --> larynx.

b. Trachea: from larynx to mediastinum.

c. Bronchi and their subdivisions: the bronchial tree.

- the trachea gives rise to the right and left primary bronchi which enter the lungs.

- once in the lungs the bronchi continue to divide (there are 23 orders); air passages under 1 mm diameter called bronchioles.

- as conducting tubes become smaller, structural changes occur:

- cartilage supports change: go from cartilage rings to plates; eventually disappear; no cartilage at bronchioles, elastic fibers in tube wall remain.
- type of epithelium changes: pseudostratified columnar to simple columnar to cuboidal.
- amount of smooth muscle increases.

- the terminal bronchioles mark the end of conducting zone.

- the respiratory zone begins at respiratory bronchioles: have occasional alveoli lining their walls; lead to alveolar ducts.

- alveolar ducts: walls almost entirely lined by alveoli; lead to clusters interconnected alveoli, alveolar sacs.

d. Alveoli (location of respiratory membrane).

- extensive network of capillaries are associated with each alveolus; capillaries are surrounded by a network of elastin fibers.
- alveolar epithelium: simple squamous (type 1 cells); also macrophages and surfactant cells (type II cells).
    - alveolar epithelium and capillary endothelial cells share a common BM.

e. Lungs and pleura

- pleura - a double layered serosa; parietal pleura, visceral pleura, pleural cavity that has pleural fluid.

II. Pulmonary ventilation.

- breathing/pulmonary ventilation: movement of air in and out of respiratory tract.

A. Basic properties of gases

- gases are compressible/expandable.

- the pressure exerted by a gas is inversely proportional to the volume it occupies.

B. Respiratory pressures (always expressed relative to atmospheric pressure, 760 mm Hg).

1. Intrapulmonary pressure: pressure within the alveoli, always driven to equalize itself to atmospheric pressure.

2. Intrapleural pressure; pressure within the pleural cavity.

- the parietal and visceral pleurae are separated by a thin film of pleural fluid; they are held together by surface tension of pleural fluid -- polar molecules in intrapleural fluid resist being pulled apart because of their attraction to each other; since parietal pleura is attached to the thoracic cavity and visceral pleura to lungs, this interaction holds lungs to thoracic wall.

- however elasticity of chest wall expands thorax outward; elasticity of alveoli pulls lungs inward; alveolar surface tension pulls alveoli inward

- as a result of the two sets of opposing forces "tugging" at the pleurae, a negative pressure is established in the intrapleural space (average -4 mm Hg, changes through insp/exp cycles).

C. Forces holding lungs and thoracic wall in close apposition

- surface tension of pleural fluid
- transmural pressure gradient
    - example of pneumothorax

D. Breathing movements.

1. Muscles/pressure changes: actions of respiratory muscles causes volume changes in the pulmonary cavity that causes pressure changes -- drive air movements in/out of lungs; air always flows from a region of high to low pressure in an attempt to create a pressure equalization.

a. Inspiration: diaphragm contracts and external intercostal contract; decreases intrapulmonary pressure, equalizes as air moves in; decrease in intrapleural pressure.

b. Expiration: diaphragm relaxes and external intercostal relax; increases intrapulmonary pressure, equalizes as air moves out.

2. Types of breathing.

a. quiet breathing: inspiration only involves diaphragm and external intercostal contractions; expiration is passive (relaxation of above muscles).

b. Forced breathing: both inspiration and expiration are forced; that is, additional accessory muscles are recruit into inspiration; contraction of a number of other muscles (internal intercostals, abdominal) also involved in bringing about expiration.

E. Resistance to breathing

- $F = P/R$

1. Primary determinant of resistance to airflow is radius of conducting airways

- occurs mostly in medium sized bronchi

- usually not an issue in healthy individual -- very small pressure gradients required to achieve adequate rates of airflow

- factors affecting bronchi diameter and therefore airway resistance:

- ANS effects: sympathetic effects produce bronchodilation; parasympathetic innervation (relaxed situations) produces bronchoconstriction
- local effects such as histamine release in allergic reaction (bronchoconstriction)

2. Chronic obstructive pulmonary disease (COPD)

a. chronic bronchitis

- long-term inflammatory condition -- triggered by irritant
- local accumulation of mucus
- pulmonary bacterial infections

b. asthma

- thickening or airway walls -- inflammation, histamine-induced edema
- plugging of airways -- excess mucus
- airway hyperresponsiveness -- SM spasms
- causes: allergens, irritants

c. emphysema

- increased trypsin secretion from macrophages
- destruction, collapse of small airways

3. Compliance: an indication of degree of expandability of lungs; any factor that decreases compliance (increase CT deposition in alveolar walls, decrease in surfactant levels) will enhance resistance to breathing

- the lower the compliance of the lungs, the larger the transmural pressure gradient that must be created during inspiration to produce normal lung expansion

- a greater than normal transmural pressure gradient during inspiration only achieved by making intrapleural pressure more subatmospheric than usual --> need greater expansion of thorax --> more vigorous contraction of respiratory muscle --> more work

4. alveolar surface tension

- in thin fluid film coating alveoli, water molecules have a greater attraction for each other than for the gas molecules they interface with

- this creates a form of tension (alveolar surface tension) that resists any increases in surface area and hence creates resistance to inspiratory movements that occur as part of breathing

- surfactant minimizes alveolar surface tension

F. Lung volumes: refer to amounts of air flushed in/out of lungs (ml).

1. Respiratory volumes:

a. Tidal volume (TV, 500 ml): the amount of air inhaled or exhaled with each breath under resting conditions.

b. Inspiratory reserve volume (IRV, 3100 ml): amount of air that can be inhaled beyond a tidal volume inhalation

c. Expiratory reserve volume (ERV, 1200 ml): amount of air that can be exhaled beyond a tidal volume exhalation.

d. Residual volume (RV, 1200 ml): the amount of air that is left in the lungs after a forced exhalation; provides air to alveoli even between breaths.

2. Respiratory capacities: sum of volumes.

a. Inspiratory capacity (IC= RV + IRV, 3600 ml): maximum volume of air a person is able to inspire after tidal volume expiration.

b. Functional residual capacity (FRC = ERV + RV, 2400 ml): the volume of air left in the lungs after the normal tidal expiration.

c. Vital capacity (VC = IRV + TV + ERV, 4800 ml): maximum volume of air that can be expired after a maximum inspiratory effort; measure of total amount of exchangeable air.

d. Total lung capacity (TLC = IRV + TV + ERV + RV): volume of air contained in the lungs after a maximum inspiratory effort.

3. Dead space (VD): volume of conducting zone airways where air does not participate in gas exchange; about 150 ml

F. Ventilation measurements: measurements of rates of gas movements in and out of respiratory tract.

1. Minute ventilation (Vm): total amount of air moved in and out of respiratory tract in one minute.

- Vm = respiratory rate (f) x TV.

2. Alveolar ventilation (VA): amount of air reaching alveoli in one minute; an adjustment of Vm for anatomical dead space; can change independently of minute volume; VA = f X (VT - VD)

- changes in TV will affect alveolar ventilation more drastically than respiratory rate changes, since anatomical dead space is always a constant for a particular individual.

III. Gas exchange and transport.

A. Properties of gases.

1. Dalton's law of partial pressures: the total pressure exerted by a mixture of gases is the sum of the pressures exerted by each individual gas in the mixture; the pressure exerted by each gas (partial pressure) is directly proportional to its percentage in the total gas mixture.

- note the differences in composition of atmospheric air and alveolar air:

a. atmospheric air: $P_{N2}$=597 mm Hg; $P_{O2}$=159 mm Hg; $P_{CO2}$ = 0.3 mm Hg; $P_{H20}$=3.7 mm Hg.

b. alveolar air: $P_{N2}$=569 mm Hg; $P_{O2}$=104 mm Hg; $P_{CO2}$ = 40 mm Hg; $P_{H20}$=47 mm Hg.

2. 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 exact volume of a gas that will dissolve in a liquid at any given partial pressure depends on the solubility of the gas in liquid.

B. Gas exchange.

1. External respiration: gas exchanges occurring between blood and alveolar air, governed by partial pressure gradients and gas solubilities.

| | **ALVEOLI** | direction of diffusion | **ENTERING BLOOD** | **LEAVING BLOOD** |
|---|---|---|---|---|
| $P_{O2}$ | 104 mm Hg | ----------> | 40 mm Hg | 104 mm Hg |
| $P_{CO2}$ | 40 mm Hg | <---------- | 45 mm Hg | 40 mmHg |

- other factors that influencing the movement of gases across respiratory membrane are the thickness of the respiratory membrane and surface area available for gas exchanges.

- note that partial pressure gradients for oxygen diffusion are much greater than those for carbon dioxide, however approximately equal amounts of these gases are exchanged due to solubility differences.

- summary: partial pressure gradients for the oxygen, carbon dioxide are key to gas exchanges; oxygen flows downhill from air --> alveoli --> tissue; carbon dioxide flows downhill from tissue --> air.

2. Internal Respiration: gas exchanges between blood and tissues.

| | **BLOOD ENTERING TISSUES** | direction of diffusion | **TISSUES** | **BLOOD LEAVING TISSUES** |
|---|---|---|---|---|
| $P_{O2}$ | 104 mm Hg | ----------> | < 40 mm Hg | 40 mm Hg |
| $P_{CO2}$ | 40 mm Hg | <---------- | > 45 mm Hg | 45 mmHg |

- note that partial pressure gradients for oxygen diffusion are much greater than those for carbon dioxide, however approximately equal amounts of these gases are exchanged due to solubility differences.

- summary: partial pressure gradients for the oxygen, carbon dioxide are key to gas exchanges; oxygen flows downhill from air --> alveoli --> tissue; carbon dioxide flows downhill from tissue --> air.

- however, the amount of both these gases transported to and from tissue would be grossly inadequate if 98.5% of dissolved oxygen didn't combine with hemoglobin (Hb) and 94.5% of dissolved carbon dioxide didn't enter a complex series of reactions in preparation for transport.

- without hemoglobin/carbon dioxide reactions the same $P_{O2}$ and $P_{CO2}$ would be achieved in blood, but blood would have a much lower oxygen/carbon dioxide carrying capacity.

C. Gas transport in the blood.

1. Oxygen transport.

- $O_2$ carried in two ways, dissolved in plasma (1.5%) and bound to Hb (98.5%).

a. Association/dissociation of oxygen and hemoglobin.

(i) one hemoglobin molecule binds four molecules of $O_2$ (review structure).

(ii) reduced or deoxygenated Hb - HHb; oxyhemoglobin ($HbO_2$).

(iii) loading/unloading of $O_2$:

HHb + O2 <----> $HbO_2$ + H+

- there is cooperation of four polypeptides of Hb molecule in binding and unbinding $O_2$; that is affinity of Hb for $O_2$ changes with the state of saturation of Hb: the greater the saturation of Hb, the greater the affinity for Hb.

b. Factors influencing the rate at which hemoglobin binds/releases oxygen.

(i) The influence of $P_{O2}$ on Hb saturation: the oxygen/hemoglobin dissociation curve.

- resting conditions $P_{O2}$ 104 mm Hg: the arterial blood is 98% saturated; 100 ml of systemic blood contains 20 ml $O_2$ ($O_2$ content is 20 vol%).

- as arterial blood flows through systemic caps: $P_{O2}$ about 40 mm Hg, 5 ml $O_2$/100 ml blood released, yielding a 75% Hb saturation and $O_2$ content of 15 vol% in venous blood.

(ii) Important features of oxygen/hemoglobin dissociation curve.

- Hb almost completely saturated at $P_{O2}$ 70 mm Hg, further increases of $P_{O2}$ cause only very small change in oxygen binding; therefore adequate oxygen loading and delivery are possible in conditions where partial pressure of oxygen of inspired air is well below the usual level.

- majority of oxygen unloading occurs in steep portions of the curve, where $P_{O2}$ changes very little; since only 20-25% of bound oxygen unloads during one systemic circuit, there are still large amounts of oxygen available in venous blood (venous reserve); therefore if $P_{O2}$ drops in tissues (as during exercise) more oxygen can dissociate from hemoglobin and be delivered to the tissues.

(iii) Influences of $P_{CO2}$, pH, BPG on Hb saturation.

- a number of factors listed above influence Hb saturation by modifying Hb 3D structure and thus its ability to bind $O_2$.

- increased temperature, $P_{CO2}$, BPG, and decreased pH will shift the dissociation curve to the right; this means that at a given $P_{O2}$, the percent of hemoglobin saturation with $O_2$ decreases dramatically, more oxygen is delivered; a shift of the curve to the left (less $O_2$ delivered at a given $P_{CO2}$) occurs if $P_{CO2}$ and temperature decrease and pH increases.

2. Carbon dioxide transport.

- occurs in three ways: dissolved in plasma, chemically bound to RBC Hb, as bicarbonate in plasma.

a. Dissolved in plasma: 7-10% of transported $CO_2$.

- however, most CO2 molecules that dissolve in plasma enter the RBC and participate in a number of chemical reactions that prepare CO2 for transport.

b. Chemically bound to hemoglobin in RBC.

- $CO_2$ + Hb ----> $HbCO_2$ quick, uncatalyzed reaction.

- reaction is influenced by PCO2 and the degree of hemoglobin oxygenation; increased PCO2, increased binding; decreased PCO2, decreased binding; HHb binds CO2 better than Hb.

c. Transported by bicarbonate in plasma.

- dissolved $CO_2$ enters RBC:

- $CO_2 + H_2O$ <---CA---> $H_2CO_3$ <------> $HCO_3^-$ + $H^+$ (CA: carbonic anhydrase)

(i) Tissues:

- hydrogen ions released cause a shift in the oxygen-hemoglobin dissociation curve to the right (Bohr effect).

- Hb binds up $H^+$, Hb + $H^+$ ----> HHb (buffering of $H^+$); HHb in turn has increased CO2 binding capacity.

- $HCO_3^-$ enters plasma, transported in this way (ionic balance maintained by $Cl^-$ shift).

(ii) Lungs:

- $HCO_3^-$ renters RBC; Cl shift.

- $HCO_3^-$ combines with $H^+$ made available by HHb + $O_2$ ---->$HbO_2$ + $H^+$; $H_2CO_3$ produced, which dissociates into $CO_2$ and $H_2O$, catalyzed by CA; $CO_2$ removed from lungs by ventilation.

(iii) Amount of $CO_2$ transported in the blood is directly affected by oxygenation of the blood (Haldane effect):

- in tissues as $CO_2$ moves into systemic blood and participates in CA reaction, due to Bohr effect (generation of $H^+$) more $O_2$ dissociates from Hg, i.e., oxygenation of blood decreases; deoxyhemoglobin can bind $CO_2$ more efficiently, so decreased Hb oxygenation increases $CO_2$ transport; furthermore, once $O_2$ dissociates from Hb, the latter binds up $H^+$ to form HHb (the CA reaction is pushed to the left), causing more CO2 to be "converted to $HCO3^-$

(iv) Alkaline reserve.

- $HCO_3^-$ ions are produced due to $CO_2$ transported in the plasma and act as an alkaline reserve.

- $CO_2$ + $H_2O$ <---CA---> $H_2CO_3$ <------> $HCO_3^-$ + $H^+$ (CA: carbonic anhydrase)

- thus changes in H+ ion concentration can have dramatic effects on $CO_2$ levels and ventilation rates; conversely, changes in respiratory rate can also have very dramatic effects in blood pH; in slow, shallow breathing $CO_2$ accumulates and causes decreased pH; in deep, rapid breathing, $CO_2$ drops and pH increase; therefore, the respiratory system provides a quick way to adjust blood pH.

IV. Regulation of respiration.

- involuntary control brought about by activity of neurons located in a number of centers in the medulla and pons, collectively called the respiratory centers; include the dorsal regulatory group, ventral regulatory group, apneustic center, pneumotaxic center.

A. Respiratory centers: respiratory cycle controlled by spontaneous, rhythmic discharge of neurons comprising the respiratory centers.

1. Medullary centers: these centers set the pace of respiration.

a. Dorsal regulatory group (DRG).

- contains neurons that control lower motor neurons innervating diaphragm and external intercostals; involved in every respiratory cycle.

b.Ventral regulatory group (VRG).

- contains a mix of neurons involved in forced expiration and maximal, forced inhalation.

Quiet breathing:

- activity of DRG increases for two seconds, stimulating inspiration muscles, inspiration occurs; after two seconds DRG stops firing, the inspiratory muscles relax and passive expiration occurs.

Forced breathing:

- activity of the DRG increases, somehow (??) the level of activity of inspiratory neurons in VRG increases; this results in stimulation of neurons that activate accessory muscles of inspiration; DRG stops firing, inspiratory neurons of VRG also is no longer active; expiratory neurons of VRG begin to fire; therefore, inspiratory muscles relax and muscles of forced expiration contract.

2. Pontine centers: adjust output of rhythmic medullary centers.

a. Apneustic center (AC): supplies continuous stimulation to DRG; during quiet breathing it helps increase intensity of inspiration every two seconds; after two seconds it is inhibited by pneumotaxic center.

b. Pneumotaxic center (PC): inhibits AC and helps to promote passive or active exhalation.

B. Factors influencing respiratory center activity.

1. Chemical controls of respiration

- aim is to hold arterial/alveolar $P_{CO2}$ constant, combat excess $H^+$, and raise the $P_{O2}$ when it begins to fall to potentially dangerous levels.

- $P_{CO2}$ is the most important variable governing ventilation; two centers involved in monitoring $P_{CO2}$2 of arterial blood: central chemoreceptors in the dorsal walls of the fourth ventricle (medulla) that monitor $H^+$ concentration of CSF; and peripheral chemoreceptors, cells in the walls of the aortic and carotid bodies, stimulated by rise in $P_{CO2}$, [H+] and drop of $P_{O2}$ or arterial blood

a. Central chemoreceptors.

- are located in the medullary area, in direct contact with CSF; monitor hydrogen ions concentration CSF.

- $CO_2$ passes through BBB into ventricle: $CO_2 + H_20$ <---CA---> $H_2CO_3$<------>$HCO_3^-$ + $H^+$

- increased $H^+$ concentration stimulates chemoreceptors that act on respiratory centers to increase rate and depth of respiration; when alveolar ventilation increases, carbon dioxide is flushed out.

b. Peripheral chemoreceptors.

- response of peripheral chemoreceptors to hypoxia

- denervation of peripheral chemoreceptors:

- response to $P_{O2}$ drop (while holding arterial $P_{CO2}$ at normal levels) is eliminated; response to increased arterial [H+] abolished (while holding arterial $P_{CO2}$ normal); response to increase in arterial $P_{CO2}$ reduced by 30%.

- thus mediate about 30% of response to increased $P_{CO2}$; also monitor $P_{O2}$; under normal conditions $P_{O2}$ effects on $V_A$ are limited to enhancing sensitivity of central receptors to increased $P_{CO2}$.

- $P_{O2}$ must drop substantially (below 60 mm Hg) for stimulation of peripheral chemoreceptors -- up to a $P_{O2}$ of 60 mm Hg, Hb is still substantially saturated with $O_2$ and adequate amounts of $O_2$ can be delivered to tissues (such as brain); furthermore, drops in $P_{O2}$ from 100 - 60 are usually associated with increased $P_{CO2}$ levels; thus even though the drop in $P_{O2}$ in this range does not stimulate increased firing of peripheral chemoreceptors, ventilation is usually increased due to response of central and peripheral chemoreceptors to increasing $P_{CO2}$ levels

- as the $P_{O2}$ falls below 60 mm Hg, however, Hb saturation levels drop substantially to the point that delivery of adequate amounts of $O_2$ to the tissues is jeopardized -- thus the ability of the central chemoreceptors to drive ventilation is questionable as they may not be fully functional (due to lack of $O_2$); thus the response of the peripheral chemoreceptors to drop in $P_{O2}$ in this range becomes the critical driving force for required ventilation increase.

2. Baroreceptor reflexes.

- increases in BP will cause a decrease in respiratory rate; decreases in BP cause an increase in respiratory rate; mediated by direct connections between vasomotor and respiratory center (effect minimal compared to chemoreceptor effects).

3. Herring-Breuer reflexes: from afferent in walls of lungs, stretch receptors.

a. Inflation reflex: increased stretch due to overinflation of lungs causes activation of HB1 stretch receptors; afferents inhibit DRG neurons and stimulate expiratory neurons of VRG.

b. Deflation reflex: severe lung deflation causes activation of HB2 receptors in the lung walls (pleura) that send impulses to RC; this inhibits expiratory neurons of VRG, and stimulates DRG neurons.