RESPIRATORY PHYSIOLOGY

The process of respiration is divided into four categories:

1. Pulmonary ventilation.
2. Diffusion of oxygen and CO\textsubscript{2} between alveoli and tissues.
3. Transport of oxygen and CO\textsubscript{2} in body fluids to and from cells.
4. Regulation of respiration

Pulmonary Ventilation

Anatomy of the Respiratory System

The respiratory system includes the lungs, the conducting airways that direct air to the gas exchange sites (alveoli), certain parts of the central nervous system, and the muscles of the chest wall and the diaphragm that are responsible for inflation and deflation of the lungs. The lungs fill most of the thoracic cavity except for the space occupied by the heart and major blood vessels.

Tissues of the Lung

The normal adult human lung weighs about 1000g and consists of about 50% blood and 50% tissue by weight. About 10% of the total lung volume is composed of various types of conducting airways and some connective tissue. The remaining 90% is the respiratory or gas exchange portion of the lung, composed of alveoli and supporting capillaries.

Airway Types:

1. The Cartilaginous Airways -- trachea and bronchi
2. The Membranous Airways -- bronchioles
3. The Gas Exchange Airways--respiratory bronchioles, ducts and alveoli collectively called the terminal respiratory unit (TRU) and site of gas exchange with the blood.
Airway Anatomy

The conducting airways consist of a series of rapidly branching tubes (conduits) that become narrower, shorter, and more numerous as they penetrate deeper into the lung. After about 23 to 25 orders of branching, the airways terminate in alveoli. The airway can be classified longitudinally or sequentially and anatomically into three distinct types.

Starting at the trachea, the airways branch in a dichotomous fashion both symmetrically and asymmetrically. The fibrous layer is encircled by smooth muscle innervated by parasympathetic nerves that cause contraction of the airway smooth muscle. This is termed bronchoconstriction. The extent and importance of sympathetic nervous system innervation in the initiation of bronchial smooth muscle relaxation is unclear. Each generation of airway branching is assigned a number, with the trachea assigned zero (0).

<table>
<thead>
<tr>
<th>Conducting Airways</th>
<th>Gas Exchange Airway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartilagenous</td>
<td>Terminal Respiratory Unit</td>
</tr>
<tr>
<td>Trachea</td>
<td>Bronchioles R.Bronchioles A.Bronchioles A.Ducts A.Sacs</td>
</tr>
<tr>
<td>No alveoli</td>
<td>Alveoli</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generation</th>
<th>0</th>
<th>1-2</th>
<th>11-13</th>
<th>16</th>
<th>17-19</th>
<th>20-22</th>
<th>23-24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchial Circulation</td>
<td></td>
<td></td>
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<tr>
<td>Gas Exchange Airway</td>
<td></td>
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</tr>
<tr>
<td>Pulmonary Circulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Air volume</td>
<td>150 ml</td>
<td>1500 ml</td>
<td>3000 ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smooth muscle</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

The gas exchange airway may be reached in as few as 10 levels of branching, but around 16th level of branching is more typical. From the trachea, the airway diameter decreases with each new generation of branching. However, the total cross-sectional area increases with each level of branching. As a result, the linear velocity of airflow decreases with each order of branching, an important consideration in determining the distribution of airway resistance.

Gas Exchange Airway: Respiratory Bronchioles, Alveolar Ducts and Sacs

The gas exchange airway is the functional unit of the lung. It consists of the respiratory bronchioles, alveolar ducts, and alveolar sacs, which collectively comprise the terminal respiratory unit (TRU). The TRU is distal to and a direct continuation of
the terminal bronchioles. It is the site of gas exchange with the pulmonary capillary blood. The gas exchange airway typically begins at about the 19th order of branching with the appearance of the respiratory bronchioles. The distinguishing feature of TRU is the presence of alveoli. The structural support for the TRU arises from the connective tissue framework of the lung. Alveoli line the walls of both the respiratory bronchioles and alveolar ducts, both of which are perfused with pulmonary capillary blood. Some smooth muscle also is present in respiratory bronchioles and alveolar ducts. This muscle can be stimulated by vasoactive substances in the pulmonary blood. There are usually 2 to 5 orders of branching of both respiratory bronchioles and alveolar ducts before the latter empty into an atrium consisting of one to three dome-shaped alveolar sacs.

**Mechanics of Ventilation**

Air is delivered to alveoli as a consequence of respiratory muscle contraction. These muscles include the diaphragm and the external intercostal muscles of the rib cage and accessory inspiratory muscles (scalenes and sternocleidomastoids which are not active in eupnea). Contraction of these muscles enlarges the thoracic cavity, creating a subatmospheric pressure in the alveoli. Contraction of the diaphragm leads to downwards displacement of the thoracic cavity and contraction of external intercostals muscles leads to lifting of the thoracic cage leading to increase in the antero-posterior diameter. As alveolar pressure declines, atmospheric air moves into the alveoli by bulk flow until the pressure is equalized. The process of inflating the lung is called inspiration. Expiration is usually passive, resulting from relaxation of the inspiratory muscles and powered by elastic recoil of lung tissue that is stretched during inspiration. With relaxation of the inspiratory muscles and lung deflation, alveolar pressure exceeds atmospheric pressure, so gases flow from the alveoli to the atmosphere by bulk flow. Active expiration is due to internal intercostals muscles and the abdominal recti muscles.
Pleural pressure is the pressure of the fluid in the thin space between the lung pleura and the chest wall pleura. Pleural pressure [-5cmH2O to -7cmH2O]

Alveolar pressure is the pressure of the air inside the lung alveoli. The alveolar Pressure [0 to -1 to 0, then 0 to +1 to 0]

Transpulmonary pressure [pressure difference between the alveolar pressure and the pleural pressure]. It is the measure of the elastic forces that leads to collapse of the lung and it is called the recoil pressure.
The Opposing Force of Pulmonary Elastance or Compliance

The lung is an elastic structure with an anatomical organization that promotes its collapse to essentially zero volume, much like an inflated balloon. The term elastic means a material deformed by a force tends to return to its initial shape or configuration when the force is removed. While the elastic properties of the lung are important to bring about expiration, they also oppose lung inflation. As a result, lung inflation depends upon contraction of the inspiratory muscles. The resistance to deformation (inflation) is termed elastance. However, compliance is the preferred term to describe the elastic properties of the lung. Compliance, as the reciprocal of elastance, is a measure of the ease of deformation (inflation).

Relationship of Elastance to Compliance

Compliance is measured as the change in volume for a given change in pressure. Thus, a structure with high elastance (very stiff) has a low compliance. A term used as a synonym for compliance is distensibility. Accordingly, an object with a high elastance would exhibit a high resistance to deformation and have a low compliance or low distensibility. On the other hand, an object with a high compliance distends readily with little pressure. Thus, in a lung with a high compliance, a small pressure change would result in a large volume change and the work performed by the respiratory muscles to inflate the lung would be less than normal. However, the expiratory force would also be less than normal in a lung with high compliance.

Lung compliance: Which equals to change in volume divided by change in pressure (1 cm = 200 ml). That is, every time the transpulmonary pressure increases 1 centimeter of water, the lung volume, after 10 to 20 seconds, will expand 200 milliliters.
- 1/3 to overcome pleural pressure
- 2/3 to overcome surface tension

If the lung is removed from the thoracic cage, it closely resembles a collapsed balloon. When pressure inside the lung equals outside pressure, or transmural pressure is 0, lung volume is close to zero. Compliance of the lung can be obtained by plotting lung relaxation or recoil pressure (x axis) as a function of lung volume (y axis). Starting from essentially zero lung volume, a measured volume of air is put into the lung and the recoil or relaxation pressure associated with the addition of that air volume is recorded. When repeated in several steps by the sequential addition of measured air volumes and recording of the corresponding recoil or relaxation
pressures, a compliance curve for the lung can be constructed. The slope of this plot is lung compliance. Normally, lung compliance is measured under static conditions, meaning no airflow is present at the time the relaxation (recoil) pressure is measured.

**Effect of thoracic cage**
Compliance of both lung + cage = 110 ml (instead of 200ml/cm)

Surface tension means the pulling force of fluid (as in rain drops). Surface tension is defined as a manifestation of attracting forces between atoms or molecules.
Surfactant: The surface active agent in water and it consists of lipids, protein and ions.

**Respiratory Distress Syndrome**

Problems with high alveolar surface tension are common in premature infants. The fetal lung does not begin to synthesize alveolar surfactant until about the fourth month of gestation. Fetal lung surfactant also is not fully functional until about the seventh month of gestation. Respiratory Distress Syndrome (RDS) is related to non-functional alveolar surfactant. RDS is characterized by severe alveolar instability, high alveolar surface tension, and high alveolar opening pressures. The respiratory muscles of premature infants frequently cannot generate sufficient pressures to open or inflate alveoli because of their high alveolar surface tension. RDS in infants is manifested by a low lung compliance and severe hypoxemia. Surfactant deficiency or inactivation can also occur in adults who breathe 100% O₂ for prolonged periods, or who have prolonged occlusion of the pulmonary artery, such as associated with heart-lung bypass procedures. Constant-volume mechanical ventilation or prolonged hypoxia or hypoxemia can also lead to surfactant inactivation.

**Work of breathing:**

1. Compliance work: against elastic forces of lung + cage
2. Tissue resistance work: against viscosity of both lung and cage
3. Airway resistance work

<table>
<thead>
<tr>
<th>Functions of Pulmonary Surfactant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. promote alveolar stability</td>
</tr>
<tr>
<td>2. prevent atelectasis</td>
</tr>
<tr>
<td>3. reduce opening or inflation pressures in collapsed or small alveoli</td>
</tr>
<tr>
<td>4. keep alveoli &quot;dry&quot;</td>
</tr>
<tr>
<td>5. decrease the work of breathing</td>
</tr>
</tbody>
</table>

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Respiratory Physiology
Prof. Zaid Al-Madfai
During quite breathing, 3-5% of total energy of the body are spent for respiration, while in heavy exercise, it increases up to 50 folds.

### Lung volumes

<table>
<thead>
<tr>
<th>Volumes</th>
<th>Capacities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Tidal vol. (500ml)</td>
<td>1- Inspiratory cap. (3500ml)</td>
</tr>
<tr>
<td>2- Inspiratory reserve vol. (3000ml)</td>
<td>2- Functional residual cap. (2300ml)</td>
</tr>
<tr>
<td>3- Expiratory reserve vol. (1100ml)</td>
<td>3- Vital cap. (4600ml)</td>
</tr>
<tr>
<td>4- Residual vol. (1200ml)</td>
<td>4- Total lung cap. (5800ml)</td>
</tr>
</tbody>
</table>

### Lung Volumes and Capacities

Lung volumes measured by spirometry are basically anatomical measurements of lung gas volumes. A lung volume refers to a basic volume of the lung, whereas lung capacities, also a volume measurement, are the sum of two or more basic lung volumes. The following lung volumes can be measured directly or indirectly with a spirometer:

**Tidal Volume (VT):** volume of gas inspired or expired during a normal spontaneous breath.

**Inspiratory Reserve Volume (IRV):** volume of gas that can be inspired at the end of a spontaneous inspiration.

**Expiratory Reserve Volume (ERV):** volume of gas that can be expired at the end of a spontaneous VT.

**Residual Volume (RV):** volume of air in lungs that cannot be forcefully expired or the volume of air in lung at end of a vital capacity.

**Vital Capacity (VC):** maximum volume of gas that can be expired after a maximal inspiration or IRV + VT + ERV.
**Inspiratory Capacity (IC):** the maximal volume of air that can be inspired from normal end-expiration or VT + IRV

**Functional Residual Capacity (FRC):** total volume of air in the lung at end of normal end-expiration or ERV + RV.

**Total Lung Capacity (TLC):** total volume of gas in lung at maximal end-inspiration or VC + RV or IRV + VT + ERV + RV.

Note that RV cannot be measured directly with a spirometer because it is not possible to expire this lung volume. Thus, any lung capacity that includes the RV cannot be measured directly with a spirometer. To measure RV or FRC, indirect gas dilution techniques or whole body plethysmography are used.

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**The minute respiratory volume:** Total amount of new air moved into the respiratory passages per minute and is equal to tidal volume (500 ml) multiplied by the respiratory rate (12/min) = 6000ml/minute.

**The Dead Space:** Is the space where no gas exchange occurs. It is either anatomically (150 ml) (anatomical dead space → nose, pharynx, larynx, trachea, bronchi, bronchioles); or physiological dead space whereby some alveoli are not functional because of absent or partial blood supply (normally it should be zero). So the total dead space is the sum of anatomical and physiological dead spaces and so equals to 150 ml. So the alveolar ventilation per minute equals to pulmonary ventilation per minute minus dead space and equals to 500-150 = 350 ml/min X 12 = 4200 ml/min.

**Respiratory passages:** Nose → trachea → bronchi → terminal bronchioles (all contain cilia and mucus), then → respiratory bronchioles → alveolar sacs → alveoli (contain mucus).
Nerve stimulation (sympathetic, i.e., adrenalin $\rightarrow$ dilatation; parasympathetic, i.e., Ach. $\rightarrow$ constriction).

Cough reflex: afferent vagus nerve $\rightarrow$ medulla $\rightarrow$ autonomic $\rightarrow$ inspiration of 2.5 liters $\rightarrow$ closure of epiglottis and vocal cords $\rightarrow$ contraction of abdominal muscles $\rightarrow$ sudden opening $\rightarrow$ expel air at a velocity of 400 miles per hour + narrowing of trachea and bronchi.
Sneeze reflex: Similar except to nasal passages instead of lower airways. Afferent is fifth cranial $\rightarrow$ medulla $\rightarrow$ similar but depression of uvula so that large amounts of air pass through the nose.

Pulmonary circulation:
Blood supply to the lungs goes to bronchi (nutrition) and respiratory units (gaseous exchange).

When $O_2$ concentration drops to 70% (73mmHg), pulmonary blood vessels constricts (opposite to other capillaries) and this is important $\rightarrow$ shift the blood to more aerated areas.
Right atrial pressure is 25 mmHg systolic and 0 mmHg diastolic.
Pulmonary artery pressure is 25mmHg systolic and 8mmHg diastolic (mean arterial pressure equals 15 mmHg).

Pressures in the Lung
Various lung intravascular and extravascular pressures influence pulmonary blood flow and its distribution in the lung. Pressure in different vascular segments (arteries, capillaries and veins), extravascular pressures (intrathoracic or intrapleural), and transmural pressure can vary considerably during both the cardiac and respiratory cycles. Because these pressures can influence the distribution of blood flow and vascular resistance, they can affect how well blood flow is matched to ventilation.

Lung zones (1, no blood flow; 2, intermittent; 3, always).

Ventilation-Perfusion Matching
The adult lung has about 300 million alveoli. Each alveolus is surrounded by a capillary mesh. Gas exchange is optimal in alveoli where ventilation is closely matched to blood flow or perfusion. More specifically, gas exchange is optimal in alveoli where the fraction of alveolar ventilation ($\frac{V_A}{Q}$) is matched to the fraction of cardiac output ($\frac{Q}{Q}$).
perfusing that alveolus. For the whole lung, an ideal ventilation to perfusion ratio ($V_A/Q$) is between 0.8 to 1.0.

However, with 300 million alveoli, it is unlikely that ventilation will be precisely matched to perfusion in each alveolus. Some alveoli may be overventilated relative to their blood flow and exhibit a $V_A/Q > 1.0$. Other alveoli may be overperfused relative to their ventilation and have a $V_A/Q$ of less than 0.8. At the extremes, some alveoli may be ventilated but receive no perfusion (infinite $V_A/Q$), whereas other alveoli may be perfused but not ventilated (very low $V_A/Q$). Normally in the upright lung, the $V_A/Q$ varies slightly from the apex to the base of the lung because of disparities in the distribution of ventilation and blood flow to these regions.

In the normal, upright adult, the lowest point in the lungs is about 30 centimeters below the highest point. This represents a 23 mm Hg pressure difference, about 15 mm Hg of which is above the heart and 8 below.

**Perfusion across capillaries:**
Capillary pressure equals 7 mmHg (while it is 17 in general circulation).
Plasma colloid equals 28 mmHg.
Interstitial colloid 14 mmHg (7 in general circulation)
-ve interstitial pressure equals 8 mmHg

Total = 29, so 29-28 = 1 mmHg which removed by lymphatics and evaporation

The pulmonary circulation receives the entire output of the right heart, but vascular pressures are considerably lower than in systemic vessels. Lung vessels lack high resistance arterioles, which accounts for their low resistance to blood flow. However, the lack of arterioles also compromises the ability of the lung to readily control the distribution of blood flow. Blood flow in the upright lung is distributed preferentially to the lung base because of the influence of gravity. However, the base also receives a greater proportion of the ventilation than does the apex. This imbalance in ventilation to perfusion in the upright lung can lead to a higher $V_A/Q$ at the apex than the base. This is reflected by a higher alveolar $P_O_2$ and lower $P_C_O_2$ in alveoli at the apex than at lung base. Two types of edema, hydrostatic and permeability, can occur in the lung. They have different etiologies and characteristics and hence, require different therapeutic approaches. Hydrostatic edema is related to increases in vascular pressure whereas permeability edema is caused by an increased leakiness of lung capillaries to fluid and protein.

The blood volume of the lungs is about 450 milliliters, about 9 per cent of the total blood volume of the entire circulatory system. Approximately 70 milliliters of this pulmonary blood volume is in the pulmonary capillaries, and the remainder is divided about equally between the pulmonary arteries and the veins.
Partial pressure of gases

Factors Affecting Composition of Alveolar Gases

1. The quantity and quality of gases delivered to and from the alveoli by ventilation
2. The diffusion rate of gases between the alveoli and pulmonary capillary blood
3. The cardiac output or blood flow through pulmonary capillaries, which remove O₂ and add CO₂ to alveoli.

Ventilatory Factors Affecting Alveolar Gas Composition

The composition of alveolar gas depends on the amount and kind of gases delivered to the alveoli by ventilation and on the rate of gas diffusion between alveoli and pulmonary capillary blood. It also depends upon pulmonary blood flow, which continuously delivers CO₂ and removes O₂ from the alveoli.

Fractional Composition of Atmospheric gases

<table>
<thead>
<tr>
<th>Atmospheric Gas</th>
<th>Fractional (F) or Percentage (%) Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen (N₂)</td>
<td>78.0%</td>
</tr>
<tr>
<td>Oxygen (O₂)</td>
<td>20.9%</td>
</tr>
<tr>
<td>Argon (Ar)</td>
<td>1.0%</td>
</tr>
<tr>
<td>Carbon dioxide (CO₂)</td>
<td>0.03%</td>
</tr>
</tbody>
</table>

Gases Comprising the Earth's Atmosphere

The earth's atmosphere is a mixture of gases consisting of about 78% molecular nitrogen (N₂), 20.9 % molecular oxygen (O₂) and 1.0 % argon (Ar). Other gases, like carbon dioxide (0.03%), are also detectable, but only in trace amounts.

Dalton's Law

Dalton's Law states that the total pressure (i.e., barometric pressure; P₀) exerted by a mixture of gases, such as the earth's atmosphere, is equal to the sum of the separate partial pressures each gas would exert if it occupied the entire volume (space) alone. That is, the total pressure exerted by a mixture of gases is equal to the sum of the individual partial pressures of the gases comprising the mixture. For the earth's atmosphere, the total or barometric pressure (P₀) is the sum of the individual partial pressures of the gases.
comprising the atmosphere. Thus, at a $P_B = 1$ atmosphere (ATM) = 760, the $P_{N_2} = 594$; $P_{O_2} = 159$; $P_{Ar} = 7.1$; and $P_{CO_2} = 0.23$.

Calculation of $P_{O_2}$ in the atmosphere

<table>
<thead>
<tr>
<th>$P_{O_2}$ at Sea level and Denver (5,280 ft above sea level)</th>
</tr>
</thead>
</table>

$P_g = F_g \times P_B$

where: $P_g$ is partial pressure of the given gas in the mixture, $F_g$ is fraction of the gas in the mixture, and $P_B$ is barometric pressure.

To calculate the $P_{O_2}$ of air at sea level (1 ATM) then:

$P_{O_2} = [0.21 \times 760] = 159 \text{ Torr}$

In Denver, Colorado, at an altitude of 1 mile, the fraction of $O_2$ in the atmosphere the same as at sea level, but the $P_B$ averages about 625 Torr. Thus, the $P_{O_2}$ at Denver's would be: $P_{O_2} = [0.21 \times 625] = 131 \text{ Torr}$

Calculation of Partial Pressures for Atmospheric Gases

Clinically, it is often necessary to determine the partial pressure of a particular gas in a gas mixture. The partial pressure ($P_g$) of a given gas (g) in a mixture of gases is computed by multiplying total gas pressure by the fractional concentration of the gas in the gas mixture. To simplify the calculation, the fraction of $O_2$ present in ambient air is generally taken to be 0.21 or 21%.

Thus, at sea level, where total pressure or $P_B = 760$ Torr, the partial pressure of $O_2$ ($P_{O_2}$) is computed by multiplying $P_B$ by the fraction of $O_2$ in the gas mixture. The fractional composition of air in Denver, Colorado is the same as at sea level. However, the $P_{O_2}$ in Denver, Colorado is less because it is 1 mile above sea level and the $P_B$ of Denver averages about 625 Torr.

The Addition of Water Vapor to Inspired Air

Ambient air inhaled into the nasal passages and tracheobronchial tree is immediately warmed to body temperature and completely saturated with water vapor. The water vapor or water gas added to inspired air exerts a partial pressure just like the other gases comprising air. The ability and capacity of air to hold water vapor increases as the temperature of the air increases and is independent of the total air pressure. At body temperature (37°C), air, saturated with water vapor has a water vapor pressure ($P_{H_2O}$) of 47 Torr, provided $P_B$ exceeds $P_{H_2O}$. In a more practical sense, the $P_{H_2O}$ in the airway of a person at sea level is the same as a person in Denver if their body temperatures are the same. Like the other gases present in air, $P_{H_2O}$ also obeys Dalton's Law. As a consequence, the addition of water vapor to inspired air reduces the partial pressure of other gases without changing the total gas pressure. For air in the tracheobronchial tree, $P_B$ is the sum of the partial pressure of atmospheric gases plus water vapor or $P_B = P_{N_2} + P_{O_2} + P_{CO_2} + P_{Ar} + P_{H_2O} + P_{other gases}$. 
Composition of gases in air:

<table>
<thead>
<tr>
<th></th>
<th>Atm.</th>
<th>Atm. + humidity</th>
<th>alveolar</th>
<th>Expired</th>
</tr>
</thead>
<tbody>
<tr>
<td>N2</td>
<td>597.0</td>
<td>563.4</td>
<td>569.0</td>
<td>566.0</td>
</tr>
<tr>
<td>O2</td>
<td>159.0</td>
<td>149.3</td>
<td>104.0</td>
<td>120.0</td>
</tr>
<tr>
<td>CO2</td>
<td>0.3</td>
<td>0.3</td>
<td>40.0</td>
<td>27.0</td>
</tr>
<tr>
<td>H2O</td>
<td>3.7</td>
<td>47.0</td>
<td>47.0</td>
<td>47.0</td>
</tr>
</tbody>
</table>

Composition of Alveolar Gases

With normal diffusion, the composition of alveolar gases is largely determined by two interacting processes.

1. **Ventilation**: the periodic partial replacement and dilution of alveolar air with fresh ambient air during inspiration and the exhalation of a portion of alveolar air during expiration.

2. **Blood flow**: blood traversing the pulmonary capillaries continuously delivers CO₂, produced by the tissues, to the alveoli for excretion, while concurrently extracting O₂ from the alveoli for transport to the tissues.

Only a portion of each tidal volume is delivered to the alveoli. The total air volume of all lung alveoli before inspiration (end-expiration) is by definition the **Functional Residual Capacity**. For a normal adult, the FRC is about 2500 ml. So, if the volume of fresh ambient air reaching the alveoli is 300 ml, it is added to an FRC of 2500 ml. As a result, the partial pressures of alveolar gases do not fluctuate markedly with each breath since only a portion of the FRC is exchanged.

Factors affecting the diffusion of gases in air:

\[ \text{Diffusion} = \frac{\text{Pressure} \times \text{Area} \times \text{Temperature}}{\text{distance} \times \sqrt{\text{Molecular Weight}}} \]

\[ \text{Diffusion coefficient} = \frac{T}{\sqrt{\text{MW}}} \] (constant)

Factors affecting pressure of gas in fluid: concentration and solubility

Solubility of O₂ = 0.024
Solubility of CO₂ = 0.57 (20 times of O₂)

Diffusion of gases through fluids depends on several factors:
1) solubility, 2) cross section, 3) distance, 4) MW, 5) solubility

\[ \text{Diffusion} = \frac{\text{Pressure} \times \text{Area} \times \text{Solubility}}{\text{distance} \times \sqrt{\text{Molecular Weight}}} \]

\[ \text{Diffusion coefficient} = \frac{S}{\sqrt{\text{MW}}} \] (constant)

\[ \Delta P \times A \]

So \[ D = \frac{\Delta P \times A}{d \times \text{diff. coef.}} \]
Respiratory Physiology
Prof. Zaid Al-Madfai

If the diff. coef. of O₂ is (1), then the relative coef of CO₂ is (20.3), CO is (0.81), N₂ is (0.53)

Diffusion of gases through tissues: all gases concerned are highly soluble in lipids, so in tissues, all factors affecting diffusion in water is the same.

Rate of exchange of gases in alveoli: residual capacity = 2300, while only 350 ml enters (1/7), so many breaths are needed to fully change the alveolar air, which is important to prevent sudden changes in respiratory control center.

**Diffusion of Gases through the Respiratory Membrane**
The respiratory unit: respiratory bronchioles, alveolar ducts, atria, and alveoli. Blood flows as a sheet.
Respiratory membrane is 0.2 micrometer thickness and composed of: 1) fluid (surfactant), 2) epithelium, 3) epithelial basement membrane, 4) interstitial fluid, 5) capillary basement membrane, 6) endothelial cells.

The total surface area is 70 m² and contain 60-140ml blood. The diameter of the capillary is 5 micrometers (RBC is 7 micrometers), so RBC squeeze inside.
Respiratory membrane diffusion capacity = volume of gas diffusing through membrane / minute for pressure difference of 1 mmHg.

The mean oxygen pressure difference across the respiratory membrane during normal, quiet breathing is about 11 mm Hg. Multiplication of this pressure by the diffusing capacity (11 × 21) gives a total of about 230 milliliters of oxygen diffusing through the respiratory membrane each minute; this is equal to the rate at which the resting body uses oxygen. In exercise, diffusion capacity increases to 65 because of (1) opening of dormant capillaries and (2) better ventilation perfusion ratio.

Diffusion capacity for CO₂ = 400-450 ml/min/mmHg and in exercise increases to 1200-1300.

Effect of ventilation perfusion ratio on alveolar gas concentration:

Ventilation-perfusion ratio (ranges from 0 to infinity):
- Alveolar Oxygen and Carbon Dioxide Partial Pressures when VA/Q Equals Zero, that is, without any alveolar ventilation-the air in the alveolus comes to equilibrium with the blood oxygen and carbon dioxide because these gases diffuse between the blood and the alveolar air. Because the blood that perfuses the capillaries is venous blood returning to the lungs from the systemic circulation, it is the gases in this blood with which the alveolar gases equilibrate. The normal venous blood has a PO₂ of 40 mm Hg and a PCO₂ of 45 mm Hg. Therefore, these are also the normal partial pressures of these two gases in alveoli that have blood flow but no ventilation.
- Alveolar Oxygen and Carbon Dioxide Partial Pressures when VA/Q Equals Infinity, there is no capillary blood flow to carry oxygen away or to bring carbon dioxide to the alveoli. Therefore, instead of the alveolar gases coming to equilibrium with the venous blood, the alveolar air becomes equal to the humidified inspired air. That is, the air that is inspired loses no oxygen to the blood and gains no carbon dioxide from the blood. And because normal inspired and humidified air has a PO₂ of 149 mm Hg and a PCO₂ of 0 mm Hg, these will be the partial pressures of these two gases in the alveoli.
- Gas Exchange and Alveolar Partial Pressures when VA/Q Is Normal, when there is both normal alveolar ventilation and normal alveolar capillary blood flow (normal alveolar perfusion), exchange of oxygen and carbon dioxide through the respiratory membrane is nearly optimal, and alveolar PO₂ is normally at a level of 104 mm Hg, which lies between that of the inspired air (149 mm Hg) and that of venous blood (40 mm Hg). Likewise, alveolar PCO₂ lies between two extremes; it is normally 40 mm Hg, in contrast to 45 mm Hg in venous blood and 0 mm Hg in inspired air. Thus, under normal conditions, the alveolar air PO₂ averages 104 mm Hg and the PCO₂ averages 40 mm Hg.

VA/Q = 0 → O₂ = 40, CO₂ = 45mmHg
VA/Q = infinity → O₂ = 149, CO₂ = 0mmHg
VA/Q = normal → O₂ = 104, CO₂ = 40mmHg

If less than normal then called physiological shunt
If more than normal then called physiological dead space
Normally at the tip of the lung, VA/Q is (2.5) times normal (phys. dead space), while at the base, it is (0.6) times normal (phys. shunt).

Normally, there are abnormal VA/Q ratios in the upper and lower portions of the lung. In the upper both ventilation and perfusion are low but VA is more than Q, so there is physiological dead space, but in the lower VA is less than Q, so there is physiological shunt.

Abnormally, as in smokers, bronchi obstruction → emphysema → (1) low ratio [no air] and (2) high ratio because of obstructed alveolar wall.

**Transport of O2 and CO2**

Blood in capillaries become fully saturated (40 → 104mmHg) in the first 1/3 of capillary passage in alveolus. In exercise, there is 20 fold increase demand for O2 but as the diffusion capacity is increased 3 folds, opening of other capillaries leading to better VA/Q ratio and the last 2/3 of the capillary length.
98% of blood become saturated with O2 and the rest (2%) is shunted (bronchial circulation), so ending in pulmonary vein O2 saturation of 95mmHg (not 104).

This blood (95mmHg) diffuse to the interstitial space (40mmHg) then to cells (23mmHg).

For CO2, intracellular (46mmHg) \rightarrow interstitial space (45mmHg) \rightarrow veins (45mmHg) \rightarrow alveoli (40mmHg).

**Transport of O2 in blood:**
97% of O2 in blood is transported by combining with hemoglobin and only 3% is dissolved.

\[ \text{O2} + \text{Hb} \rightleftharpoons \text{HbO2} \]
Partial pressure of blood leaving the lung is 95mmHg = 97% saturation and venous blood contains 40mmHg (75% saturation).
Each gram of Hb binds to 1.34ml O2, so 1.34 X 15gm = 20.1ml O2 in 100% saturation. So 95mmHg (97%) blood carries 19.4ml O2 → tissues (40% saturation) → veins (70%) carrying 14.4mlO2.
All this is in the resting state, in exercise, PO2 in tissues is low to 15mmHg, where more O2 is delivered leaving blood with only 4.4ml O2.

**Shape of the Oxy-Hb Dissociation Curve**

The sigmoidal shape of the oxy-Hb dissociation curve has physiological importance for both the loading of O2 in the lungs and for unloading O2 in the tissue capillaries. The upper portion of the curve, between a PO2 of 70 to 100 Torr, is nearly flat. This portion of the curve is often referred to as the association part of the curve because it is important in the loading of O2 (association of O2 with Hb) in the lung capillary. The association part of the curve insures oxygenation of most of the Hb even when alveolar PO2 is decreased due to altitude ascension or pulmonary disease. The SbO2 decreases from 97.5% at a PO2 of 100 Torr to 92% at a PO2 of 70 Torr with only a change of 1.0 vol% in blood O2 content. Thus, this flat portion of the oxy-Hb dissociation curve insures nearly normal loading of Hb with O2 even when the alveolar PO2 is reduced from normal.
On the other hand, the steep sloping part of the curve, between a PO$_2$ of 50 and 20 Torr is termed the dissociation portion of the curve. The dissociation portion of the curve is important in the tissue capillaries where a large amount of O$_2$ can be unloaded for a relatively small change in the PO$_2$. For example, a decrease in the PO$_2$ from 50 to 20 Torr reduces the blood O$_2$ content by over 10 vol% or by nearly 50%. Thus, a sizable portion of the O$_2$ carried by Hb is available for use by the tissues for a relatively small change in the PO$_2$. In other words, Hb relinquishes a relatively large amount of O$_2$ for a small change in the PO$_2$. The transition from the association to dissociation portion of the curve is normally at a PO$_2$ of around 60 Torr. The curve is very steep below, and relatively flat above this PO$_2$.

**Shifts in the Oxyhemoglobin Dissociation Curve**

The oxy-Hb dissociation curve is also capable of shifting to the right or to the left. An increase in the blood PCO$_2$ or hydrogen ion concentration [H$^+$] (decrease pH) shifts the curve to the right, whereas a decrease in PCO$_2$ or [H$^+$] (increase pH) shifts the curve to the left. Shifts in the oxy-Hb dissociation curve due to changes in the blood PCO$_2$ or pH are termed the Bohr effect. An increase in blood temperature or 2,3-diphosphoglycerate (2,3-DPG) levels in the RBC also shift the oxy-Hb dissociation curve to the right, while a decrease in temperature or 2,3-DPG shifts the curve to the left. A shift in the oxy-Hb
dissociation curve to the right means that more O$_2$ is liberated for a given decrease in the PO$_2$. Stated another way, a shift in the curve to the right indicates that the affinity of Hb for O$_2$ is reduced, so that for a given plasma PO$_2$, more O$_2$ is freed from Hb. In contrast, a shift in the curve to the left means more O$_2$ will be attached to Hb (increased affinity) for a given PO$_2$. Thus, less O$_2$ is available to the tissues or is freed from Hb at a given PO$_2$.

Bohr effect: in the lungs, removal of CO2 from blood $\Rightarrow$ shift to the left $\Rightarrow$ more O2 binding, while in tissues, increase CO2 in blood $\Rightarrow$ shift to the right $\Rightarrow$ easy release of O2.

**Factors Affecting O$_2$ Delivery an CO$_2$ Removal from the Tissues**

Blood flow rate is the primary factor that affects O$_2$ delivery to the tissues. An increase in blood flow typically results in an equivalent increase in O$_2$ delivery. Increasing the number of open capillaries is another way to increase O$_2$ delivery to a tissue. An increase in the partial pressure gradient between the capillary and tissue also enhances O$_2$ delivery. Shifts in the oxy-Hb dissociation curve related to changes in the acid-base characteristics of the blood can also alter O$_2$ delivery to tissues. Likewise, an increase in the number of RBCs or hematocrit (i.e., [Hb]) also increases the amount of O$_2$ delivered to the tissues. Many of the above factors that increase O$_2$ delivery also facilitate CO$_2$ removal.
Transport of CO2 in blood

Under normal conditions, 4ml of CO2/100ml blood. CO2 leaves the cell → interstitial fluid → blood in dissolved state. Inside the capillary, it is either dissolved (7%), or as bicarbonates (depends on carbonic anhydrase which increase the reaction to 5000 times, this enzyme is found in RBCs), where bicarbonates diffuse outside the RBC and chloride is shifted inside (bicarbonate-chloride shift carrier protein) and hydrogen ion is buffered by Hb (70%), and the rest is carried as carbaminohemoglobin compound (23%).

Haldane effect: opposite to Bohr effect, when O2 binds to Hb → CO2 is released, which is more important for the transport of CO2 than O2. In other words, when Hb loses O2, it becomes a stronger base or weaker acid, making more sites available to buffer H+. When O2 combine with hemoglobin in the lungs → acid Hb → less combination with CO2 to form carbaminohemoglobin and also acid Hb → release of H+ which combines with HCO3⁻ → H₂CO₃ → CO₂ + H₂O.
Regulation of respiration

1- Dorsal group (inspiration)
2- Ventral group (expiration and inspiration)
3- Pneumotaxic center (rate and pattern)
4- Apneustic center

**Dorsal group** (located in the medulla) receive from the vagus (peripheral chemoreceptors, baroreceptors and lung receptors). They are responsible for the rhythm (unknown cause). Normal inspiration.

**Ventral group**: Located at the medulla, they remain inactive during quite breathing but on increase need, signals from the dorsal to ventral → contribution of ventral to respiration. They cause inspiration and expiration. Active expiration.

**Pneumotaxic center**: Located at the upper one-third of the pons, it sends signals to the inspiratory center to switch off inspiratory ramp. When the pneumotaxic signal is strong, inspiration is terminated in 0.5 seconds, but when weak, then termination occurs after 5 seconds. So this center can affect the rate of respiration.

**Apneustic center**: Located at the lower two-thirds of the pons, may send signals to the dorsal to prevent or retard the switch off of the respiratory ramp → lung filled with air.

**Lung inflation signals:**
The Hering-Breuer **Inflation reflex** (also called inhibito-inspiratory reflex) is initiated by stretch receptors (sensors) located in the smooth muscles surrounding both large and small airways. With lung inflation, these stretch receptors are stimulated and send neural signals via vagal afferents that appear to be inhibitory to the pontine apneustic center. Thus, they function to facilitate termination of inspiration. There is also a Hering-Breuer **Deflation reflex** (or excito-inspiratory reflex). This reflex is initiated either by decreased activity in the same airway stretch receptors involved in the inflation reflex or by stimulation of other proprioceptors that are activated by lung deflation. This information is also conveyed via vagal afferents to the brain stem respiratory centers to encourage inspiration. While Hering-Breuer reflexes are readily demonstrated in anesthetized animals, they are more difficult to demonstrate in...
humans, except at large tidal volumes. These reflexes are detectable in infants and are probably important in regulating the work of breathing. In humans, this reflex is activated when the tidal volume is more than 1.5 liters, so it is a protective reflex.

**Chemical control of respiration**

The chemoreceptors are specialized cells capable of detecting changes in the concentration of physically dissolved O$_2$, CO$_2$, or hydrogen ion (H$^+$) in the extracellular fluid immediately surrounding them. These chemosensitive cells are divided functionally, anatomically and geographically into the **peripheral** and **central chemoreceptors**. They function to regulate ventilation so CO$_2$ is maintained nearly constant and at a level consistent with CO$_2$ production and O$_2$ consumption by the tissues of the body.

In the central chemoreceptors, **CO2 and H$^+$ effect**: H$^+$ are the most potent stimulator, but they do not cross the blood brain barrier, but when CO$_2$ increases, it passes the BBB and so it forms H$^+$ to stimulate the chemosensitive area in the medulla near the respiratory center.

It has a very acute effect (in hours), but after 1-2 days, it decreases because of renal HCO$_3^-$ formation.

The peripheral chemoreceptors are located in discrete structures known as the **carotid and aortic bodies**.

O$_2$ has no direct effect but through peripheral chemoreceptors (aortic and carotid bodies). They have little effect compared to CO$_2$ and H$^+$. The carotid send impulses through Hering's nerve → glossopharangeal nerve to dorsal group. Aortic → vagus → dorsal group.

These receptors (aortic and carotid bodies) are sensitive to O$_2$ (30-60mmHg). They are also sensitive to CO$_2$ and H$^+$ but the effect of CO$_2$ and H$^+$ on the respiratory center is stronger than on the chemoreceptors.
Acclimatization: mountain climbers, after 1-2 days, the CO2 effect will be lost and O2 will increase ventilation to 400-500%.

In exercise, increase ventilation is due to (1) motor stimulation of muscles spread to respiratory center, (2) joint movement also.

Other factors controlling respiration:
  1- Voluntary control
  2- Pulmonary irritant receptors
  3- Lung j-receptors (at the junction of alveoli to capillaries). The Pulmonary J-receptors, an abbreviated name for the pulmonary juxtapulmonary-capillary receptors, are located in, or near, the walls of pulmonary microvessels. They appear to be stimulated by vascular emboli, interstitial edema, and certain chemicals (phenyldiguanide or capsaicin). Information from the J-receptors is also delivered via vagal afferents to the brain stem. Their stimulation results in rapid shallow breathing (tachypnea). These receptors are thought to be responsible for the psychological sensation of "air hunger", also known as dyspnea. Dyspnea is characterized by the sensation of labored breathing and "shortness" of breath.

Periodic breathing: deep and shallow, for example:
Chyne-Stokes breathing: on fast breathing, CO2 is decreased and O2 is increased → respiratory depression and after few seconds, it recurs. It is found in all normal subjects but damped by the fluids of blood, and the brain contains dissolved CO2 and O2 to minimize the effect but it can occur in:
  1- Severe heart failure, where slow blood circulation to the brain
  2- Brain damage → reverse feed-back

Classification of Lung Disorders by Spirometry

By comparing recorded values of the resting VC, FVC and FEV1.0 obtained from the spirogram to the predicted values obtained from nomograms, it is possible to group respiratory diseases or disorders into two broad categoyries of restrictive or obstructive impairments.

Respiratory Investigations

1- Blood pH
2- Blood CO2
3- Blood O2
4- Maximum expiratory flow (400ml/min) (Peak Expiratory Flow Meter)
5- FVC (forced vital capacity) and FEV1 (forced vital capacity in the first second).
**Restrictive Disorders or Diseases**

Restrictive impairments are characterized by limited lung expansion, reduced lung volumes, and usually decreased expiratory flow rates from predicted values. Thus, the recorded FVC and FEV\(_{1.0}\) are below the predicted normal. However, with a strictly restrictive disorder, airway resistance is normal, so the ratio of the actual FEV\(_{1.0}\) to the FVC of the subject is normal (i.e., FEV\(_{1.0}/\text{FVC}>80\%\)). The loss of lung volume with restrictive disorders is reflected by reductions in other lung volumes (RV, FRC) and a reduced FEF\(_{25-75\%}\) from predicted values. Some examples of restrictive disorders include pregnancy, excessive abdominal fat, or even tight-fitting undergarments that limit normal descent of the diaphragm. Some restrictive diseases include pulmonary fibrosis, sarcoidosis, pleural effusion, spinal cord injury that affects innervation to the respiratory muscles, or spinal nerve paralysis such as with polio. Injury or disease to the respiratory control centers of the brain stem might also be reflected as a restrictive impairment.

**Obstructive Disorders or Diseases**

Obstructive impairments are characterized by increased airway resistance causing reduced expiratory airflow rates. Obstructive disorders are always associated with airway dysfunction. Examples of obstructive diseases include asthma, chronic bronchitis, and emphysema. However, even a severe cold with pulmonary congestion might be manifested as an obstructive disorder. With obstructive impairments, the actual (recorded) FEV\(_{1.0}/\text{FVC}\) is less than 80% and the FEV\(_{1.0}\) and FEF\(_{25-75\%}\) are 75% or less of the predicted values. How obstructive disorders affect other lung volumes, including the FVC, depends upon the severity or stage of the disease. For example, with mild asthma, the FVC may be normal but the FEV\(_{1.0}\) and FEF\(_{25-75\%}\) reduced from normal.
During the early stages of emphysema, the VC and FVC may be within normal limits, but with advanced emphysema the FVC is reduced. With advanced emphysema, the lung becomes hypercompliant (more distensible with less recoil), leading to air trapping reflected by an increase in the RV and FRC, even though TLC is unchanged, or possibly increased from normal. If the FEV\textsubscript{1.0} or FEF\textsubscript{25-75\%} increases after inhalation of a bronchodilator (i.e., beta-agonist), a portion of the obstruction is likely due to bronchospasm. The potential reversibility of an obstructive impairment is indicated when the FEV\textsubscript{1.0} is increased by 15\% or more after inhalation of a bronchodilator.

Abnormalities:

1- **Emphysema**: excess air in the lungs. Chronic infection → increase mucus → chronic obstruction → air remain in alveoli → overstretching of alveoli → alveolar obstruction. So it leads to obstruction and damage → decrease diffusing capacity → very low VA/Q (shunt) and very high VA/Q (dead space). At the end, damage to alveolar wall → damage to capillaries → pulmonary hypertension → right sided heart failure.
2- **Pneumonia**: any inflammatory condition of the lung where the alveoli are filled with fluid and blood cells. So in infection, the damage to alveoli → filling with fluid and blood → consolidation → reduction of available surface and reduction of VA/Q → hypoxemia and hypercapnia.

3- **Atelectasis** (airway obstruction or lack of surfactant): leads to collapse of the lungs, so in blockage → air entrapment → air absorption → collapse of alveoli (pliable lung) or alveoli filled with fluid (rigid lung), so increase resistance to blood flow and in addition, hypoxia → vasodilatation, so blood flow to other areas and VA/Q is not much suffered.

4- **Asthma**: spastic contraction of smooth muscles of bronchioles because of hypersensitivity.

**Hypoxia**: decrease O2 to the cells. It is divided into (1) circulatory, (2) histotoxic, (3) anemic, (4) hypoxic hypoxia.

### Circulatory Hypoxemia

Circulatory hypoxemia, also known as stagnant hypoxemia, is characterized by, or a result of inadequate blood flow to a particular tissue. The failure to deliver adequate O2 results from a problem with the cardiovascular system. Circulatory arrest could result from heart failure or vasomotor collapse, or locally, from vascular disease or emboli that limit blood flow to a particular organ. If blood flow to the brain is blocked for about 10 seconds, consciousness is lost, mostly as a result of hypoxemia. In the eye, occlusion of vessels can lead to vision loss in 6 seconds. With circulatory arrest, products of anaerobic metabolisms are not cleared. This can potentially compound the damage from the hypoxemia.

### Histotoxic Hypoxemia

With histotoxic hypoxemia, tissues are unable to use O2 properly because the enzymes of aerobic metabolism are dysfunctional. Several poisons, such as cyanide and mercury, interfere with the oxidative enzymes so that O2 can no longer serve as the final proton acceptor for the cytochrome enzymes. Arterial blood PO2 and content are often normal with histotoxic hypoxemia, whereas systemic venous and mixed venous blood PO2 and content are higher than normal, reflecting the inability of oxidative enzymes to use O2.

### Anemic Hypoxemia

Anemic hypoxemia is characterized by a low blood O2 content due to either a low [Hb] or an inability of Hb to bind and hence transport O2. With anemic hypoxemia, however, the systemic arterial PO2 is usually close to normal. Because the arterial chemoreceptors are located in the systemic arterial circulation and only detect the physically dissolved O2 (PaO2) and not the O2 attached to Hb (HbO2), they can be fooled by this form of hypoxemia. With anemic hypoxemia, the arterial PO2 is often close to normal. As a result, the peripheral chemoreceptors fail to detect any change in blood O2 content. Also,
the central chemoreceptors are not responsive to hypoxemia, so breathing is not markedly stimulated.

**Hypoxic Hypoxemia**

Hypoxic hypoxemia differs from anemic hypoxemia in that the arterial blood PO\(_2\) is reduced along with the O\(_2\) content. With hypoxic hypoxemia, breathing is stimulated by the hypoxemia. The most common clinical example of hypoxic hypoxemia is a right-to-left shunt, where blood travels through the lung from the right to left heart without undergoing complete oxygenation. This is common in conditions where pulmonary diffusion is impaired, so gas exchange between the alveoli and pulmonary capillary blood is diminished. Hypoxic hypoxemia can also result from hypoventilation associated with injury or disease to the brain stem respiratory control centers, spinal cord, or motor nerves innervating the respiratory muscles. Individuals with emphysema often exhibit hypoxic hypoxemia characterized by a low arterial PO\(_2\) and blood O\(_2\) content. However, such individuals may also have an elevated arterial PCO\(_2\). Another example of hypoxic hypoxemia is altitude ascension. This causes a decline in blood PO\(_2\) because atmospheric PO\(_2\) is reduced with altitude. This decline in the PO\(_2\) causes the peripheral chemoreceptors to stimulate breathing. The increase ventilation typically results in a lowering of both blood and CSF PCO\(_2\) and [H\(^+\)]. Diminished levels of these potent stimuli to breathing can act to counter a portion of the hypoxic stimulation to ventilation.

**Hypercapnia:** increase CO\(_2\) in body fluids
It is not always associated with hypoxia but only in hypoventilation and circulatory failure.

**Cyanosis:** Blue skin due to increase deoxygenated blood. It appears when deoxygenated blood is more than 5gm/100ml, so it does not appear in anemia.

**Dyspnea:** mental anguish associated with inability to ventilate enough leading to air hunger. It is caused by (1) abnormality of respiratory gases in body fluids, specially hypercapnia, (2) amount of work by respiratory muscles increases, (3) state of the mind.