Respiratory System Physiology

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The underlined headings correspond to the eight Respiratory System videos.

1. Anatomy and Mechanics

Introduction

The respiratory system carries out several homeostatic functions, including:
1. **gas exchange** between the atmosphere and the blood to provide an adequate supply of oxygen to tissues and to remove carbon dioxide (CO$_2$) generated in oxidative metabolism.
   $$O_2 + \text{Food} = \text{CO}_2 + H_2O + \text{ATP}$$
2. regulation of body pH by either retaining or eliminating CO$_2$
3. conversion of angiotensin I to angiotensin II which acts to control blood pressure
4. protection from inhaled particles.

In the respiratory system, air flow occurs by **bulk flow** from regions of high pressure to lower pressure with the pressure differences generated by a muscular pump. Resistance to air flow is influenced primarily by the radius of the tube ($1/r^4$) through which air is flowing.

$$F = (P_1 - P_2)/R$$

The movement of fresh air into the lung (inspired) or out of the lung (exhaled) is called **ventilation**. Both the rate and size of the breath (tidal volume) can change in response to needs of the body.

Anatomy

The respiratory system consists of structures involved in moving air into and out of the lungs (bulk flow) and in gas exchange (diffusion).

**Lungs and chest wall** act as a unit. Each lung is surrounded by a membranous sac (pleura) filled with a thin film of fluid (Fig. 1). This intrapleural fluid serves as a lubricant so the lungs can move freely within the chest wall and functionally connects the lungs to the chest wall such that expansion of the chest expands the lungs.

**Conducting zone** leads from the external environment to the gas exchange surfaces of the lungs (Fig. 1). This zone includes a series of tubes (nasal cavity, pharynx, trachea, bronchus, and bronchioles) with small radii and small surface areas. Their total volume is about **150 ml**. Since no gas exchange occurs in the conducting zone, it is often called the **anatomical dead space**.
RESPIRATORY ZONE is the region of the lung where gas exchange occurs (Fig. 2). The respiratory zone is much larger than the conducting zone and has a volume of about 3 L. It consists of respiratory bronchioles, alveolar ducts and alveoli. The alveoli are small sac-like structures with very thin walls wrapped by capillaries (Fig. 2). The 300 million alveoli provide a surface area of about 70 m². Here oxygen (O₂) diffuses from the air space to the blood and carbon dioxide (CO₂) diffuses from the blood to the air space. The distance that gas has to diffuse is very short, about 0.2 microns, making the alveolus-capillary unit ideally suited for gas exchange.

**TYPE I CELLS** are thin epithelial cells that line about 90% of the surface area of the alveoli. Gases diffuse across the type I cells to and from the blood (Fig. 2).

**TYPE II CELLS** are interspersed among the type I cells. Type II cells synthesize, secrete, and metabolize alveolar surfactant. Surfactant is a lipid-rich substance that lines the alveoli and helps keep lungs from collapsing.

**ALVEOLAR MACROPHAGES** are the third type of cell found in alveoli. Macrophages engulf inspired particles such as bacteria. These cells are mobile and are attracted to areas of either infection or trauma.

**Pulmonary Function**

**BREATHING** is the process of **inspiration** (air flows into the lung) and **exhalation** (air flows out of the lung).

**Inspiration** begins when the diaphragm and the intercostal muscles of the chest wall contract in response to neural impulses from the brain stem (Fig. 3). Contraction of the diaphragm causes it to descend and contraction of the intercostal muscles raises the ribs; the chest cavity expands. Because the lungs are functionally connected to the chest wall by the pleural sac, the lungs also expand (Fig. 3). This increase in lung volume reduces the air pressure in the alveolar ducts and alveoli. When the pressure in the alveoli (Pₐ) becomes less than the pressure at the mouth, which is ordinarily atmospheric pressure (P atm), air flows in until Pₐ = P atm (Fig. 3).

**Exhalation** occurs when the muscles of inspiration relax. The lung returns passively to its pre-inspiratory volume due to its elastic properties. This reduction in volume raises the pressure in the lung causing air to flow out.
VENTILATION CYCLE is one inspiration and exhalation. Ventilation rate (f) is in the range of 10-18 breaths per min. Both the rate and depth can be changed by output from the respiratory centers in the brain stem (medulla oblongata). During heavy exercise air flow can increase 20-fold and blood flow 3-fold. To expel such increased volumes, active exhalation is required in which abdominal muscles and internal intercostals muscles contract. These actions actively decrease the size of the thorax (chest cavity).

2. Lung volumes and compliance

LUNG VOLUMES are determined by the interaction of the lung and chest wall. The lungs are elastic like a rubber band. They expand during inspiration and recoil passively during exhalation. Functional residual capacity (FRC) is the resting volume of the lung and chest wall. It occurs when the elastic recoil of the lung (pulling inward) balances the pressure of the chest wall to expand (pulling outward). When chest wall muscles are weak, FRC decreases.

Lung volumes play a major role in gas exchange and in the work of breathing. They are measured under dynamic and static conditions. Dynamic volumes refer to measurements made when volumes are changing, i.e., during gas flow. Static volumes can be measured between two points where there is no flow, for example before and after inspiration.

There are four standard lung volumes (Fig. 4). There are also four standard lung capacities, which consist of a combination of two or more volumes. A spirometer is used to measure lung volumes directly. All volumes except the residual volume (amount of air remaining in the lung at all times) can be measured with a spirometer.

**Figure 4.** Lung volumes and capacities. Image by Vihsadas (modified), [http://commons.wikimedia.org/wiki/File:LungVolume.jpg](http://commons.wikimedia.org/wiki/File:LungVolume.jpg), public domain

**Residual volume (RV):** Amount of air in the lungs at the end of maximal exhalation (~ 1.5 L young men).

**Tidal volume (TV):** Volume of air inhaled or exhaled with each breath (in adult males ~ 0.5L; in females usually about 20-25% less).
**Inspiratory reserve volume (IRV):** Volume of air that can be inspired after a normal inspiration (~3.0 L in males).

**Expiratory reserve volume (ERV):** Maximal volume of air that can be expired (exhaled) from resting expiratory level (~1.0 L in males).

**Inspiratory capacity (IC=TV+IRV):** Maximal volume of air that can be inspired from resting expiratory level (~3.5 L in males).

**Functional residual capacity: (FRC=RV+ERV):** Volume of air in lungs at end of a normal exhalation. (~2.5 L in males) (see Fig. 4).

**Vital capacity (VC=ERV+TV+IRV):** Volume of air that can be exhaled after maximal inspiration (~4.5 L)

**Total lung capacity (TLC=RV+ERV+TV+IRV):** Volume in lungs at end of maximal inspiration (~6 L).

Changes in lung volumes are some of the earliest indicators of lung disease. One of the most informative is the ratio of RV and TLC. Normally RV/TLC ratio is less than 0.25, that is the air trapped in the lung is ~25% of the total lung volume. In obstructive lung diseases the amount of trapped air (RV) increases, hence RV/TLC increases. In restrictive lung disease in which the lung can not fill normally, RV/TLC also increases but in this case, total lung volume (TLC) is reduced disproportionate to residual volume.

**Elastic Recoil and Compliance**

**LUNG COMPLIANCE** is defined as the stretchability of the lung for any 1-cm change in pressure across the lung.

$$C_L = \frac{\Delta V_L}{(P_A - P_{ip})}$$

The greater the compliance, the easier it is to expand the lungs at any given change in transpulmonary pressure. **Compliance is the inverse of elastic recoil or stiffness.**

The most common way to obtain a compliance curve is to have an individual inspire to total lung capacity and then exhale slowly in small increments. When airflow is temporarily stopped, volume and transpulmonary pressure are recorded. A pressure-volume curve is constructed (Fig. 5). The **slope of the pressure-volume curve at any given point is lung compliance at that point.**

Note that the pressure-volume curve is not linear (Fig. 5). At high lung volumes, the lungs are almost maximally stretched and a large change in pressure produces only a small change in
volume. Therefore, compliance is usually measured in the mid-range of the pressure-volume curve during tidal volume breathing. A normal value for lung compliance at this point is 0.2 liter/cm H₂O.

Lung compliance is determined in part by the elastic tissue of the lung. A lung with high compliance is easy to stretch. The disease emphysema destroys this elastic tissue and thus increases lung compliance. A lung with low compliance is stiff and hard to stretch and so is hard to fill with air. This is seen in the disease fibrosis (Fig. 5).

Compliance of the lung is determined also by the surface tension generated at the air-water interfaces within the alveoli. The alveoli are air filled sacs lined with water. The attractive force between the water molecules (known as surface tension) resists stretching. The surface tension of pure water is so great that were the alveoli lined by water alone, lung expansion would require exhausting muscular effort and the lungs would tend to collapse. The detergent-like substance, surfactant, markedly reduces this surface tension and thereby increases lung compliance.

Lung surfactant is synthesized by the alveolar type II cell and secreted into the alveolar space by stretching the type II cells during breathing. The major component in surfactant is a phospholipid which is inserted perpendicularly into the gas-liquid interface so that its non-polar, hydrophobic fatty acids are pointed toward the gas and its polar end is in the liquid. The phospholipids form a monolayer that generates a film pressure opposing the surface tension. When this film is compressed (as the volume of the lungs is reduced) the film pressure rises and surface tension falls even further. This property stabilizes the lungs.

The lungs of many premature babies are unable to produce adequate amounts of functional surfactant. Approximately 50% of babies born before the 31st week of gestation will suffer from Respiratory Distress Syndrome. Because of the lack of surfactant, the surface tension in their lungs is high, which increases the tendency of the lungs to collapse. Do these lungs have high or low compliance?

Surfactant stabilizes the alveoli. The surface tension of the alveoli tends to pull inward creating a pressure. The relationship between surface tension and pressure is shown in Figure 6 and is defined by the law of Laplace.

\[
\text{Transmural Pressure} = \frac{2T}{r}
\]

According to Laplace, transmural pressure is equal to twice the surface tension divided by the radius:

\[
\text{Transmural Pressure} = \frac{2T}{r}
\]

If surface tension were equal in alveoli of different sizes, the pressure in the smaller alveolus would be greater than the pressure in the large alveolus and the smaller alveolus would collapse into the larger one.

Figure 6. Stabilizing effect of surfactant on lung alveoli.

Alveolar collapse does not normally happen because the surface tension in a lung with surfactant is not constant. Instead surfactant reduces surface tension in a nonlinear fashion; i.e., as area is reduced, surface tension is reduced even further. By lowering surface tension proportionately
more in smaller alveoli, surfactant makes it possible for alveoli of different radii to coexist and to be stable at low lung volumes.

During normal tidal breathing, the surface area of the lung remains fairly constant and with time the surfactant becomes “inactivated” through poorly understood mechanisms. A deep sigh or a yawn will increase the surface area of the lungs and new surfactant will spread at the air-liquid interface.

3. Pressure changes and resistance
Pressure Changes Affect Lung Volumes
In a normal lung, air flows in and out when a pressure gradient is created. Gas always flows from a higher to a lower pressure. During inspiration, expansion of the thorax causes the intrapleural and alveolar pressures to decrease, gas flows into the lung. During exhalation passive recoil of the lung causes the intrapleural pressure and alveolar pressure to increase; gas flows out of the lung. **Note that during inspiration and exhalation the pleural pressure is always less than the pressure in the alveoli.**

The transpulmonary pressure (Fig. 7) also increases and decreases with lung volume. By convention, the transpulmonary pressure is always positive ($P_{tp} = P_A - P_{ip}$).

At the end of an unforced exhalation when no air is flowing, then the following conditions exist:

- **alveolar pressure** = 0 mmHg
- **intrapleural pressure** (i.e., pressure in pleural cavity) = -5 mmHg
- **transpulmonary pressure** ($P_A - P_{ip}$) = +5 mmHg.

When there is no airflow in or out of the lungs, the transpulmonary pressure and intrapleural pressure are **equal in magnitude but opposite in sign** (Fig. 7).

**Figure 7.** In ventilation, air flow is determined by the difference between atmospheric and alveolar pressures. Lung size is determined by the balance between the transpulmonary pressure and elastic recoil.
At rest, the volume of the lung is a balance between the expansion of the chest wall and the inward elastic recoil of the lungs. The lung at rest is in a partially expanded state (stretched). A pneumothorax, can occur with trauma or surgery. In this instance, the chest wall is pierced without damaging the lung. Atmospheric air enters the intrapleural space raising its pressure to 0 mmHg. This input of air causes the lung to collapse since its elastic recoil is no longer opposed. Concurrently the chest wall moves outward.

**Airway Resistance Determined by Driving Pressure & Flow**

Thus far we have discussed the changes in pressure that are required to overcome the elastic recoil tendencies of the respiratory system. An additional force that must be overcome during normal breathing is the **resistance to airflow**. Measurement of airway resistance is an extremely useful diagnostic tool because changes in airway resistance accompany aging and many lung diseases.

Air flow (F) will depend upon the driving pressure (P) and the resistance (R) according to the equation:

\[ F = \frac{(P_{\text{atm}} - P_A)}{R} \]

Factors that influence airway resistance include airway diameter, lung volume, and elastic recoil of the lung.

1. **AIRWAY DIAMETER**: It is probably intuitive that the more narrow the airway, the higher the resistance in that individual airway. What may not be intuitive is that most of the resistance to airflow is found in the mouth, trachea and large bronchi. The reason for this is that as the airways divide and become narrower, they also become more numerous. The small airways divide more rapidly than their diameter decreases, therefore, the resistance of each individual airway is relatively high, but their total-cross sectional area is so great that their combined resistance is low.

2. **LUNG VOLUME**: The diameter of the airway lumen is affected by lung volume. The airways are not rigid and are capable of being distended and compressed. At high lung volumes, the airways such as bronchi and bronchioles, are "pulled" open and their resistance is lower than at low lung volumes. Patients with increased airway resistance frequently have high lung volumes in an attempt to compensate.

3. **ELASTIC RECOIL**: Airway diameter will be affected by the transmural pressure across them (Fig. 8). Although the airways are embedded in the lung, the pressure that they are exposed to on their outside wall is close to intrapleural pressure. If elastic recoil is reduced, then intrapleural pressure will be less negative than normal. The transmural pressure across the airways will be reduced, the airway diameter will be smaller than normal, and resistance will be higher than normal. Patients with emphysema often have destruction of lung tissue, decreased elastic recoil (increased compliance), and increased airway resistance.
At the equal pressure point, pressure inside the airway equals that in the pleural space. In normal lungs this occurs in the large airways which are surrounded by cartilage. However, in diseases associated with airway obstruction, resistance to flow is increased and the pressure gradient for flow is reduced. Consequently the equal pressure point moves into airways that do not contain cartilage causing these airways to close completely (premature airway collapse) (Fig. 8). This premature airway closure can be heard as crackles.

4. MUSCLE TONE Constriction of bronchial smooth muscle will decrease the diameter of the airways and increase airway resistance. Parasympathetic stimulation causes contraction of bronchial smooth muscle; sympathetic stimulation causes relaxation. Asthmatics often have hyper-reactive airways and smooth muscle contraction. Drugs which stimulate β-adrenergic receptors (βAR) in the bronchioles cause relaxation and are often used to treat asthmatics.

4. Pulmonary function tests and alveolar ventilation

FORCED EXPIRATORY VITAL CAPACITY TEST provides an indirect assessment of airway resistance. In this pulmonary function test, the subject inhales to total lung capacity and then exhales into a spirometer as forcefully, rapidly, and as completely as possible. The volume expired under these conditions is called the forced vital capacity (FVC) (Fig. 9).

The forced expiratory vital capacity test also measures the volume exhaled in 1 second, called the 1-second forced expiratory volume (FEV1). This value is often expressed as a % of FVC (i.e., FEV1/FVC %). Normally FEV1 is at least 80% of FVC (curve Y). Patients with restrictive lung disease will have a normal value of 80% (curve Z). In patients such as asthmatics, who have obstructed airways, this value will be reduced (<80%) (curve X).
Exchange of Gases in Alveoli & Tissues

Respiration involves two processes:
1. Delivery of O\(_2\) to and removal of CO\(_2\) from the cells of the body.
2. Use of O\(_2\) in oxidative metabolism to generate ATP, water, and CO\(_2\).

In a steady state, the amount of O\(_2\) that is consumed by the cells per unit time is equal to the amount of O\(_2\) added to the blood in the lungs during the same time period. Likewise the rate at which CO\(_2\) is generated by the cells is equal to the rate at which CO\(_2\) leaves the blood in the lungs and is exhaled.

Gases move by diffusion from regions of high concentration to regions of low concentration. Therefore to provide adequate gradients for diffusion, the pulmonary system must increase the amount of oxygen in the alveoli above that found in the mixed venous (MV) blood of the lung. Additionally it must lower the carbon dioxide in the alveoli below that of mixed venous blood.

A second set of gradients must exist at the tissue-blood interface. Here the amount of O\(_2\) consumed by cells and CO\(_2\) produced are not necessarily identical and depend on the fuel source consumed. The ratio of CO\(_2\) produced to O\(_2\) consumed is called the respiratory quotient (RQ).

For a mixed diet, 8 molecules of CO\(_2\) are produced for every 10 molecules of O\(_2\) consumed (i.e., RQ = 0.8). For a diet composed of carbohydrates, the RQ is 1.0. For a diet of fat, the RQ is 0.7.

Minute & Alveolar Ventilation

Minute ventilation (V\(_E\)) is the total volume of gas entering (or leaving) the lung per minute. It is equal to the tidal volume (TV) multiplied by the respiratory rate (f).

\[
\text{Minute ventilation} = V_E = TV \times f
\]

At rest, a normal person moves ~450 ml/breath x 10 breath/min = 4500 ml/min.

However, because of the anatomical dead space (V\(_D\)), not all of this entering air is available for exchange with the blood (Fig. 10). Recall that the conducting airway (anatomical dead space) has a volume of ~150 ml. As illustrated in figure 10, when 450 ml of fresh air is inspired, the first gas to reach the respiratory zone comes from this anatomical dead space (150 ml). Then 300 ml of fresh gas reaches the respiratory zone and the last 150 ml of inspired gas remains in the dead space. Thus, the total amount of fresh air reaching the alveoli during each inspiration equals the tidal volume minus the volume of the anatomical dead space:

\[
TV - V_D = 450 - 150 = 300 \text{ ml.}
\]

Alveolar ventilation (V\(_A\)) is the total volume of fresh air entering the alveoli per minute. It is calculated as:

\[
\text{Alveolar ventilation} = V_A = (TV - V_D) \times f
\]
When evaluating the efficiency of ventilation, one should focus on the alveolar ventilation not minute ventilation.

For example, in the table below, Subjects A and B have the same minute ventilation ($V_E = 6 \text{ L}$) but very different alveolar ventilations ($V_A$). Subject A has no alveolar ventilation and would become unconscious in a few minutes but Subject B is breathing normally.

<table>
<thead>
<tr>
<th>Subject</th>
<th>$TV$</th>
<th>$f$</th>
<th>$V_E$</th>
<th>$V_D$</th>
<th>$V_A$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>150ml</td>
<td>40</td>
<td>6000ml</td>
<td>150ml</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>500ml</td>
<td>12</td>
<td>6000ml</td>
<td>150ml</td>
<td>4200ml</td>
</tr>
</tbody>
</table>

One other important point shown in the table above is that the depth of breathing ($TV$) is far more effective in elevating the alveolar ventilation than an increase in ventilation rate ($f$). This is because for each tidal breath a fixed volume is dead space. As tidal volume decreases, the fraction going to dead space increases. The respiratory system will respond to $O_2$ need (as in exercise) by reflexively increasing ventilation by increasing the depth of breathing.

The anatomical dead space is not the only type of dead space in the lung. Some fresh air is not used for gas exchange even though it reaches the alveoli because some alveoli may have little or no blood supply (i.e., blood perfusion). This volume of air is called alveolar dead space. In normal individuals this is quite small but may be large in several kinds of lung disease. As we will discuss later, a mismatch in ventilation and blood perfusion is minimized by local mechanisms that match air and blood flow. The sum of the anatomical dead space and alveolar dead space is the physiologic dead space.

### Partial Pressure of Gases

The amount of various gases can be measured by comparing the pressure they exert. Gas molecules behave like individual particles that are in a constant state of motion. When the particles collide with one another or the sides of the container they exert a pressure. The pressure exerted depends on the number of collisions. Two factors affect the number of collisions: the temperature of the gas and the number of gas molecules. Dalton’s law states that in a mixture of gases, the pressure exerted by each gas is the same as it would be if that gas alone occupied the entire container. These individual pressures are called partial pressures and are denoted as $P$ in front of the symbol for the gas.

To calculate the partial pressure of gas "X":

$$P_X = P_{atm} \times F_X$$

Where, $P_{atm}$ is the atmospheric pressure (at sea level = 760 mm Hg), and $F_X$ is the fractional concentration of gas $X$.

Atmospheric air contains mostly nitrogen (79%) and oxygen (21% $O_2$) with trace amounts of $CO_2$ and other gases. Air also contains water vapor. At sea level, water vapor is 47 mm Hg. For simplicity, respiratory physiologists and physicians generally assume that room air is always dry. Since 21% of dry room air is oxygen, the fraction of $O_2$ in inspired air (FiO$_2$) is:

$$FiO_2 \times P_{atm} = 0.21 \times 760 \text{ mm Hg} = 160 \text{ mm Hg}.$$  

The concentration of carbon dioxide in room air is so low (0.04%), it is considered to be 0.
When inspired, the room air is warmed to 37°C and becomes humidified as it passes through the nasal passages. The water vaporizes into the air until the $P_{H_2O} = 47$ mm Hg. What this means is that only 760 - 47 mm Hg or 713 mm Hg is available for other gases besides water. Therefore,

$$PO_2 \text{ of inspired gas} = 0.21 \times (760 \text{ mm Hg} - 47 \text{ mm Hg}) = 150 \text{ mmHg}.$$ 

5. Oxygen transport

Partial Pressures of Alveolar Gases

In the alveoli, the partial pressures of oxygen and carbon dioxide vary during the respiratory cycle. As gas exchange occurs, the alveolar partial pressure of carbon dioxide will rise and the alveolar partial pressure of oxygen will fall. Because these fluctuations are small (a few mm Hg) as compared with the 3000 ml present at the end of tidal exhalation, they are generally ignored and only mean values $PO_2$ and $PCO_2$ are considered.

The relationship between $PO_2$ and $PCO_2$ in the alveoli is described by the alveolar gas equation:

$$PAO_2 = (P_{atm} - P_{H_2O}) \times FiO_2 - PACO_2/RQ$$

Because diffusion is so rapid and complete in the lung, the $PACO_2$ and $PAO_2$ in the alveoli normally determine these gas pressures in arterial blood ($PaCO_2$ and $PaO_2$). But there is a slight difference between alveolar and arterial gas pressures even in normal subjects such that $PAO_2$ and $PaO_2$ differ by 5-15 mm Hg. This difference is due to anatomical shunting of blood (reduced perfusion) and to the mismatch between ventilation and perfusion that exists even in normal lungs. Both of these conditions will be discussed later in detail.

Normal values for arterial $PaO_2$ and $PaCO_2$ are:

$PaO_2 = 100$ mm Hg
$PaCO_2 = 40$ mm Hg.

The $PaO_2$ and $PaCO_2$ can be measured directly from arterial blood draws. $PAO_2$ is calculated by the alveolar gas equation. For a patient breathing room air at sea level, this equation simplifies to:

$$PAO_2 = 150 - \frac{PaCO_2}{0.8}$$

Notice that alveolar $PO_2$ is determined by three factors:

1. $PO_2$ of atmospheric air
2. Alveolar ventilation rate
3. Rate of tissue $O_2$ consumption (RQ).

Each of these factors can change independent of another. For example, a decrease in either $PO_2$ of the atmospheric air (changes with altitude) or in alveolar ventilation (hypoventilation) will decrease the amount of fresh air entering the alveoli per unit time. Likewise, an increase in the rate of total body $O_2$ consumption will decrease $PO_2$ in the alveoli.

Because there is essentially no $PCO_2$ in inspired air, only the rate of ventilation and the rate of tissue metabolism affect the $PCO_2$ levels in the alveoli. In this instance, hypoventilation (Fig. 11) and/or increased cellular metabolism will increase $PCO_2$ in the alveoli.
Hypoventilation exists when there is an increase in the ratio of CO₂ production to alveolar ventilation. That is the alveolar ventilation cannot keep up with CO₂ production resulting in a rise in alveolar PACO₂ > 40 mm Hg (Fig. 11). Hypoventilation can be caused by drugs such as barbiturates that depress the part of the central nervous system that drives breathing, or by damage to the chest wall, lungs, or respiratory muscles and when the movement of the chest wall is limited (e.g., caused by arthritis or deformation of the thoracic cavity).

Hyperventilation exists when there is a decrease in the ratio of CO₂ production to alveolar ventilation. That is the alveolar ventilation is too great for the CO₂ produced resulting in PACO₂ < 40mmHg (Fig. 11). Hyperventilation will occur in response to hypoxia, high altitude, or some drugs such as cocaine which can cause anxiety attacks.

***Notice that hyperventilation is not the increased ventilation that accompanies mild to moderate aerobic exercise. In aerobic exercise the increase in production of CO₂ is matched to increased alveolar ventilation (depth and rate of breathing).

Transport of Oxygen and Carbon Dioxide

To enhance delivery and transport of O₂ and CO₂ to and from tissues, specialized mechanisms (O₂-hemoglobin and bicarbonate transport of CO₂) have evolved.

OXYGEN TRANSPORT

Oxygen is not very soluble in water and therefore requires the carrier, hemoglobin (Hb), for transport in blood. Blood normally contains about 15 g of Hb per 100 ml. This effectively raises the solubility of O₂ from 3ml/L of plasma (blood minus the red blood cells) to 200 ml/L plasma. Since oxygen consumption ranges from 250 to 1500 L/min, this extra O₂ carrying capacity of Hb enables the heart and lungs to provide for the O₂ needs of the body.

Hemoglobin binds up to 4 molecules of O₂ tightly, cooperatively, and reversibly. Normally Hb is almost completely saturated (96%) when exposed to room air (FiO₂ = 21%). This occurs because of
the transit time (0.75 seconds) for the red blood cell through the alveolus-capillary unit and the rapid equilibration (0.3 seconds) for both carbon dioxide and oxygen within this region of the lung.

This rapid equilibration reflects the driving pressure for diffusion and the solubility of the gas. The driving pressure for diffusion of CO₂ in the alveolus-capillary unit is lower (PMVCO₂ - PaCO₂ = 46 mm Hg - 40 mm Hg = 6 mm Hg) than that for O₂ (PaO₂ - PMVO₂ = 100 - 40 = 60 mm Hg), but the solubility of CO₂ in plasma is much greater. The net result is that the rates of diffusion for CO₂ and O₂ are approximately equal in the alveolus-capillary unit. This means that in normal lungs there is **ALWAYS adequate time to saturate Hb with O₂ regardless of ventilatory rate.**

Oxygen concentration in the blood is dependent on the Hb concentration in the red blood cells, the number of red blood cells (hematocrit), and on the adequacy of perfusion of the lungs rather than on diffusion rate itself.

Not all of the O₂ bound to Hb is released in the tissues. At rest only about 25% of the O₂ in blood is released (Fig. 12). This provides a large driving force for diffusion and a large reservoir of O₂ to be called upon when needed as in exercise.

The Hb-O₂ dissociation curve (Fig. 12) is **S-shaped** because the interaction of oxygen with hemoglobin is **cooperative**. That is, when one oxygen molecule binds, it increases the affinity of the hemoglobin for the next oxygen molecule. Each hemoglobin molecule can bind four oxygen molecules.

The plateau of the Hb-O₂ dissociation curve is called the **“association part”** of the curve, because oxygen is loaded in the lungs at relatively high partial pressures. Increasing the partial pressure above 100 or down to about 80 mm Hg, **does not result** in a large change in the % saturation. This tends to stabilize arterial O₂ content, making it relatively insensitive to moderate changes in breathing or altitude.

The **“dissociation part”** of the curve is the steep part of the curve (Fig. 12). In this region a small change in PO₂ results in a large change in % saturation which allows for large quantities of oxygen to be dumped in the tissues.

The P50 is the partial pressure of oxygen required to saturate 50% of the hemoglobin. A normal P50 is about 26-27 mm Hg. This value is a useful measure of the affinity of hemoglobin for O₂.

Oxygen-Hb binding and association is affected by a number of parameters including temperature, the red blood cell metabolite 2,3 diphosphoglycerate (DPG), and pH. Elevated temperature, low pH and increased 2,3 DPG shift the curve to the right (**decrease affinity**) which **enhances unloading of O₂ from Hb** (Fig. 13). Note that these are conditions found within...
the interstitial tissue surrounding actively contracting muscle. Hypoxic conditions also result in increased formation of 2,3-DPG by the red blood cells.

Conversely, a decrease in temperature, high pH and a decrease in 2,3, DPG shifts the $O_2$-Hb dissociation curve to the left (increase affinity) which promotes loading of $O_2$ onto Hb (Fig. 13).

6. **CO2 transport and V/Q mismatch**

**CARBON DIOXIDE TRANSPORT**

Carbon dioxide is a product of oxidative metabolism. Unlike $O_2$, CO$_2$ is very soluble in water and does not need a carrier for transport in the blood. Most (60%) of the carbon dioxide in blood is transported as bicarbonate ($HCO_3^-$). The conversion of CO$_2$ to bicarbonate is catalyzed by the enzyme carbonic anhydrase located inside red blood cells.

$$CO_2 + H_2O = H_2CO_3 = HCO_3^- + H^+$$

Once formed, the $HCO_3^-$ is transported out of the RBC into the plasma in exchange for Cl$^-$. About 10% of the total CO$_2$ in blood is transported as dissolved CO$_2$. The amount dissolved is proportional to the PCO$_2$, and to the solubility coefficient for CO$_2$. At PaCO$_2$ = 40 mm Hg, there would be approximately 26.8 ml CO$_2$/L of plasma.

The remaining 30% of the CO$_2$ combines with Hb to form carbamino-hemoglobin compounds.

Because CO$_2$ diffuses 20X more rapidly than $O_2$, a rise in blood CO$_2$ can be compensated by an increase in ventilatory rate. Hyperventilation increases the amount of CO$_2$ removed from the body and increases the unloading of CO$_2$ from the blood in the lung.

**Ventilation & Perfusion**

Ventilation is the process of bringing air in and out of the lungs. Perfusion is the process of bringing blood in and out of the lung capillary bed to allow for gas exchange. The right ventricle delivers blood to the lungs at relatively low pressures (mean pressure of 15 mmHg). However, lung perfusion pressure can increase for multiple reasons including obstruction of vessels (i.e., embolism) or increased resistance to flow (i.e., fibrosis). The lung will compensate for lowered blood flow (1) by recruiting other capillary beds within the lung and (2) by distention of small vessels. If these responses are inadequate, then pressure within the pulmonary artery will rise causing a rise in right ventricular pressure. This is called pulmonary hypertension.

Under normal conditions, regulatory mechanisms within the lung match ventilation (V) to perfusion (Q) to optimize the oxygenation of the blood. V/Q mismatch can occur when ventilated alveoli are not perfused giving a V/Q ratio of infinity and conversely, when unventilated alveoli are perfused, giving a V/Q ratio of zero. This latter condition is equivalent to shunting venous blood from the right to the left side of the heart bypassing the lungs. Usually lung disease is progressive. It leads to a gradual worsening of either ventilation or perfusion and therefore the V/Q mismatch is intermediate between zero and infinity. Many believe that V/Q mismatching is the most common cause of low PaO$_2$.

In a normal individual at the level of the lung, alveolar ventilation is about 4.0 L/min and pulmonary blood flow is about 5.0 L/min. This gives a V/Q = 0.8 overall.
Note that V/Q mismatch occurs within the normal lung because blood flow is never perfectly uniform in this organ. In a normal person while standing, gravitational pull causes the apex of the lung to be more expanded than within the base thereby compressing the capillaries and reducing perfusion; V/Q ratios are greater than 1 in the apex (Fig. 14). In contrast, perfusion is greater than ventilation at the base of the lung in an upright individual; V/Q ratios are less than 1 (Fig. 14).

One mechanism that compensates for V/Q mismatch is the vasoconstriction of the lung vasculature in response to hypoxia (low O₂). [Note that this is in contrast to the smooth muscle of the systemic vasculature which dilates in response to low O₂ conditions.] Vasoconstriction of the lung vasculature to hypoxia enables the blood to be shunted away from poorly ventilated areas. This occurs without an increase in pulmonary artery perfusion pressure because of the large capacity of the pulmonary capillaries.

A second compensation that compensates for V/Q mismatch occurs when PACO₂ falls (e.g. when V/Q ratio increases). In this instance, the concentration of hydrogen ions (H+) in and around the smooth muscle of the airways (bronchioles) decreases. This reduction in H+ results in airway constriction and a shift of ventilation away from the areas which are over ventilated (i.e., not perfused).

7. Regulation of breathing
Control of Respiration
Breathing is essentially automatic and can only be altered temporarily by voluntary efforts. You cannot consciously stop breathing for long. You breathe when you are asleep, awake, or even anesthetized. Breathing is finely tuned to meet metabolic demands, such that during exercise ventilation increases to maintain arterial PO₂, PCO₂ and pH within a narrow range. To achieve this tight regulation, peripheral receptors send information to a CNS respiratory center whose output adjusts initiation, duration, depth, and rate of breathing.

The intercostal muscles and diaphragm are skeletal muscles that will not contract unless stimulated. Thus breathing depends on cyclical excitation of the motor neurons that innervate these muscles. Destruction of these nerves by the polio virus for example results in paralysis and death if the individual is not ventilated.

The underlying respiratory rhythm is established by respiratory centers in the medulla of the brain stem. The general term for this integration center is the respiratory rhythm generator. Inspiratory neurons located in the respiratory center initiate respiratory rhythm by sending signals to the motor neurons that innervate the effector skeletal muscles (intercostals and diaphragm). This rhythm is modified by input from peripheral sensors (chemoreceptors and mechanoreceptors) located in blood vessel walls and by central receptors (chemoreceptors) in the brain.
**Inspiration** is limited by several inputs including stretch of the lungs and innate rhythm generators within the brain stem (medulla). The medullary inspiratory neurons are quite sensitive to drugs such as barbiturates and morphine. Death from an overdose of these drugs is often due to cessation of breathing.

**Inspiratory receptors in the lung include:**

1. **Pulmonary stretch receptors** located in the smooth muscle of the large and small airways of the lung are mechanoreceptors that fire with the inflation of the lung. These receptors **stop inspiration** as part of the Hering-Breuer reflex. In the adult this reflex is evoked only under conditions of large tidal volumes as in rigorous exercise.

2. **J Receptors** located in the walls of the pulmonary capillaries which are stimulated by pulmonary vascular congestion, edema, air emboli (air in the blood), and low lung volumes. Stimulation of these receptors can result in **rapid breathing (hyperpnea)**, and or labored breathing (dyspnea).

3. **Pulmonary irritant receptors** located in airway epithelium and the nasal mucosa. Mechanical or chemical irritation elicits a **cough reflex** and **bronchoconstriction**.

**Transport of Hydrogen Ions**

Metabolism generates protons (H+) which are extruded to the interstitial fluid surrounding cells and eventually enter the blood by diffusion. As blood flows through the tissues, a fraction of the oxy-hemoglobin (O$_2$-Hb) loses its oxygen to become deoxy-Hb. Deoxy-Hb has a much higher affinity for H+ and thus binds most of the newly generated H+.

$$\text{HbO}_2 + \text{H}^+ = \text{HbH} + \text{O}_2$$

This effectively removes the H+ from the blood and thereby buffers the blood. As a consequence venous blood is slightly more acidic (pH of 7.36) than arterial blood (pH 7.4).

As venous blood passes through the lungs, HbH is converted to HbO$_2$ and H+ is released. The H+ reacts with the bicarbonate (HCO$_3^-$) in the blood to give carbonic acid (H$_2$CO$_3$) which dissociates to H$_2$O + CO$_2$. The CO$_2$ diffuses into the alveoli to be expired. Normally all of the H+ will be removed by this process and none will appear in the arterial blood.

$$\text{H}^+ + \text{HCO}_3^- = \text{H}_2\text{CO}_3 = \text{H}_2\text{O} + \text{CO}_2$$

However, if an individual is either **hypoventilating** or has a lung disease that prevents normal elimination of CO$_2$, then the PaCO$_2$ will rise and the arterial H+ concentration will rise (by mass action). Increased arterial H+ concentration due to CO$_2$ retention is called **respiratory acidosis**.

Conversely, if a person is **hyperventilating**, then PaCO$_2$ and H+ concentration will decrease, producing **respiratory alkalosis**.

**Ventilation is Regulated by Chemoreceptors**

Respiratory rate and tidal volume can increase or decrease over a wide range. At rest, chemoreceptors located in the periphery and centrally within the CNS provide feedback to regulate these two factors.
Peripheral chemoreceptors are the carotid receptors and aortic bodies. They are stimulated by:

a. decrease in \( \text{PaO}_2 \) (hypoxia)
b. increase in \( \text{PaCO}_2 \) (respiratory acidosis)
c. decrease in pH within the arterial blood (metabolic acidosis).

Of the two, the carotid receptor is the predominate input in controlling respiration.

Central chemoreceptors are widely distributed throughout the brain stem. They respond to an increase in blood \( \text{PCO}_2 \). These receptors actually sense \( \text{H}^+ \) concentration in the interstitial fluid of the brain. They are not affected by changes in arterial pH because the blood brain-barrier is not permeable to \( \text{H}^+ \) or \( \text{HCO}_3^- \). Instead, \( \text{CO}_2 \) equilibrates across this barrier, causing a change in the interstitial fluid pH. Because the interstitial fluid and the adjoining cerebrospinal fluid contain little protein, they are not well buffered. Hence small changes in \( \text{PCO}_2 \) produce large changes in pH in this area.

**Ventilatory Response to Oxygen**

The ventilatory response to hypoxia is shown in the graph below (Fig. 15). \( \text{PaO}_2 \) must decrease to about 50-60 mm Hg before respiration is increased. It has been suggested that the carotid chemoreceptors (which respond to changes in \( \text{PaO}_2 \)), are designed to protect the organism against hypoxia rather than to regulate respiration. Note that the stimulation to hypoxia is arterial \( \text{PO}_2 \) not arterial \( \text{O}_2 \) content. That means that individuals with anemia do not have increased ventilation because their \( \text{PaO}_2 \) is normal.

**Ventilatory Response to Carbon Dioxide**

A very small increase in \( \text{PaCO}_2 \) (2-4 mm Hg) provides a powerful stimulus to increase respiration (doubles alveolar ventilation) (Fig. 16). What is the physiologic role of this response? Recall that changes in \( \text{PaCO}_2 \) have profound effects on pH. Thus this tight regulation of \( \text{PaCO}_2 \) allows for tight control of acid-base balance. For example, in emphysema patients retention of \( \text{CO}_2 \) occurs because of the decrease in the elastic recoil. This raises their \( \text{PaCO}_2 \) leading to increased minute ventilation (i.e., “blowing down” the \( \text{CO}_2 \) in the blood). Of the two sets of receptors involved in this reflex response to elevated \( \text{PaCO}_2 \), the central chemoreceptors are more important accounting for ~70% of the increased ventilation.

Hypoxia (low \( \text{PO}_2 \)) potentiates the effects of \( \text{CO}_2 \). The response curve is shifted to the left and has a steeper slope. Thus a lower \( \text{PaO}_2 \) will result in a stronger ventilatory response for the same arterial \( \text{PCO}_2 \).

Very high levels of carbon dioxide (greater than 70-80 mm Hg) can depress respiration, cause headaches, restlessness, faintness, and even unconsciousness or coma.
Changes in pH without changes in PaCO$_2$
Excess retention or elimination of CO$_2$ causes respiratory acidosis or alkalosis, respectively. However, many normal and pathological conditions can change arterial H$^+$ levels in which the primary cause is not a change in PCO$_2$. These conditions are called metabolic acidosis (increased H$^+$ concentration) and metabolic alkalosis (decreased H$^+$ concentration). Which chemoreceptors play a major role in these instances, central or peripheral? Why?

For example, in strenuous exercise, lactic acid is released by the working muscle. The addition of lactic acid to the blood lowers the pH and causes hyperventilation almost entirely by stimulating the peripheral chemoreceptors. Recall that H$^+$ do not cross the blood brain barrier, but CO$_2$ does and is converted in the interstitial fluid to H$^+$ and HCO$_3^-$.

Predict what happens when arterial H$^+$ concentration is decreased by vomiting (loss of acid from the stomach). Is ventilation increased or decreased? Answer: The peripheral chemoreceptors will reflexively decrease ventilation to conserve CO$_2$ in the blood. Thus the respiratory system compensates for metabolic acidosis by increasing ventilation (hyperventilation) and for metabolic alkalosis by decreasing ventilation (hypoventilation). Notice that maintenance of PCO$_2$ levels is not as important as maintenance of H$^+$ concentration in the blood. This is because most enzymes of the body function best at physiological pH (pH = 7.4).

8. Exercise and hypoxia

Exercise Affects Ventilation
With moderate physical activity, both oxygen consumption and carbon dioxide production increase. Minute ventilation can increase up to 25-fold. It would seem logical to guess that the increase in CO$_2$ production increases PaCO$_2$ which would, in turn, stimulate ventilation. However, measurements of PaCO$_2$ during moderate exercise show that it does not change appreciably (Fig. 17). In fact, neither does PaO$_2$ nor pH (Fig. 17). However, at near maximal exercise, arterial H$^+$ concentration does rise and PaCO$_2$ falls. Why does the H$^+$ concentration increase while PaCO$_2$ decreases?

The mediators that cause increased ventilation in response to moderate exercise are likely to include increased body temperature, increased epinephrine level, reflex input from the mechanoreceptors of the joints and muscles, and conditioned behavior (feed forward). The deep breathing after exercise removes the oxygen debt restoring oxygen storing molecule (myoglobin) and energy storing (creatine phosphate) in the muscles, as well as removing lactic acid and H$^+$.

Figure 17. Effect of exercise on ventilation, arterial gas pressures and arterial H$^+$ concentration.
Hypoxia (Low $\text{PO}_2$) & Ventilatory Control

Hypoxia is defined as a deficiency of oxygen at the tissue level. There are many causes of hypoxia but they can be grouped into four classes.

1. **hypoxia- hypoxia** in which arterial $\text{PO}_2$ is reduced.
2. **anemic hypoxia** in which arterial $\text{PO}_2$ is normal but the content of $\text{O}_2$ is reduced because of inadequate numbers of red blood cells or incompetent Hb or competition of carbon monoxide for Hb.
3. **ischemic hypoxia** in which blood flow to the tissues is too low.
4. **histotoxic hypoxia** in which the $\text{O}_2$ content in the tissue is normal but the cell is unable to utilize it because a toxic agent (such as cyanide) interferes with oxidative metabolism.

Individuals who reside at high altitudes (where $\text{O}_2$ tension is reduced) or who have sleep apnea syndrome (that is, they stop breathing for prolonged periods during sleep) may have diminished hypoxia drive to breathe. This is due to the “resetting” of their chemoreceptors set point.

The effects of $\text{O}_2$ deprivation vary from individual to individual but most people who ascend rapidly to altitudes above 10,000 ft experience some degree of *altitude sickness*. The symptoms of altitude sickness are headache, nausea, vomiting, fatigue and possible mental confusion. In severe cases, life threatening pulmonary edema can occur due to pulmonary hypertension. Over a course of a several days these symptoms will disappear due to acclimatization which includes increased hematocrit (more red blood cells), increased 2,3, DPG and a shift in the $\text{O}_2$ dissociation curve to the right to facilitate unloading in the tissues.

During sleep, breathing frequency and inspiratory flow rate are reduced and minute ventilation decreases. This is accompanied by a relaxation of the skeletal muscle tone throughout the body including those muscles associated with the larynx, pharynx and tongue. Relaxation of muscle tone in these areas can cause partial obstruction of the upper airways and *snoring*. However, in some individuals the airways are completely occluded which can lead to *sleep apnea*. In sleep apnea, respiration stops for long periods (30-60 sec) and $\text{PaCO}_2$ rises; the respiratory center is stimulated. The individual reacts by gasping and often awakens.