I. LUNG VOLUMES AND CAPACITIES

A. Lung volumes (Figure 4-1)

1. Tidal volume (TV)
   - is the volume inspired or expired with each normal breath.

2. Inspiratory reserve volume (IRV)
   - is the volume that can be inspired over and above the tidal volume.
   - is used during exercise.

3. Expiratory reserve volume (ERV)
   - is the volume that can be expired after the expiration of a tidal volume.

4. Residual volume (RV)
   - is the volume that remains in the lungs after a maximal expiration.
   - cannot be measured by spirometry.

5. Dead space
   a. Anatomic dead space
      - is the volume of the conducting airways.
      - is normally approximately 150 mL.
   b. Physiologic dead space
      - is a functional measurement.
      - is defined as the volume of the lungs that does not participate in gas exchange.
      - is approximately equal to the anatomic dead space in normal lungs.
      - may be greater than the anatomic dead space in lung diseases in which there are ventilation/perfusion (V/Q) defects.
      - is calculated by the following equation:

\[
V_D = V_T \times \frac{P_{A_{CO_2}} - P_{E_{CO_2}}}{P_{A_{CO_2}}}
\]

where:
- \(V_D\) = physiologic dead space (mL)
- \(V_T\) = tidal volume (mL)
- \(P_{A_{CO_2}}\) = \(P_{CO_2}\) of alveolar gas (mm Hg) = \(P_{CO_2}\) of arterial blood
- \(P_{E_{CO_2}}\) = \(P_{CO_2}\) of expired air (mm Hg)
In words, the equation states that physiologic dead space is tidal volume multiplied by a fraction. The fraction represents the dilution of alveolar PCO₂ by dead-space air, which does not participate in gas exchange and does not therefore contribute CO₂ to expired air.

6. Ventilation rate
   a. Minute ventilation is expressed as follows:
   
   \[ \text{Minute ventilation} = \text{Tidal volume} \times \text{Breaths/min} \]

   b. Alveolar ventilation is expressed as follows:
   
   \[ \text{Alveolar ventilation} = (\text{Tidal volume} - \text{Dead space}) \times \text{Breaths/min} \]

   **Sample problem:** A person with a tidal volume (Vₜ) of 0.5 L is breathing at a rate of 15 breaths/min. The P\text{CO}_₂ of his arterial blood is 40 mm Hg, and the P\text{CO}_₂ of his expired air is 36 mm Hg. What is his rate of alveolar ventilation?

   \[
   \text{Dead space} = V_t \times \frac{P_{\text{A CO}_2} - P_{\text{E CO}_2}}{P_{\text{A CO}_2}} \\
   = 0.5 \text{ L} \times \frac{40 \text{ mm Hg} - 36 \text{ mm Hg}}{40 \text{ mm Hg}} \\
   = 0.05 \text{ L} \\
   \text{Alveolar ventilation} = (0.5 \text{ L} - 0.05 \text{ L}) \times 15 \text{ Breaths/min} \\
   = 6.75 \text{ L/min}
   \]

B. Lung capacities (see Figure 4-1)

1. **Inspiratory capacity**
   - is the sum of tidal volume and IRV.

2. **Functional residual capacity (FRC)**
   - is the sum of ERV and RV.
   - is the volume remaining in the lungs after a tidal volume is expired.
   - includes the RV, so it cannot be measured by spirometry.
3. **Vital capacity (VC), or forced vital capacity (FVC)**
   - is the sum of tidal volume, IRV, and ERV.
   - is the volume of air that can be forcibly expired after a maximal inspiration.

4. **Total lung capacity (TLC)**
   - is the sum of all four lung volumes.
   - is the volume in the lungs after a maximal inspiration.
   - includes RV, so it cannot be measured by spirometry.

C. **Forced expiratory volume (FEV₁)** [Figure 4-2]
   - FEV₁ is the volume of air that can be expired in the first second of a forced maximal expiration.
   - FEV₁ is normally 80% of the forced vital capacity, which is expressed as:

     \[
     \text{FEV}_1 / \text{FVC} = 0.8
     \]

   - In obstructive lung disease, such as **asthma**, FEV₁ is reduced more than FVC so that \( \text{FEV}_1 / \text{FVC} \) is decreased.
   - In restrictive lung disease, such as **fibrosis**, both FEV₁ and FVC are reduced and \( \text{FEV}_1 / \text{FVC} \) is either normal or is increased.

II. MECHANICS OF BREATHING

A. **Muscles of inspiration**

1. **Diaphragm**
   - is the most important muscle for inspiration.
   - When the diaphragm contracts, the abdominal contents are pushed downward, and the ribs are lifted upward and outward, increasing the volume of the thoracic cavity.

2. **External intercostals and accessory muscles**
   - are not used for inspiration during normal quiet breathing.
   - are used during exercise and in respiratory distress.

B. **Muscles of expiration**
   - Expiration is normally passive.
Because the lung–chest wall system is elastic, it returns to its resting position after inspiration.

Expiratory muscles are used during exercise or when airway resistance is increased because of disease (e.g., asthma).

1. **Abdominal muscles**
   - compress the abdominal cavity, push the diaphragm up, and push air out of the lungs.

2. **Internal intercostal muscles**
   - pull the ribs downward and inward.

### C. Compliance of the respiratory system

- is described by the following equation:
  
  \[ C = \frac{V}{P} \]

  where:
  
  \( C \) = compliance (mL/mm Hg)
  
  \( V \) = volume (mL)
  
  \( P \) = pressure (mm Hg)

- describes the distensibility of the lungs and chest wall.
- is inversely related to elastance, which depends on the amount of elastic tissue.
- is inversely related to stiffness.
- is the slope of the pressure–volume curve.
- is the change in volume for a given change in pressure. Pressure refers to transmural, or transpulmonary, pressure (i.e., the pressure difference across pulmonary structures).

1. **Compliance of the lungs** (Figure 4-3)
   - Transmural pressure is alveolar pressure minus intrapleural pressure.
   - When the pressure outside of the lungs (i.e., intrapleural pressure) is negative, the lungs expand and lung volume increases.
   - When the pressure outside of the lungs is positive, the lungs collapse and lung volume decreases.
   - Inflation of the lungs (inspiration) follows a different curve than deflation of the lungs (expiration); this difference is called hysteresis.
   - In the middle range of pressures, compliance is greatest and the lungs are most distensible.
   - At high expanding pressures, compliance is lowest, the lungs are least distensible, and the curve flattens.

![FIGURE 4-3 Compliance of the lungs. Different curves are followed during inspiration and expiration (hysteresis).](image)
2. **Compliance of the combined lung–chest wall system** (Figure 4-4)
   a. **Figure 4-4** shows the pressure–volume relationships for the lungs alone (hysteresis has been eliminated for simplicity), the chest wall alone, and the lungs and chest wall together.

   - **Compliance of the lung–chest wall system** is less than that of the lungs alone or the chest wall alone (the slope is flatter).

   b. At rest (identified by the filled circle in the center of Figure 4-4), lung volume is at FRC and the pressure in the airways and lungs is equal to atmospheric pressure (i.e., zero). Under these equilibrium conditions, there is a collapsing force on the lungs and an expanding force on the chest wall. At FRC, these two forces are **equal and opposite** and, therefore, the combined lung–chest wall system neither wants to collapse nor expand (i.e., equilibrium).

   c. As a result of these two opposing forces, **intrapleural pressure is negative** (subatmospheric).

   - If air is introduced into the intrapleural space (**pneumothorax**), the intrapleural pressure becomes equal to atmospheric pressure. The lungs will collapse (their natural tendency) and the chest wall will spring outward (its natural tendency).

   d. **Changes in lung compliance**

   - In a patient with **emphysema**, lung compliance is increased and the tendency of the lungs to collapse is decreased. Therefore, at the original FRC, the tendency of the lungs to collapse is less than the tendency of the chest wall to expand. The lung–chest wall system will seek a **new, higher FRC** so that the two opposing forces can be balanced; the patient’s chest becomes **barrel-shaped**, reflecting this higher volume.

   - In a patient with **fibrosis**, lung compliance is decreased and the tendency of the lungs to collapse is increased. Therefore, at the original FRC, the tendency of the lungs to collapse is greater than the tendency of the chest wall to expand. The lung–chest wall system will seek a **new, lower FRC** so that the two opposing forces can be balanced.

D. **Surface tension of alveoli and surfactant**

   1. **Surface tension of the alveoli** (Figure 4-5)

   - results from the attractive forces between liquid molecules lining the alveoli.
creates a collapsing pressure that is directly proportional to surface tension and inversely proportional to alveolar radius (Laplace's law), as shown in the following equation:

\[ P = \frac{2T}{r} \]

where:
- \( P \) = collapsing pressure on alveolus (or pressure required to keep alveolus open) [dynes/cm²]
- \( T \) = surface tension (dynes/cm)
- \( r \) = radius of alveolus (cm)

a. **Large alveoli** (large radii) have low collapsing pressures and are easy to keep open.

b. **Small alveoli** (small radii) have high collapsing pressures and are more difficult to keep open.

In the absence of surfactant, the small alveoli have a tendency to collapse (atelectasis).

### 2. Surfactant (see Figure 4-5)

- lines the alveoli.
- reduces surface tension by disrupting the intermolecular forces between liquid molecules. This reduction in surface tension prevents small alveoli from collapsing and increases compliance.
- is synthesized by **type II alveolar cells** and consists primarily of the phospholipid dipalmitoyl phosphatidylcholine (DPPC).
- In the fetus, surfactant synthesis is variable. Surfactant may be present as early as gestational week 24 and is almost always present by gestational week 35.
- Generally, a lecithin:sphingomyelin ratio greater than 2:1 in amniotic fluid reflects mature levels of surfactant.
- **Neonatal respiratory distress syndrome** can occur in premature infants because of the lack of surfactant. The infant exhibits atelectasis (lungs collapse), difficulty reinflating the lungs (as a result of decreased compliance), and hypoxemia (as a result of decreased V/Q).

### E. Relationships between pressure, airflow, and resistance

are analogous to the relationships between blood pressure, blood flow, and resistance in the cardiovascular system.

#### 1. Airflow

- is driven by, and is directly proportional to, the pressure difference between the mouth (or nose) and the alveoli.
is inversely proportional to airway resistance; thus, the higher the airway resistance, the lower the airflow. This inverse relationship is shown in the following equation:

$$Q = \frac{\Delta P}{R}$$

where:
- $Q$ = airflow (mL/min or L/min)
- $\Delta P$ = pressure gradient (cm H$_2$O)
- $R$ = airway resistance (cm H$_2$O/L/min)

2. Resistance of the airways

- is described by Poiseuille’s law, as shown in the following equation:

$$R = \frac{8\eta l}{\pi r^4}$$

where:
- $R$ = resistance
- $\eta$ = viscosity of the inspired gas
- $l$ = length of the airway
- $r$ = radius of the airway

Notice the powerful inverse fourth-power relationship between resistance and the size (radius) of the airway.

For example, if airway radius decreases by a factor of 4, then resistance will increase by a factor of 256 ($4^4$), and airflow will decrease by a factor of 256.

3. Factors that change airway resistance

- The major site of airway resistance is the medium-sized bronchi.
- The smallest airways would seem to offer the highest resistance, but they do not because of their parallel arrangement.

a. Contraction or relaxation of bronchial smooth muscle

- changes airway resistance by altering the radius of the airways.
  (1) Parasympathetic stimulation, irritants, and the slow-reacting substance of anaphylaxis (asthma) constrict the airways, decrease the radius, and increase the resistance to airflow.
  (2) Sympathetic stimulation and sympathetic agonists (isoproterenol) dilate the airways via $\beta_2$ receptors, increase the radius, and decrease the resistance to airflow.

b. Lung volume

- alters airway resistance because of the radial traction exerted on the airways by surrounding lung tissue.
  (1) High lung volumes are associated with greater traction and decreased airway resistance. Patients with increased airway resistance (e.g., asthma) “learn” to breathe at higher lung volumes to offset the high airway resistance associated with their disease.
  (2) Low lung volumes are associated with less traction and increased airway resistance, even to the point of airway collapse.

c. Viscosity or density of inspired gas

- changes the resistance to airflow.
- During a deep-sea dive, both air density and resistance to airflow are increased.
- Breathing a low-density gas, such as helium, reduces the resistance to airflow.
F. Breathing cycle—description of pressures and airflow (Figure 4-6)

1. At rest (before inspiration begins)
   a. Alveolar pressure equals atmospheric pressure.
      ■ Because lung pressures are expressed relative to atmospheric pressure, alveolar pressure is said to be zero.
   b. Intrapleural pressure is negative.
      ■ The opposing forces of the lungs trying to collapse and the chest wall trying to expand create a negative pressure in the intrapleural space between them.
      ■ Intrapleural pressure can be measured by a balloon catheter in the esophagus.
   c. Lung volume is the FRC.

2. During inspiration
   a. The inspiratory muscles contract and cause the volume of the thorax to increase.
      ■ As lung volume increases, alveolar pressure decreases to less than atmospheric pressure (i.e., becomes negative).
      ■ The pressure gradient between the atmosphere and the alveoli now causes air to flow into the lungs; airflow will continue until the pressure gradient dissipates.
   b. Intrapleural pressure becomes more negative.
      ■ Because lung volume increases during inspiration, the elastic recoil strength of the lungs also increases. As a result, intrapleural pressure becomes even more negative than it was at rest.
      ■ Changes in intrapleural pressure during inspiration are used to measure the dynamic compliance of the lungs.
c. Lung volume increases by one TV.
   - At the peak of inspiration, lung volume is the FRC plus one TV.

3. During expiration
   a. Alveolar pressure becomes greater than atmospheric pressure.
      - The alveolar pressure becomes greater (i.e., becomes positive) because alveolar gas is compressed by the elastic forces of the lung.
      - Thus, alveolar pressure is now higher than atmospheric pressure, the pressure gradient is reversed, and air flows out of the lungs.
   b. Intrapleural pressure returns to its resting value during a normal (passive) expiration.
      - However, during a forced expiration, intrapleural pressure actually becomes positive. This positive intrapleural pressure compresses the airways and makes expiration more difficult.
      - In chronic obstructive pulmonary disease (COPD), in which airway resistance is increased, patients learn to expire slowly with "pursed lips" to prevent the airway collapse that may occur with a forced expiration.
   c. Lung volume returns to FRC.

G. Lung diseases (Table 4-1)

1. Asthma
   - is an obstructive disease in which expiration is impaired.
   - is characterized by decreased FVC, decreased FEV1, and decreased FEV1/FVC.
   - Air that should have been expired is not, leading to air trapping and increased FRC.

2. COPD
   - is a combination of chronic bronchitis and emphysema.
   - is an obstructive disease with increased lung compliance in which expiration is impaired.
   - is characterized by decreased FVC, decreased FEV1, and decreased FEV1/FVC.
   - Air that should have been expired is not, leading to air trapping, increased FRC, and a barrel-shaped chest.
   a. “Pink puffers” (primarily emphysema) have mild hypoxemia and, because they maintain alveolar ventilation, normocapnia (normal Pco2).
   b. “Blue bloaters” (primarily bronchitis) have severe hypoxemia with cyanosis and, because they do not maintain alveolar ventilation, hypercapnia (increased Pco2). They have right ventricular failure and systemic edema.

3. Fibrosis
   - is a restrictive disease with decreased lung compliance in which inspiration is impaired.
   - is characterized by a decrease in all lung volumes. Because FEV1 is decreased less than FVC, FEV1/FVC is increased (or may be normal).

<table>
<thead>
<tr>
<th>Table 4-1 Characteristics of Lung Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>Fibrosis</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease; FEV1 = volume expired in first second of forced expiration; FRC = functional residual capacity; FVC = forced vital capacity.
III. GAS EXCHANGE

A. Dalton's law of partial pressures

- can be expressed by the following equation:

\[
\text{Partial pressure} = \text{Total pressure} \times \text{Fractional gas concentration}
\]

1. In dry inspired air, the partial pressure of O\textsubscript{2} can be calculated as follows. Assume that total pressure is atmospheric and the fractional concentration of O\textsubscript{2} is 0.21.

\[
P_{O_2} = 760 \text{ mm Hg} \times 0.21
\]
\[
= 160 \text{ mm Hg}
\]

2. In humidified tracheal air at 37°C, the calculation is modified to correct for the partial pressure of H\textsubscript{2}O, which is 47 mm Hg.

\[
P_{\text{Total}} = 760 \text{ mm Hg} - 47 \text{ mm Hg}
\]
\[
= 713 \text{ mm Hg}
\]
\[
P_{O_2} = 713 \text{ mm Hg} \times 0.21
\]
\[
= 150 \text{ mm Hg}
\]

B. Partial pressures of O\textsubscript{2} and CO\textsubscript{2} in inspired air, alveolar air, and blood (Table 4-2)

- Approximately 2% of the systemic cardiac output bypasses the pulmonary circulation ("physiologic shunt"). The resulting admixture of venous blood with oxygenated arterial blood makes the PO\textsubscript{2} of arterial blood slightly lower than that of alveolar air.

C. Dissolved gases

- The amount of gas dissolved in a solution (such as blood) is proportional to its partial pressure. The units of concentration for a dissolved gas are mL gas/100 mL blood.

- The following calculation uses O\textsubscript{2} in arterial blood as an example:

\[
\text{Dissolved}[O_2] = P_{O_2} \times \text{Solubility of O}_2 \text{ in blood}
\]
\[
= 100 \text{ mm Hg} \times 0.03 \frac{\text{mL O}_2}{\text{L mm Hg}}
\]
\[
= 0.3 \frac{\text{mL O}_2}{\text{100 mL blood}}
\]

where:

\[
\text{[O}_2\text{]} = \text{O}_2 \text{ concentration in blood}
\]
\[
P_{O_2} = \text{Partial pressure of } O_2 \text{ in blood}
\]
\[
0.03 \text{ mL O}_2/\text{L mm Hg} = \text{Solubility of O}_2 \text{ in blood}
\]

D. Diffusion of gases such as O\textsubscript{2} and CO\textsubscript{2}

- The diffusion rates of O\textsubscript{2} and CO\textsubscript{2} depend on the partial pressure differences across the membrane and the area available for diffusion.

- For example, the diffusion of O\textsubscript{2} from alveolar air into the pulmonary capillary depends on the partial pressure difference for O\textsubscript{2} between alveolar air and pulmonary capillary blood. Normally, capillary blood equilibrates with alveolar gas; when the partial pressures of O\textsubscript{2} become equal (see Table 4-2), then there is no more net diffusion of O\textsubscript{2}.

E. Perfusion-limited and diffusion-limited gas exchange (Table 4-3)

1. Perfusion-limited exchange

- is illustrated by N\textsubscript{2}O and by O\textsubscript{2} under normal conditions.
In perfusion-limited exchange, the gas equilibrates early along the length of the pulmonary capillary. The partial pressure of the gas in arterial blood becomes equal to the partial pressure in alveolar air.

Thus, for a perfusion-limited process, diffusion of the gas can be increased only if blood flow increases.

2. Diffusion-limited exchange

- is illustrated by CO and by O₂ during strenuous exercise.
- is also illustrated in disease states. In fibrosis, the diffusion of O₂ is restricted because thickening of the alveolar membrane increases diffusion distance. In emphysema, the diffusion of O₂ is decreased because the surface area for diffusion of gases is decreased.
- In diffusion-limited exchange, the gas does not equilibrate by the time blood reaches the end of the pulmonary capillary. The partial pressure difference of the gas between alveolar air and pulmonary capillary blood is maintained. Diffusion continues as long as the partial pressure gradient is maintained.

### IV. OXYGEN TRANSPORT

- O₂ is carried in blood in two forms: dissolved or bound to hemoglobin (most important).
- Hemoglobin, at its normal concentration, increases the O₂-carrying capacity of blood 70-fold.

#### A. Hemoglobin

1. Characteristics—globular protein of four subunits

- Each subunit contains a heme moiety, which is iron-containing porphyrin.
- The iron is in the ferrous state (Fe²⁺), which binds O₂.

#### Table 4-3 Perfusion-limited and Diffusion-limited Gas Exchange

<table>
<thead>
<tr>
<th>Gas</th>
<th>Perfusion-limited</th>
<th>Diffusion-limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>O₂</td>
<td>O₂ (normal conditions)</td>
<td>O₂ (emphysema, fibrosis, exercise)</td>
</tr>
<tr>
<td>CO₂</td>
<td>CO</td>
<td>CO</td>
</tr>
<tr>
<td>N₂O</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Actually, slightly <100 mm Hg because of the "physiologic shunt."*
Each subunit has a polypeptide chain. Two of the subunits have α chains and two of the subunits have β chains; thus, normal adult hemoglobin is called α₂β₂.

2. Fetal hemoglobin [hemoglobin F (HbF)]

- In fetal hemoglobin, the β chains are replaced by γ chains; thus, fetal hemoglobin is called α₂β₂.
- The O₂ affinity of fetal hemoglobin is higher than the O₂ affinity of adult hemoglobin (left-shift) because 2,3-diphosphoglycerate (DPG) binds less avidly.
- Because the O₂ affinity of fetal hemoglobin is higher than the O₂ affinity of adult hemoglobin, O₂ movement from mother to fetus is facilitated (see IV C 2 b).

3. Methemoglobin

- Iron is in the Fe³⁺ state.
- Does not bind O₂.

4. Hemoglobin S

- causes sickle cell disease.
- Two β chains are replaced by two γ chains.
- In the deoxygenated form, deoxyhemoglobin forms sickle-shaped rods that deform red blood cells (RBCs).

5. O₂-binding capacity of blood

- is the maximum amount of O₂ that can be bound to hemoglobin in blood.
- is dependent on the hemoglobin concentration in blood.
- limits the amount of O₂ that can be carried in blood.
- is measured at 100% saturation.

6. O₂ content of blood

- is the total amount of O₂ carried in blood, including bound and dissolved O₂.
- depends on the hemoglobin concentration, the PO₂, and the P₅₀ of hemoglobin.
- is given by the following equation:

\[
O_2 \text{ content} = (O_2\text{-binding capacity} \times \% \text{ saturation}) + \text{Dissolved O}_2
\]

where:

- O₂ content = amount of O₂ in blood (mL O₂/100 mL blood)
- O₂-binding capacity = maximal amount of O₂ bound to hemoglobin at 100% saturation (mL O₂/100 mL blood)
- % saturation = % of heme groups bound to O₂ (%)
- Dissolved O₂ = unbound O₂ in blood (mL O₂/100 mL blood)

B. Hemoglobin–O₂ dissociation curve (Figure 4-7)

1. Hemoglobin combines rapidly and reversibly with O₂ to form oxyhemoglobin.
2. The hemoglobin–O₂ dissociation curve is a plot of percent saturation of hemoglobin as a function of PO₂.
   a. At a PO₂ of 100 mm Hg (e.g., arterial blood)
      - hemoglobin is 100% saturated; O₂ is bound to all four heme groups on all hemoglobin molecules.
   b. At a PO₂ of 40 mm Hg (e.g., mixed venous blood)
      - hemoglobin is 75% saturated, which means that, on average, three of the four heme groups on each hemoglobin molecule have O₂ bound.
   c. At a PO₂ of 25 mm Hg
      - hemoglobin is 50% saturated.
The PO2 at 50% saturation is the P50. Fifty percent saturation means that, on average, two of the four heme groups of each hemoglobin molecule have O2 bound.

3. The sigmoid shape of the curve is the result of a change in the affinity of hemoglobin as each successive O2 molecule binds to a heme site (called positive cooperativity).

   - Binding of the first O2 molecule increases the affinity for the second O2 molecule, and so forth.
   - The affinity for the fourth O2 molecule is the highest.
   - This change in affinity facilitates the loading of O2 in the lungs (flat portion of the curve) and the unloading of O2 at the tissues (steep portion of the curve).

a. In the lungs

   - Alveolar gas has a PO2 of 100 mm Hg.
   - Pulmonary capillary blood is “arterialized” by the diffusion of O2 from alveolar gas into blood, so that the PO2 of pulmonary capillary blood also becomes 100 mm Hg.
   - The very high affinity of hemoglobin for O2 at a PO2 of 100 mm Hg facilitates the diffusion process. By tightly binding O2, the free O2 concentration and O2 partial pressure are kept low, thus maintaining the partial pressure gradient (that drives the diffusion of O2).
   - The curve is almost flat when the PO2 is between 60 and 100 mm Hg. Thus, humans can tolerate changes in atmospheric pressure (and PO2) without compromising the O2-carrying capacity of hemoglobin.

b. In the peripheral tissues

   - O2 diffuses from arterial blood to the cells.
   - The gradient for O2 diffusion is maintained because the cells consume O2 for aerobic metabolism, keeping the tissue PO2 low.
   - The lower affinity of hemoglobin for O2 in this steep portion of the curve facilitates the unloading of O2 to the tissues.

C. Changes in the hemoglobin–O2 dissociation curve (Figure 4-8)

1. Shifts to the right

   - occur when the affinity of hemoglobin for O2 is decreased.
The $P_{50}$ is increased, and unloading of $O_2$ from arterial blood to the tissues is facilitated.

For any level of $P_{O_2}$, the percent saturation of hemoglobin is decreased.

a. Increases in $P_{CO_2}$ or decreases in $pH$

- shift the curve to the right, decreasing the affinity of hemoglobin for $O_2$ and facilitating the unloading of $O_2$ in the tissues (Bohr effect).
- For example, during exercise, the tissues produce more $CO_2$, which decreases tissue $pH$ and, through the Bohr effect, stimulates $O_2$ delivery to the exercising muscle.

b. Increases in temperature (e.g., during exercise)

- shift the curve to the right.
- The shift to the right decreases the affinity of hemoglobin for $O_2$ and facilitates the delivery of $O_2$ to the tissues during this period of high demand.

c. Increases in 2,3-DPG concentration

- shift the curve to the right by binding to the $\beta$ chains of deoxyhemoglobin and decreasing the affinity of hemoglobin for $O_2$.
- The adaptation to chronic hypoxemia (e.g., living at high altitude) includes increased synthesis of 2,3-DPG, which binds to hemoglobin and facilitates unloading of $O_2$ in the tissues.

2. Shifts to the left

- occur when the affinity of hemoglobin for $O_2$ is increased.
- The $P_{50}$ is decreased, and unloading of $O_2$ from arterial blood into the tissues is more difficult.
For any level of PO2, the percent saturation of hemoglobin is increased.

a. **Causes of a shift to the left**
   - are the mirror image of those that cause a shift to the right.
   - include decreased PCO2, increased pH, decreased temperature, and decreased 2,3-DPG concentration.

b. **HbF**
   - does not bind 2,3-DPG as strongly as does adult hemoglobin. Decreased binding of 2,3-DPG results in increased affinity of HbF for O2, decreased P50, and a shift of the curve to the left.

c. **Carbon monoxide (CO) poisoning** (Figure 4-9)
   - CO competes for O2-binding sites on hemoglobin. The affinity of hemoglobin for CO is 200 times its affinity for O2.
   - CO occupies O2-binding sites on hemoglobin, thus decreasing the O2 content of blood.
   - In addition, binding of CO to hemoglobin increases the affinity of remaining sites for O2, causing a shift of the curve to the left.

**D. Causes of hypoxemia and hypoxia (Table 4-4 and Table 4-5)**

1. **Hypoxemia**
   - is a decrease in arterial PO2.
   - **A–a gradient** can be used to compare causes of hypoxemia, and is described by the following equation:

   \[
   \text{A–a gradient} = PA_{a}O_2 - PaO_2
   \]

   where:
   - A–a gradient = difference between alveolar PO2 and arterial PO2
   - \(PA_{a}O_2\) = alveolar PO2 (calculated from the alveolar gas equation)
   - \(PaO_2\) = arterial PO2 (measured in arterial blood)
Alveolar PO2 is calculated from the alveolar gas equation as follows:

\[
PAO_2 = PI_O2 - PACO_2 / R
\]

where:
- \(PAO_2\) = alveolar PO2
- \(PI_O2\) = inspired PO2
- \(PACO_2\) = alveolar PCO2 = arterial PCO2 (measured in arterial blood)
- \(R\) = respiratory exchange ratio or respiratory quotient (CO2 production/O2 consumption)

The normal A–a gradient is < 10 mm Hg. Since O2 normally equilibrates between alveolar gas and arterial blood, PAO2 is approximately equal to PaO2.

The A–a gradient is increased (>10 mm Hg) if O2 does not equilibrate between alveolar gas and arterial blood (e.g., diffusion defect, V/Q defect, and right-to-left shunt).

2. Hypoxia

- is decreased O2 delivery to the tissues.
- \(O_2\) delivery is described by the following equation:

\[
O_2 \text{ delivery} = \text{Cardiac output} \times O_2 \text{ content of blood}
\]

- \(O_2\) content of blood depends on hemoglobin concentration, \(O_2\)-binding capacity of hemoglobin, and % saturation of hemoglobin by \(O_2\) (which depends on \(PO_2\)).
- Thus, hypoxia can be caused by decreased cardiac output, decreased \(O_2\)-binding capacity of hemoglobin, or decreased arterial PO2.

### V. CO2 TRANSPORT

A. Forms of CO2 in blood

- CO2 is produced in the tissues and carried to the lungs in the venous blood in three forms:

1. Dissolved CO2 (small amount), which is free in solution

### Causes of Hypoxia

<table>
<thead>
<tr>
<th>Cause</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>(↓) Cardiac output</td>
<td>(↓) Blood flow</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>(↓) PO2 causes (↓) % saturation of hemoglobin</td>
</tr>
<tr>
<td>Anemia</td>
<td>(↓) Hemoglobin concentration causes (↓) O2 content of blood</td>
</tr>
<tr>
<td>Carbon monoxide poisoning</td>
<td>(↓) O2 content of blood</td>
</tr>
<tr>
<td>Cyanide poisoning</td>
<td>(↓) O2 utilization by tissues</td>
</tr>
</tbody>
</table>

\(PO_2 = \) arterial PO2.
2. Carbaminohemoglobin (small amount), which is CO₂ bound to hemoglobin
3. HCO₃⁻ (from hydration of CO₂ in the RBCs), which is the major form (90%)

B. Transport of CO₂ as HCO₃⁻ (Figure 4-10)

1. CO₂ is generated in the tissues and diffuses freely into the venous plasma and then into the RBCs.
2. In the RBCs, CO₂ combines with H₂O to form H₂CO₃, a reaction that is catalyzed by carbonic anhydrase. H₂CO₃ dissociates into H⁺ and HCO₃⁻.
3. HCO₃⁻ leaves the RBCs in exchange for Cl⁻ (chloride shift) and is transported to the lungs in the plasma. HCO₃⁻ is the major form in which CO₂ is transported to the lungs.
4. H⁺ is buffered inside the RBCs by deoxyhemoglobin. Because deoxyhemoglobin is a better buffer for H⁺ than is oxyhemoglobin, it is advantageous that hemoglobin has been deoxygenated by the time blood reaches the venous end of the capillaries (i.e., the site where CO₂ is being added).
5. In the lungs, all of the above reactions occur in reverse. HCO₃⁻ enters the RBCs in exchange for Cl⁻. HCO₃⁻ recombines with H⁺ to form H₂CO₃, which decomposes into CO₂ and H₂O. Thus, CO₂, originally generated in the tissues, is expired.

VI. PULMONARY CIRCULATION

A. Pressures and cardiac output in the pulmonary circulation

1. Pressures
   - are much lower in the pulmonary circulation than in the systemic circulation.
   - For example, pulmonary arterial pressure is 15 mm Hg (compared with aortic pressure of 100 mm Hg).

2. Resistance
   - is also much lower in the pulmonary circulation than in the systemic circulation.

3. Cardiac output of the right ventricle
   - is pulmonary blood flow.
   - is equal to cardiac output of the left ventricle.
Although pressures in the pulmonary circulation are low, they are sufficient to pump the cardiac output because resistance of the pulmonary circulation is proportionately low.

**B. Distribution of pulmonary blood flow**

- When a person is supine, blood flow is nearly uniform throughout the lung.  
- When a person is standing, blood flow is unevenly distributed because of the effect of gravity. Blood flow is lowest at the apex of the lung (zone 1) and highest at the base of the lung (zone 3).

1. **Zone 1—blood flow is lowest.**
   - Alveolar pressure > arterial pressure > venous pressure.
   - The high alveolar pressure may compress the capillaries and reduce blood flow in zone 1. This situation can occur if arterial blood pressure is decreased as a result of hemorrhage or if alveolar pressure is increased because of positive pressure ventilation.

2. **Zone 2—blood flow is medium.**
   - Arterial pressure > alveolar pressure > venous pressure.
   - Moving down the lung, arterial pressure progressively increases because of gravitational effects on hydrostatic pressure.
   - Arterial pressure is greater than alveolar pressure in zone 2, and blood flow is driven by the difference between arterial pressure and alveolar pressure.

3. **Zone 3—blood flow is highest.**
   - Arterial pressure > venous pressure > alveolar pressure.
   - Moving down toward the base of the lung, arterial pressure is highest because of gravitational effects, and venous pressure finally increases to the point where it exceeds alveolar pressure.
   - In zone 3, blood flow is driven by the difference between arterial and venous pressures, as in most vascular beds.

**C. Regulation of pulmonary blood flow—hypoxic vasoconstriction**

- In the lungs, hypoxia causes vasoconstriction.
- This response is the opposite of that in other organs, where hypoxia causes vasodilation.
- Physiologically, this effect is important because local vasoconstriction redirects blood away from poorly ventilated, hypoxic regions of the lung and toward well-ventilated regions.
- Fetal pulmonary vascular resistance is very high because of generalized hypoxic vasoconstriction; as a result, blood flow through the fetal lungs is low. With the first breath, the alveoli of the neonate are oxygenated, pulmonary vascular resistance decreases, and pulmonary blood flow increases and becomes equal to cardiac output (as occurs in the adult).

**D. Shunts**

1. **Right-to-left shunts**
   - normally occur to a small extent because 2% of the cardiac output bypasses the lungs.
   - may be as great as 50% of cardiac output in certain congenital abnormalities.
   - are seen in tetralogy of Fallot.
   - always result in a decrease in arterial Po2 because of the admixture of venous blood with arterial blood.
   - The magnitude of a right-to-left shunt can be estimated by having the patient breathe 100% O2, and measuring the degree of dilution of oxygenated arterial blood by nonoxygenated shunted (venous) blood.

2. **Left-to-right shunts**
   - are more common than right-to-left shunts because pressures are higher on the left side of the heart.
are usually caused by congenital abnormalities (e.g., patent ductus arteriosus) or traumatic injury.

Do not result in a decrease in arterial $P_O2$. Instead, $P_O2$ will be elevated on the right side of the heart because there has been admixture of arterial blood with venous blood.

VII. V/Q DEFECTS

A. V/Q ratio

- is the ratio of alveolar ventilation ($V$) to pulmonary blood flow ($Q$). Ventilation and perfusion matching is important to achieve the ideal exchange of $O_2$ and $CO_2$.
- If the frequency, tidal volume, and cardiac output are normal, the V/Q ratio is approximately 0.8. This V/Q ratio results in an arterial $P_O2$ of 100 mm Hg and an arterial $P_CO2$ of 40 mm Hg.

B. V/Q ratios in different parts of the lung (Figure 4-11 and Table 4-6)

- Both ventilation and blood flow (perfusion) are nonuniformly distributed in the normal upright lung.
  1. Blood flow is lowest at the apex and highest at the base because of gravitational effects.
  2. Ventilation is lower at the apex and higher at the base, but the regional differences for ventilation are not as great as for perfusion.
  3. Therefore, the V/Q ratio is higher at the apex of the lung and lower at the base of the lung.
  4. As a result of the regional differences in V/Q ratio, there are corresponding differences in the efficiency of gas exchange and in the resulting pulmonary capillary $P_O2$ and $P_CO2$. Regional differences for $P_O2$ are greater than those for $P_CO2$.
    a. At the apex (higher V/Q), $P_O2$ is highest and $P_CO2$ is lower because gas exchange is more efficient.
    b. At the base (lower V/Q), $P_O2$ is lowest and $P_CO2$ is higher because gas exchange is less efficient.

C. Changes in V/Q ratio (Figure 4-12)

1. V/Q ratio in airway obstruction

- If the airways are completely blocked (e.g., by a piece of steak caught in the trachea), then ventilation is zero. If blood flow is normal, then V/Q is zero, which is called a shunt.
There is no gas exchange in a lung that is perfused but not ventilated. The $P_O_2$ and $P_CO_2$ of pulmonary capillary blood (and, therefore, of systemic arterial blood) will approach their values in mixed venous blood.

- There is an increased $A–a$ gradient.

2. **V/Q ratio in pulmonary embolism**

- If blood flow to a lung is completely blocked (e.g., by an embolism occluding a pulmonary artery), then blood flow to that lung is zero. If ventilation is normal, then $V/Q$ is infinite, which is called dead space.

- There is no gas exchange in a lung that is ventilated but not perfused. The $P_O_2$ and $P_CO_2$ of alveolar gas will approach their values in inspired air.

### VIII. CONTROL OF BREATHING

- Sensory information ($P_CO_2$, lung stretch, irritants, muscle spindles, tendons, and joints) is coordinated in the **brain stem**.
- The output of the brain stem controls the respiratory muscles and the breathing cycle.

#### Table 4-6: V/Q Characteristics of Different Areas of the Lung

<table>
<thead>
<tr>
<th>Area of Lung</th>
<th>Blood Flow</th>
<th>Ventilation</th>
<th>V/Q</th>
<th>Regional Arterial $P_O_2$</th>
<th>Regional Arterial $P_CO_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apex</td>
<td>Lowest</td>
<td>Lower</td>
<td>Higher</td>
<td>Highest</td>
<td>Lower</td>
</tr>
<tr>
<td>Base</td>
<td>Highest</td>
<td>Higher</td>
<td>Lower</td>
<td>Lowest</td>
<td>Higher</td>
</tr>
</tbody>
</table>

V/Q = ventilation/perfusion ratio.

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*There is no gas exchange* in a lung that is perfused but not ventilated. The $P_O_2$ and $P_CO_2$ of pulmonary capillary blood (and, therefore, of systemic arterial blood) will approach their values in mixed venous blood.

There is an increased $A–a$ gradient.

#### FIGURE 4-12

Effect of ventilation/perfusion (V/Q) defects on gas exchange. With airway obstruction, the composition of systemic arterial blood approaches that of mixed venous blood. With pulmonary embolus, the composition of alveolar gas approaches that of inspired air. $P_AO_2 = \text{alveolar } P_O_2$; $P_ACO_2 = \text{alveolar } P_CO_2$; $P_AO_2 = \text{arterial } P_O_2$; $P_ACO_2 = \text{arterial } P_CO_2$.
A. Central control of breathing (brain stem and cerebral cortex)

1. Medullary respiratory center

   a. Dorsal respiratory group

   - is primarily responsible for inspiration and generates the basic rhythm for breathing.
   - Input to the dorsal respiratory group comes from the vagus and glossopharyngeal nerves. The vagus nerve relays information from peripheral chemoreceptors and mechanoreceptors in the lung. The glossopharyngeal nerve relays information from peripheral chemoreceptors.
   - Output from the dorsal respiratory group travels, via the phrenic nerve, to the diaphragm.

   b. Ventral respiratory group

   - is primarily responsible for expiration.
   - is not active during normal, quiet breathing, when expiration is passive.
   - is activated, for example, during exercise, when expiration becomes an active process.

2. Apneustic center

   - is located in the lower pons.
   - stimulates inspiration, producing a deep and prolonged inspiratory gasp (apneusis).

3. Pneumotaxic center

   - is located in the upper pons.
   - inhibits inspiration and, therefore, regulates inspiratory volume and respiratory rate.

4. Cerebral cortex

   - Breathing can be under voluntary control; therefore, a person can voluntarily hyperventilate or hypoventilate.
   - Hypoventilation (breath-holding) is limited by the resulting increase in P CO2 and decrease in P O2. A previous period of hyperventilation extends the period of breath-holding.

B. Chemoreceptors for CO2, H+, and O2 (Table 4-7)

1. Central chemoreceptors in the medulla

   - are sensitive to the pH of the cerebrospinal fluid (CSF). Decreases in the pH of the CSF produce increases in breathing rate (hyperventilation).
   - H+ does not cross the blood–brain barrier as well as CO2 does.

   a. CO2 diffuses from arterial blood into the CSF because CO2 is lipid-soluble and readily crosses the blood–brain barrier.

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**Table 4-7** Comparison of Central and Peripheral Chemoreceptors

<table>
<thead>
<tr>
<th>Type of Chemoreceptor</th>
<th>Location</th>
<th>Stimuli that Increase Breathing Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>Medulla</td>
<td>↓ pH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ [PCO2]</td>
</tr>
<tr>
<td>Peripheral</td>
<td>Carotid and aortic bodies</td>
<td>↓ P O2 (if &lt; 60 mm Hg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ P CO2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ pH</td>
</tr>
</tbody>
</table>
b. In the CSF, CO₂ combines with H₂O to produce H⁺ and HCO₃⁻. The resulting H⁺ acts directly on the central chemoreceptors.

c. Thus, increases in PCO₂ and [H⁺] stimulate breathing, and decreases in PCO₂ and [H⁺] inhibit breathing.

d. The resulting hyperventilation or hypoventilation then returns the arterial PCO₂ toward normal.

2. Peripheral chemoreceptors in the carotid and aortic bodies

   a. Decreases in arterial PO₂
      ■ stimulates the peripheral chemoreceptors and increase breathing rate.
      ■ PO₂ must decrease to low levels (<60 mm Hg) before breathing is stimulated. When PO₂ is less than 60 mm Hg, breathing rate is exquisitely sensitive to PO₂.

   b. Increases in arterial PCO₂
      ■ stimulates peripheral chemoreceptors and increase breathing rate.
      ■ potentiates the stimulation of breathing caused by hypoxemia.
      ■ The response of the peripheral chemoreceptors to CO₂ is less important than the response of the central chemoreceptors to CO₂ (or H⁺).

   c. Increases in arterial [H⁺]
      ■ stimulates the carotid body peripheral chemoreceptors directly, independent of changes in PCO₂.
      ■ In metabolic acidosis, breathing rate is increased (hyperventilation) because arterial [H⁺] is increased and pH is decreased.

C. Other types of receptors for control of breathing

   1. Lung stretch receptors
      ■ are located in the smooth muscle of the airways.
      ■ When these receptors are stimulated by distention of the lungs, they produce a reflex decrease in breathing frequency (Hering–Breuer reflex).

   2. Irritant receptors
      ■ are located between the airway epithelial cells.
      ■ are stimulated by noxious substances (e.g., dust and pollen).

   3. J (juxtacapillary) receptors
      ■ are located in the alveolar walls, close to the capillaries.
      ■ Engorgement of the pulmonary capillaries, such as that may occur with left heart failure, stimulates the J receptors, which then cause rapid, shallow breathing.

   4. Joint and muscle receptors
      ■ are activated during movement of the limbs.
      ■ are involved in the early stimulation of breathing during exercise.

IX. INTEGRATED RESPONSES OF THE RESPIRATORY SYSTEM

A. Exercise (Table 4-8)

1. During exercise, there is an increase in ventilatory rate that matches the increase in O₂ consumption and CO₂ production by the body. The stimulus for the increased ventilation rate is not completely understood. However, joint and muscle receptors are activated during movement and cause an increase in breathing rate at the beginning of exercise.
2. The **mean values for arterial PO₂ and PCO₂ do not change** during exercise.

   - **Arterial pH** does not change during moderate exercise, although it may decrease during strenuous exercise because of **lactic acidosis**.

3. On the other hand, **venous PCO₂ increases** during exercise because the excess CO₂ produced by the exercising muscle is carried to the lungs in venous blood.

4. **Pulmonary blood flow increases** because cardiac output increases during exercise. As a result, more pulmonary capillaries are perfused, and more gas exchange occurs. The **distribution of V/Q ratios** throughout the lung is **more even** during exercise than when at rest, and there is a resulting **decrease in the physiologic dead space**.

**B. Adaptation to high altitude (Table 4-9)**

1. **Alveolar PO₂ is decreased** at high altitude because the barometric pressure is decreased. As a result, arterial PO₂ is also decreased (**hypoxemia**).

2. **Hypoxemia stimulates the peripheral chemoreceptors** and increases the ventilation rate (**hyperventilation**). This hyperventilation produces **respiratory alkalosis**, which can be treated by administering **acetazolamide**.

3. **Hypoxemia also stimulates renal production of erythropoietin**, which increases the production of RBCs. As a result, there is **increased hemoglobin concentration**, increased O₂-carrying capacity of blood, and increased O₂ content of blood.

4. **2,3-DPG concentrations are increased**, shifting the hemoglobin–O₂ dissociation curve to the right. There is a resulting decrease in affinity of hemoglobin for O₂ that facilitates unloading of O₂ in the tissues.

5. **Pulmonary vasoconstriction** is another result of hypoxemia (**hypoxic vasoconstriction**). Consequently, there is an increase in pulmonary arterial pressure, increased work of the right side of the heart against the higher resistance, and hypertrophy of the right ventricle.