Chapter Objectives

By studying this chapter, you should be able to do the following:

1. Identify the basic structures of the conducting and respiratory zones of the ventilation system.
2. Explain the role of minute ventilation and its relationship to the function of the heart in the production of energy at the tissues.
3. Identify the different ways in which carbon dioxide is transported from the tissues to the lungs.
4. Explain the respiratory advantage of breathing depth versus rate during a treadmill exercise.
5. Describe the composition of ambient air and alveolar air and the pressure changes in the pleural and pulmonary spaces.
6. Diagram the three ways in which carbon dioxide is transported in the venous blood to the lungs.
7. Define pleural pressure. What happens to alveolar volume when pleural pressure decreases?

Name two things that cause pleural pressure to decrease.

8. Describe the mechanics of ventilation with respect to the changes in pulmonary pressures.

9. Identify the muscles involved in inspiration and expiration at rest.

10. Describe the partial pressures of oxygen and carbon dioxide in the alveoli, lung capillaries, tissue capillaries, and tissues.

11. Describe how carbon dioxide is transported in the blood.

12. Explain the significance of the oxygen–hemoglobin dissociation curve.

13. Discuss the effects of decreasing pH, increasing temperature, and increasing 2,3-diphosphoglycerate on the HbO₂ dissociation curve.

14. Distinguish between and explain external respiration and internal respiration.

Chapter Outline

**Pulmonary Structure and Function**
- Anatomy of Ventilation
- Lungs
- Mechanics of Ventilation
  - Inspiration
  - Expiration
  - Pressure Changes

**Pulmonary Volumes and Capacities**
- Lung Volumes and Capacities
- Pulmonary Ventilation
  - Minute Ventilation
  - Alveolar Ventilation
Chapter 2  Pulmonary Ventilation

Gas Exchange in the Lungs and the Body

Gas Exchange
- Ambient Air
- In the Trachea
- Alveolar Air
- In Tissues

Oxygen and Carbon Dioxide Transport
- Oxygen Transport in the Blood
  - In Physical Solution
  - Combined with Hemoglobin
- Carbon Dioxide Transport in the Blood
  - In Solution
  - As Carbamino Compounds
  - As Bicarbonate
- Diffusing Capacity and Transit Time
- Ventilation–Perfusion Ratio
- Oxygen Delivery and Utilization

Pulmonary Structure and Function

The respiratory system is responsible for the movement of air in and out of the lungs through a process called pulmonary ventilation. This system, also known as the ventilation system, meets the body’s needs for gas exchange at the lungs and at the tissues. The primary function of pulmonary ventilation is to make oxygen available to the blood, which is transported by the cardiovascular system throughout the body to all the cells. The exchange of oxygen (O₂) and carbon dioxide (CO₂) at the cellular level is necessary to produce energy for muscle contraction while regulating the internal environment of the tissues.

Anatomy of Ventilation

The respiratory and circulatory systems work together to bring in oxygen and transport it to the tissues throughout the body. Together, both systems are known as the cardiorespiratory system. This system is primarily responsible for aerobic capacity, which is a significant factor in health and athletics. With an increase in the capacity of the cardiorespiratory system to make more oxygen available at the tissues, more energy can be produced for muscle contraction. This allows the muscles to do more work.

Lungs

Oxygen is moved in and out of the lungs through the conduction zone of the lung tree. This is necessary to bring the atmospheric air temperature to body temperature. The air is also filtered and humidified as it passes through the nose, mouth, and the trachea, which divides into right and left primary bronchi that divide further into the secondary bronchi within each lung (Figure 2-1). The branching tubes become narrower and more numerous as they divide into segmental bronchi, terminal bronchioles, respiratory bronchioles, and, finally, alveolar ducts, which are lined with tiny air sacs called alveoli.

The conducting zone extends from the trachea to the terminal bronchioles. It is composed of 16 generations of tubes branching into smaller tubes supported by a composition of 15–20 C-shaped cartilage rings and smooth muscle to help ensure that the inspired air gets to the respiratory zone. The parasympathetic}

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division of the autonomic nervous system causes the smooth muscle to constrict, and the sympathetic division causes the smooth muscle to relax (or dilate).

Aside from warming and humidifying the air, the conducting zone is lined with ciliated mucous membranes that filter incoming air to keep the passageways clean. During rest, with each inspiration, about 500 mL of air enters the conducting zone (called tidal volume; \( V_T \)) to reach the alveoli (the respiratory zone), where each alveolus is surrounded by capillaries to permit gas exchange of oxygen and carbon dioxide (Figure 2-2). Because no exchange of gases takes place in the conducting zone, it is called the anatomical dead space.

The dead space volume can be estimated as 1 mL of air for each 1 lb of ideal body weight. Thus, a \( V_T \) of 500 mL per breath minus the dead space of 150 mL of air for a 150-lb person would approximate the volume of air transported to the alveoli (350 mL). This means 30% of the \( V_T \) (150 + 500 = 0.3 \times 100 = 30\%) does not participate in the gas exchange and constitutes wasted air (Table 2-1).

**Figure 2-1** The respiratory system. (A) The upper and lower airway divisions. (B) Alveoli.

**Figure 2-2** Exchange of gases in the lungs.
Chapter 2 Pulmonary Ventilation

**Conducting zone** The nose, pharynx, larynx, trachea, bronchi, bronchioles, and terminal bronchioles function to filter, warm, and moisten air, and conduct it to the alveoli.

**Tidal volume** The amount of air that is inspired or expired in a normal breathing cycle.

**Respiratory zone** The respiratory zone is the site of oxygen and carbon dioxide exchange with the blood.

**Anatomical dead space** All airways such as the mouth, nose, pharynx, larynx, trachea, bronchi, and bronchioles that do not participate directly in the diffusion of oxygen from the alveoli into the pulmonary capillaries.

**Gas exchange** The diffusion of oxygen and carbon dioxide down their concentration gradients that occur between the pulmonary capillaries and alveoli and between the systemic capillaries and the tissues.

**Hemoglobin** The protein portion of the red blood cell that binds with oxygen. It consists of four iron-containing pigments called hemes and a protein called globin.

**Oxyhemoglobin** When hemoglobin is combined with oxygen, it is referred to as oxyhemoglobin.

**Ventilation** The movement of air into and out of the lungs.

**Barometric (atmospheric) pressure** The reading given by a mercury barometer that determines pressure exerted by the earth’s atmosphere. Standard sea-level pressure, by definition, equals 760 mmHg.

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**Table 2-1 Anatomical Dead Space in the Lungs Varies with Body Size**

<table>
<thead>
<tr>
<th>Body Size</th>
<th>Dead Space (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 lb</td>
<td>130 ml</td>
</tr>
<tr>
<td>150 lb</td>
<td>180 ml</td>
</tr>
<tr>
<td>200 lb</td>
<td>230 ml</td>
</tr>
</tbody>
</table>

An estimate of anatomical dead space in milliliters is body weight expressed in pounds. Anatomical dead space is body weight × 1.3 ml. For example, a 180 lb subject has an estimated anatomical dead space of 234 ml (180 lb × 1.3 ml/lb = 234 ml).

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The respiratory zone extends from the terminal bronchioles to the alveolar ducts, alveolar sacs, and alveoli, where gas exchange between the lungs and blood takes place. First, the terminal bronchioles divide to form the respiratory bronchioles, which become even smaller bronchioles with some capacity for gas exchange as they ultimately give rise to alveolar ducts that end as clusters of thin-walled, inflatable alveolar sacs composed of alveoli. Macrophages in the alveoli protect the alveoli from foreign particles. Each alveolus is surrounded by a dense network of pulmonary capillaries that facilitate diffusion of oxygen and carbon dioxide.

Respiratory gas exchange by simple diffusion occurs between the alveoli and the pulmonary capillaries. There are about 300 million to 500 million alveoli in the two lungs with an internal surface area for diffusion that is the equivalent of 60–80 m² (i.e., the size of a tennis court). Inspired oxygen diffuses from the alveoli to the pulmonary capillaries to gain entrance into the blood where it is bound to hemoglobin (Hb), forming oxyhemoglobin (HbO₂).

**Mechanics of Ventilation**

Ventilation is the movement of air into and out of the lungs. It requires a pressure gradient from outside of the body to the alveoli and, then, from the alveoli to the ambient air. The barometric (atmospheric) pressure is the outside pressure. At sea level, the pressure is 760 mmHg, or 760 torr. The pressure unit torr was named in honor of Evangelista Torricelli (1608–1647), who invented the barometer. If air is to move out of the lungs, the intra-alveolar pressure must exceed the barometric air pressure. The exchange of oxygen and carbon dioxide between the lungs and the atmosphere is referred to as external respiration.

The respiratory exchange of oxygen and carbon dioxide at the muscle tissue level is referred to as internal respiration. As the tissues consume oxygen, they produce carbon dioxide, which diffuses into the blood. This is termed cellular respiration. During rest, about 250 mL · min⁻¹ of oxygen leaves the alveoli to enter the blood, and about 200 mL · min⁻¹ of carbon dioxide diffuses from the blood into the alveoli. The VCO₂/VO₂ ratio, known as the respiratory exchange ratio (RER), increases from approximately 0.8 at rest (i.e., 200 ÷ 250 = 0.8) to 0.9 or 1.0 or higher at moderate to maximum exercise. An RER of 0.8 means that approximately 80 molecules of CO₂ are exhaled from the lungs for every 100 molecules of O₂ that diffuse from the alveoli into the pulmonary capillary blood.

**Inspiration**

Inspiration begins with the contraction of the diaphragm, which forms the floor of the thoracic cavity. As the large, dome-shaped skeletal muscle contracts, it elongates the thoracic cavity and thereby increases the thoracic volume during inspiration. Three fourths of the work of enlarging the thoracic cavity during quiet inspiration is accomplished by the diaphragm. During more forceful inspirations, the muscles...
between the ribs (external intercostals) along with other muscles lift the rib cage superiorly and laterally (Figure 2-3). Contraction of these muscles brings about a greater decrease in the pressure inside the pleural cavity (i.e., intrapleural pressure) to 754 mmHg as a result of expansion of the thorax. This causes the lungs to expand in size, which decreases the pressure inside the lungs (intrapulmonary pressure; also known as intra-alveolar pressure) below the atmospheric (barometric) pressure (757 mmHg vs. 760 mmHg). This pressure difference of 3 mmHg between the lungs and ambient air drives the air into the lungs. Other accessory muscles of inspiration include the sternocleidomastoid muscles, which originate from the manubrium sterni and medial third of the clavicle. These muscles are responsible for lifting the rib cage up and outward. During strenuous exercise, in particular, they contribute increasingly more to the inspiration along with the pectoralis major and minor muscles, the trapezius, and the serratus anterior muscles.

Expiration

Expiration begins with the relaxation of the diaphragm and external intercostals, which allows for a passive decrease in the thoracic volume. At the same time, the internal intercostals contract to cause the pressure inside the pleural cavity momentarily to increase, which decreases the alveolar volume and increases the intra-alveolar (intrapulmonary) pressure over the barometric air pressure. Air flows out

Figure 2-3  Muscles used for ventilation.
of the lungs due to the pressure differential. During forced expiration such as during exercise when pulmonary ventilation is 15–20 times greater than at rest, contraction of the abdominal wall muscles (external oblique, internal oblique, transversus abdominis, and rectus abdominis) helps to increase intra-abdominal pressure to push the diaphragm upward. This decreases the vertical dimension of the thoracic cavity. The result is an increase in both the intrapleural and intra-alveolar pressures, which aids in expiration.

### Pressure Changes

At the end of a normal respiration, **intrapleural pressure** (also known as the intrathoracic pressure) within the pleural sac is less than atmospheric (barometric) pressure. It averages 756 mmHg, or 4 mmHg less than barometric pressure (760 mmHg). The intrapulmonary pressure (or intra-alveolar pressure) is equal to barometric pressure. During inspiration, as described in Box 2-1, the volume of the thoracic cavity increases resulting in the expansion of the volume of gas in the pleural space. As the molecules move farther apart, the intrapleural pressure is decreased on average $–2$ mmHg (or to 754 mmHg). At the same time, the lungs are expanded, and gas molecules in the lung move farther apart. The intrapulmonary pressure is decreased below barometric air pressure (on average, $–3$ mmHg, or to 757 mmHg). This pressure difference of 3 mmHg between the atmospheric pressure and the intrapulmonary pressure causes the movement of air into the lungs. Alveolar pressure increases and becomes equal to barometric pressure at the end of inspiration.

During expiration, the steps are reversed. While the lungs are passively recoiling, the internal intercostals assist by contracting to decrease the size of the thoracic cavity further. The increase in intrapleural pressure now compresses the air molecules in the previously inflated lung into a smaller volume. Thus, the intrapulmonary (intra-alveolar) pressure is increased above the barometric (or atmospheric) pressure. As air flows out of the lungs down its pressure gradient, alveolar pressure decreases and becomes equal to barometric pressure at the end of expiration. Because a pressure

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**Box 2-1  **Muscles Involved During Normal Inspiration and Forced Expiration

<table>
<thead>
<tr>
<th>Inspiration</th>
<th>Expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal breathing</strong></td>
<td>The diaphragm is the primary muscle of respiration. Contraction and flattening of the diaphragm enlarges the chest cavity, thus lowering the air pressure within the lungs. Also, the contraction of the external intercostals helps to increase the thoracic and lung volume further, which decreases the intrapulmonary pressure.</td>
</tr>
<tr>
<td><strong>Forced breathing</strong></td>
<td>In addition to what is required for normal inspiration, forced breathing requires additional nerve input via the phrenic nerves to the diaphragm and the nerves to the external intercostals and the sternocleidomastoid and scalene muscles to decrease the intrapulmonary pressure further to allow for a large inspired volume.</td>
</tr>
</tbody>
</table>
Pulmonary Volumes and Capacities

The pressure in the pleural space remains negative to protect the lungs from collapsing. If the intra-pleural pressure equals the atmospheric pressure, the lungs would collapse at the end of expiration.

**Pulmonary Volumes and Capacities**

There are primarily four factors that influence the measurement of respiratory volumes and capacities. They are physical conditioning, age, body size, and gender. As an example, because the lungs of a female are on average smaller than those of a male, the female's vital capacity is about 25% less. The same logic applies to a person who is 6 ft tall versus someone who is 5 ft tall. A well-trained male or female will have a larger vital capacity than an active or sedentary subject.

**Lung Volumes and Capacities**

For the most part, lung volumes are correlated with body size, age, and even height of the individual. A larger person tends to have a larger lung volume than that of a smaller person. An average resting $V_t$ of a 70-kg (154-lb) subject is about 500 mL per breath ($\text{mL} \cdot \text{br}^{-1}$). That means the subject would breathe in 500 mL of air and breathe out 500 mL during each cycle of quiet breathing. Under no circumstances is the volume expired less than the inspired volume. The range in $V_t$ is between 400 and 1000 mL $\cdot \text{br}^{-1}$ depending on the subject’s size (Figure 2-4).

**Figure 2-4** Respiratory volumes and capacities.

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At the end of a normal inspiration, an additional volume of air can be inhaled into the lungs. That volume is approximately 3000 mL during maximal inspiration. In a 70-kg man, this sixfold increase over the normal V_t is referred to as the inspiratory reserve volume (IRV). It requires contraction of the accessory respiratory muscles in addition to the diaphragm and external intercostal muscles. The reverse is true for the expiratory reserve volume (ERV). In this case, during the expiration phrase of a normal V_t, the subject is asked to continue exhaling while forcing out of the lungs as much air as possible. On average, the range is between 1000 and 1200 mL for a 70-kg man. It will be lower in a woman. During exercise, V_t is increased because of the increased reliance on IRV and ERV, but primarily IRV.

When V_t is maximal, it is called vital capacity (VC). It represents the maximum volume of air exhaled after a maximal inspiration (i.e., the sum of the IRV, V_t, and ERV). As in V_t, vital capacity is correlated to body size. The average total air moved in one breath from a full inspiration is 4000 to 5000 mL in healthy men and a liter less in healthy women. The volume of air that remains in the lungs after a forced vital capacity (FVC) is the residual lung volume (RLV). It is approximately 1200 mL. Together, vital capacity and the residual volume (RV) constitute the total lung capacity (TLC = VC + RV). It is approximately 5800 mL.

To assess accurately the lungs of a person with severe lung disease, measurement of vital capacity by itself is not enough. Vital capacity can be normal, but the percentage of vital capacity achieved in 1 s (FEV_1,0) will be decreased. Another measure of pulmonary ventilation is FEV_1,0 to FVC, which reflects the expiratory power and resistance to expiration (i.e., the maximal airflow rate). With emphysema, asthma, chronic obstructive pulmonary disease (COPD), chronic bronchitis, or other bronchial restriction to air movement in the lungs, the FEV_1,0 /FVC ratio is decreased to one half that of an average response (i.e., 40 vs. 80% of FVC in 1 s).

The maximum amount of air that can be inhaled and exhaled in 1 min is termed maximum voluntary ventilation (MVV). It is of theoretical importance in assessing the maximal working capacity of the respiratory muscles. If the subject is a patient being tested, the MVV procedure is done over a 15-s time period before being extrapolated to a value for 1 min expressed as liters per minute. For healthy subjects, the range is 140–180 L · min⁻¹ for men and 80–120 L · min⁻¹ for women. Maximal pulmonary function can reach 200 L · min⁻¹ in some athletes.

**Pulmonary Ventilation**

Pulmonary ventilation exchanges gases between the ambient air and the alveoli of the lungs. Ventilation, which is mechanical in nature, depends on a difference between the atmospheric air pressure and the pressure in the alveoli. Gases flow from areas of higher pressure to areas of lower pressure. For inspiration, the atmospheric pressure is greater than the alveolar pressure. The reverse is true for expiration.

**Minute Ventilation**

The volume of air inspired or expired per minute is known as V_E. It is the product of an average breathing frequency (Fb) of 12 br · min⁻¹ (also referred to as respiratory rate) and an average V_T of 500 mL · br⁻¹. At rest, V_E averages about 6000 mL · min⁻¹ (12 br · min⁻¹ × 500 mL · br⁻¹) or 6 L · min⁻¹ (6000 mL · min⁻¹ ÷ 1000 mL · L⁻¹ = 6.0 L · min⁻¹) with a range between 5 and 8 L · min⁻¹. With exercise, V_E is increased as a direct function of the oxygen needed at the cell level and the carbon dioxide produced by the muscles. Either an increase in Fb or V_T or both will increase V_E.
Of course, it is better to increase \( \dot{V}_E \) during exercise with an increase in \( V_T \) rather than \( F_b \). For example, the \( \dot{V}_E \) for subject A at 600 kpm on the bicycle ergometer is 46 L \( \cdot \) min\(^{-1}\), which is the product of a \( V_T \) of 2 L per breath and an \( F_b \) of 23 br \( \cdot \) min\(^{-1}\). Subject B at the same workload has the same \( \dot{V}_E \), but his product values are very different. His \( V_T \) is 1.6 L per breath, and his \( F_b \) is 29 br \( \cdot \) min\(^{-1}\). Both subjects are processing oxygen to produce energy for muscle contraction. The difference is that the respiratory effort for subject B is much greater in that his \( \dot{V}_E \) is dependent upon \( F_b \) given the reduced \( V_T \). This alone increases the energy requirement of the respiratory muscles, which ultimately detracts from the oxygen available to the muscular system.

During maximal exercise, the \( F_b \) of healthy subjects is about 40 br \( \cdot \) min\(^{-1}\). Their \( V_T \) is about 2.6 L per breath with a \( \dot{V}_E \) of 104 L \( \cdot \) min\(^{-1}\) to help sustain a \( \dot{V}_O_2 \) max of about 3 L \( \cdot \) min\(^{-1}\). In contrast, highly trained athletes can achieve \( F_b \) values of about 60 breaths \( \cdot \) min\(^{-1}\) and a \( V_T \) of 3 L per breath to produce a substantial increase in \( \dot{V}_E \) of 180 L \( \cdot \) min\(^{-1}\). In terms of the maximal minute ventilation (\( \dot{V}_E \) max) that is critical to achieving a high \( \dot{V}_O_2 \) max value, the \( \dot{V}_E \) max is \( \sim \)15 times the resting value of 7 L \( \cdot \) min\(^{-1}\). In the highly trained athlete, \( \dot{V}_E \) max can reach 180 L \( \cdot \) min\(^{-1}\), which is a 26-fold increase over this athlete’s average resting \( \dot{V}_E \) (Box 2-2).

**Alveolar Ventilation**

Given the anatomical design of the lungs, at first it was expected that all of the air that enters the lungs reaches the alveoli. Yet, it is clear this is not the case. A small portion of the \( V_T \) remains in the dead space (DS). This means that not all of the \( \dot{V}_E \) effort takes part in the exchange of oxygen for carbon dioxide at the alveolar–capillary membrane. That part of the \( V_T \) that does not reach the alveoli remains in the conducting airways collectively termed the anatomical dead space (nose, mouth, trachea, bronchi, and bronchioles).

For a subject who weighs 150 lb, the volume of air that does not participate in gas exchange is about 0.25 of the resting \( \dot{V}_E \) of 6 L \( \cdot \) min\(^{-1}\) or 6000 mL \( \cdot \) min\(^{-1}\), which equals 1500 mL \( \cdot \) min\(^{-1}\) (6000 \( \times \) 0.25), or an average of 150 mL \( \cdot \) br\(^{-1}\) (1500 \( \div \) 10 br \( \cdot \) min\(^{-1}\)). At rest the \( F_b \) is 10 to 14 br \( \cdot \) min\(^{-1}\). Note that this volume in the anatomical dead space approximates body weight in pounds. For a subject weighing 250 lb, the estimate for anatomical dead space in the calculation of alveolar ventilation (\( \dot{V}_A \)) is 250 mL. In this case, the 250 mL \( \cdot \) br\(^{-1}\) is not used for gas exchange.

**Alveolar ventilation** is the most important variable in gas exchange. It is calculated by subtracting the anatomical dead space from \( V_T \), which is then multiplied by

**Box 2-2  Mean Values in Healthy Young Men for Ventilation and Oxygen Consumption**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest</th>
<th>Low</th>
<th>Moderate</th>
<th>Maximum (Untrained)</th>
<th>Maximum (Athlete)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \dot{V}_O_2 ) (L ( \cdot ) min(^{-1}))</td>
<td>0.25</td>
<td>1.6</td>
<td>2.6</td>
<td>3.4</td>
<td>~5</td>
</tr>
<tr>
<td>( \dot{V}_C O_2 ) (L ( \cdot ) min(^{-1}))</td>
<td>0.20</td>
<td>0.85</td>
<td>2.4</td>
<td>3.5</td>
<td>6</td>
</tr>
<tr>
<td>( \dot{V}_E ) (L ( \cdot ) min(^{-1}))</td>
<td>6</td>
<td>30.6</td>
<td>71.3</td>
<td>116.1</td>
<td>180</td>
</tr>
<tr>
<td>( V_T ) (L)</td>
<td>0.5</td>
<td>1.7</td>
<td>2.3</td>
<td>2.7</td>
<td>3.0</td>
</tr>
<tr>
<td>( F_b ) (breaths ( \cdot ) min(^{-1}))</td>
<td>12</td>
<td>18</td>
<td>31</td>
<td>43</td>
<td>60</td>
</tr>
</tbody>
</table>

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the Fb. For example, for a 150-lb subject at rest, that part of \( \dot{V}_E \) that mixes with air in the alveoli is 4200 mL \( \cdot \) min\(^{-1} \) (500 mL \( \cdot \) br\(^{-1} \) – 150 mL = 350 mL \( \cdot \) br\(^{-1} \) \( \times \) 12 br \( \cdot \) min\(^{-1} \) = 4200 mL \( \cdot \) min\(^{-1} \)). This means that 70% of the \( \dot{V}_E \) mixes with alveolar air. What is important to recognize is that \( \dot{V}_E \) by itself does not mean that an adequate gaseous exchange is maintained. To better understand this point, what would happen if the size of the dead space is increased? A dead-space air of 200 mL per breath would decrease resting \( \dot{V}_A \) to 3600 mL \( \cdot \) min\(^{-1} \). This means that 60% of the \( \dot{V}_E \) mixes with alveolar air. The dead-space air has increased to 40% of \( \dot{V}_E \). Thus, \( \dot{V}_E \) remained the same, but \( \dot{V}_A \) decreased. This result can have a negative effect on gas exchange.

Conversely, if the subject’s resting \( V_T \) increased from 500 to 600 mL \( \cdot \) br\(^{-1} \) while \( \dot{V}_E \) remained unchanged, \( \dot{V}_A \) is increased (6000 \( \div \) 600 = 10 breaths \( \cdot \) min\(^{-1} \)). Alveolar ventilation is now 4500 mL \( \cdot \) min\(^{-1} \) or an increase of 20% in the \( \dot{V}_E \) that mixes with the alveolar air. Stated somewhat differently, this means that 80% of the inspired air per minute ventilates the alveoli. The lungs are more efficient when \( V_T \) is increased than when relying on an increase in breathing rate.

Similarly, with regard to \( \dot{V}_E \) during exercise, the size of the \( V_T \) is more important than Fb. Because anatomical dead space is constant, the increased \( V_T \) at a given breathing frequency is the most efficient means of increasing the volume of air exchanged between the atmosphere and alveoli per minute. Although this is true, there is the assumption that all the atmospheric air entering the alveolar sacs participates in gas exchange with the blood in the capillaries. What if the alveoli are not equally ventilated with air or only partly in contact with capillary blood? If one or both occurred, the assumption of a match between air and blood would be wrong.

The point is that it is always likely that some unknown percentage of ventilated alveoli is not adequately perfused with blood. This is termed alveolar dead space (or physiologic dead space). The important thing to remember is that among healthy subjects, alveolar dead space is of little importance.

### Gas Exchange in the Lungs and the Body

#### Gas Exchange

Gas exchange takes place primarily in two areas of the body. The first exchange is between the alveoli and the pulmonary capillaries. Oxygen from the lungs diffuses into the blood, and carbon dioxide in the blood diffuses into the lungs. The force behind the diffusion is the partial pressure of each gas. Because oxygen moves from the lungs into the blood, the pressure exerted by the oxygen gas molecules causes the oxygen to enter the blood where the concentration of oxygen and the pressure are smaller.

The opposite takes place with carbon dioxide. At the cell level, given the higher partial pressure of oxygen in the blood versus the tissues, oxygen dissociates from the hemoglobin and moves from the blood into the mitochondria of the tissues. The high metabolic state of the muscles increases the concentration of carbon dioxide within the tissues. This means the partial pressure of carbon dioxide (\( \text{PaCO}_2 \)) is higher than the arterial blood carbon dioxide (\( \text{PaCO}_2 \)) that surrounds the muscle cells, so carbon dioxide leaves the cells and enters the venous side of the arterial system to be transported to the lungs.
**Ambient Air**

Understanding gas exchange begins with acknowledging the concentration of gases in the air and their individual pressures. Ambient (atmospheric) air is a mixture of oxygen, carbon dioxide, nitrogen, water vapor, and small quantities of inert gases. Oxygen makes up 20.93% of the ambient air, carbon dioxide is 0.03%, and nitrogen is 79.04% of the ambient air. Each gas consists of molecules that collide with each other. The pressure exerted by a gas is dependent on the number of collisions. The higher a gas concentration is in a given volume, the higher the partial pressure of the gas. Because oxygen is not the only gas in ambient air, its pressure is only part of the total pressure of the mix of gases.

The partial pressure of oxygen, like other gases, is dependent on its fractional concentration and the barometric pressure. At sea level, oxygen equals 20.93% of the total 760 mmHg pressure exerted by the air mixture. This means oxygen exerts a partial pressure of 159 mmHg (760 mmHg × 0.2093). Carbon dioxide exerts a pressure of 0.3 mmHg, and nitrogen exerts the largest pressure (760 mmHg × 0.7904 = 600.7 mmHg). It is common practice to designate the partial pressure of individual gases in a mixture with a capital “P” followed by the symbol for the gas. Thus, the partial pressure of oxygen is $P_{O_2}$, carbon dioxide is $P_{CO_2}$, and nitrogen is $P_{N_2}$.

**In the Trachea**

As the ambient air enters the respiratory tract, it becomes saturated with water vapor. This process dilutes the inspired air mixture. At body temperature, the partial pressure of water ($P_{H_2O}$) molecules in humidified air equals 47 mmHg. This value must be subtracted from 760 mmHg (760 – 47 = 713 mmHg). This means the partial pressure of the inspired oxygen at 159 mmHg is decreased in the trachea (713 mmHg × 0.2093) to 149 mmHg. At this point, this is not a problem because the partial pressure of oxygen in the pulmonary capillaries is about 40 mmHg at rest. There is still a considerable pressure differential to ensure that the oxygen leaves the alveoli to enter the blood.

**Alveolar Air**

The composition of alveolar air is fairly constant. It is saturated with water vapor and contains a higher concentration of carbon dioxide than that of the atmospheric air. Gas exchange between the blood and the alveoli is continuous. The alveoli always have gases in them, thus making the alveoli independent of the respiratory activity. The driving pressure for oxygen and carbon dioxide is the partial pressure of each gas, where partial pressure is the product of the percentage gas concentration and total pressure of the gas mixture. As it turns out, the percentage of oxygen concentration in the alveoli averages about 14.5%. This means the average alveolar partial pressure of oxygen ($P_{AO_2}$) is 103 mmHg (760 – 47 = 713 mmHg × 0.145), or an alveolar average of about 100 mmHg (Box 2-3).

Even though the partial pressure of oxygen is about 60 mmHg lower than that of the dry ambient air, the partial pressure of 100 mmHg produces an average driving pressure of 60 mmHg for oxygen to diffuse from the alveoli into the venous blood (i.e., an area of lower partial pressure and an average $P_{O_2}$ of 40 mmHg). Because the pulmonary blood has a higher partial pressure of carbon dioxide ($P_{CO_2} = 46$ mmHg on average) than that of the alveoli, carbon dioxide molecules leave the blood to enter the alveoli. This increases the percentage of carbon dioxide in the alveoli from 0.03%...
**Box 2-3  Gas Partial Pressures in Ambient Air (Sea Level) and Alveolar Air (Sea Level)**

<table>
<thead>
<tr>
<th>Gases</th>
<th>Percentage (%)</th>
<th>P_a (mmHg)</th>
<th>P (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambient air</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O_2</td>
<td>20.93</td>
<td>760</td>
<td>159*</td>
</tr>
<tr>
<td>CO_2</td>
<td>0.03</td>
<td>760</td>
<td>0.3</td>
</tr>
<tr>
<td>N_2</td>
<td>79.04</td>
<td>760</td>
<td>600.7</td>
</tr>
<tr>
<td>H_2O</td>
<td>0.00</td>
<td>760</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>760</td>
<td></td>
</tr>
<tr>
<td>Alveolar air</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O_2</td>
<td>~13.7</td>
<td>760 - 47 = 713*</td>
<td>~104</td>
</tr>
<tr>
<td>CO_2</td>
<td>~5.3</td>
<td>760 - 47 = 713</td>
<td>~40</td>
</tr>
<tr>
<td>N_2</td>
<td>~79.8</td>
<td>760 - 47 = 713</td>
<td>~569</td>
</tr>
<tr>
<td>H_2O</td>
<td></td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>760</td>
<td></td>
</tr>
</tbody>
</table>

Note: The partial pressure (P) of a gas is a measure of the concentration of a gas in a mixture of gases. Atmospheric pressure at sea level is approximately 760 mmHg. P_a stands for barometric pressure.

* Oxygen constitutes 21% of the atmosphere, so its partial pressure is 21% of 760, or 159 mmHg.

+ The Ph_2o of 47 mmHg is subtracted from 760 mmHg before calculating Po_2, Pco_2, and Pn_2.

In the ambient air entering the alveoli to an average of 5.5% in the alveolar air (713 x 0.055). Thus, the average partial pressure of carbon dioxide (P_{CO_2}) is equal to 39 mmHg. In general, the alveolar partial pressure of carbon dioxide (P_{ACO_2}) is taken to be 40 mmHg. This represents a small pressure gradient of 6 mmHg for carbon dioxide to diffuse from the blood (P_{CO_2} = 46 mmHg) to the lungs.

**In Tissues**

As the blood leaves the lungs to the left side of the heart to be pumped to the tissues, blood arriving at the tissues has been normalized for its carbon dioxide and saturated with oxygen. The partial pressures for oxygen and carbon dioxide are approximately 100 mmHg and 40 mmHg, respectively. **Cellular metabolism** is dependent upon both gases in the arterial blood remaining in their respective ranges. At rest, the average P_{O_2} within the muscles is around 40 mmHg while the P_{CO_2} is about 46 mmHg. This means that there is a driving force of 60 mmHg for oxygen to leave the blood through the capillary wall and enter the tissues. Likewise, because the P_{CO_2} is higher in muscle than in the arterial blood, carbon dioxide diffuses from the muscles to the blood. This increases the P_{CO_2} of the venous blood to an average of 46 mmHg. The diffusion of oxygen from the arterial blood to the muscle cell leaves the venous blood with a P_{O_2} of 40 mmHg.

As the venous blood from the tissues leaves the right ventricle on its way to the lungs, the P_{CO_2} of 46 mmHg at rest relative to the alveolar P_{CO_2} of 40 mmHg drives the carbon dioxide from the pulmonary capillaries into the alveoli. During exercise, carbon dioxide pressure in the tissues increases to 70, 80, or even 90 mmHg depending upon the intensity of the exercise. If the venous P_{CO_2} is 70 mmHg, the driving
pressure to move carbon dioxide into the lungs to be exhaled would be 30 mmHg (i.e., 70 mmHg, venous − 40 mmHg, alveolar). This is a fivefold increase in pressure, thus helping to ensure that with exercise and the faster movement of blood through the pulmonary capillaries, the excess carbon dioxide is moved to the lungs in a timely fashion. The opposite is true with oxygen, given the \( P_{O_2} \) of 100 mmHg in the alveoli and possibly 20 or even 10 mmHg in the venous blood (which reached equilibrium with the pressure in the active muscle tissue). The pressure differential of 80 or 90 mmHg between the alveoli and the capillary blood results in a very fast diffusion of oxygen into the blood.

**Oxygen and Carbon Dioxide Transport**

The transport of oxygen and carbon dioxide occurs both via the liquid portion of the blood (plasma) and the hemoglobin (Hb) in red blood cells (erythrocytes). Only a very small amount of oxygen is transported in the plasma; this is dissolved oxygen. It would be impossible to live on this volume. This is not the case with oxygen that diffuses across the respiratory membrane into blood to combine with hemoglobin to form oxyhemoglobin (HbO₂). This method of transport of oxygen increases the oxygen carrying capacity 65 times above that of plasma.

Stated somewhat differently, approximately 98.5% of the oxygen transported in the blood is in combination with hemoglobin in red blood cells, and the remaining 1.5% is dissolved in the water part of the plasma. As the tissue cells use oxygen in aerobic respiration, they produce carbon dioxide that diffuses from the cells to the blood. At the venous end of the capillaries, carbon dioxide is transported dissolved in the plasma, in combination with hemoglobin, and in the form of bicarbonate ions.

**Oxygen Transport in the Blood**

**In Physical Solution**

About 0.3 mL of oxygen is dissolved in the plasma of 100 mL of blood (or 3 mL · L⁻¹). As the average volume of blood is about 5 L, a very small amount of oxygen is dissolved in the fluid portion of the blood (3 mL · L⁻¹ × 5 L = 15 mL). Because oxygen consumption (\( V_{O_2} \)) at rest is about 250 mL · min⁻¹, the dissolved oxygen of 15 mL is not enough to sustain life. In fact, cardiac output (\( Q \)) would have to increase 16.7 times the resting blood flow per minute (e.g., \( Q = 5 \text{ L} \cdot \text{min}^{-1} = 250 \text{ mL} \cdot \text{min}^{-1} \)), thus 250 ÷ 15 = 16.7, then, 5 × 16.7 = 83.5 L · min⁻¹). Obviously, the heart cannot pump 84 L · min⁻¹. What then is the purpose of the oxygen transported in the physical solution? The dissolved oxygen establishes the \( P_{O_2} \) of the arterial and venous blood (i.e., the amount dissolved is directly proportional to the \( P_{O_2} \) of the blood). In other words, as mentioned earlier, at an arterial \( P_{O_2} \) of 100 mmHg, only 3 mL of oxygen can dissolve in 1 L of blood. Thus, the oxygen bound to hemoglobin does not contribute to the \( P_{O_2} \) of the blood.

**Combined with Hemoglobin**

Hemoglobin (Hb) in red blood cells contains iron (heme) and protein (globin). Each of the four iron atoms within the heme portions of a hemoglobin molecule can combine with one oxygen molecule to form oxyhemoglobin. In men, each 100 mL of blood contains an average of 15 g of Hb. Women have slightly less hemoglobin.
per 100 mL of blood, about 13 g. Because oxygen is transported in the blood to the tissues by hemoglobin, the higher oxygen transport capacity of men gives them a physiologic advantage over women. As an example, when 1 g of Hb combines with oxygen (i.e., becomes saturated with O₂), it is the equivalent of 1.34 mL of oxygen transported by the blood. Thus, it is a matter of multiplying hemoglobin (in grams per 100 mL of blood) by the oxygen capacity of hemoglobin. In the case of men, 15 g of Hb per 100 mL of blood (15 g · 100 mL⁻¹) equals 20 mL of oxygen (15 × 1.34 = 20.1) per each 100 mL of blood (or 20 volumes percent). In contrast, women have the same capacity to saturate the hemoglobin with oxygen but have less Hb per 100 mL of blood (e.g., 13 g per 100 mL × 1.34 mL = 17.4 mL of oxygen for every 100 mL of blood).

To achieve full oxygen saturation of hemoglobin (SbO₂ %) means that each of the four heme groups is bound to oxygen. Naturally, it is important fully to saturate the hemoglobin that is exposed to alveolar gas. To determine the percentage saturation of hemoglobin with oxygen (SbO₂ %), the total oxygen actually combined with hemoglobin is divided by the oxygen carrying capacity of hemoglobin. For example, if oxygen capacity is 20 volumes percent and the actual amount of oxygen combined with hemoglobin is 15 volumes percent, then SbO₂ % is 15 / 20 × 100, which equals 75%. This means that the arterial blood is transporting 25% less oxygen than it should transport for each 100 mL of blood pumped from the left ventricle. Hemoglobin that is not bound to oxygen is referred to as deoxyhemoglobin (or reduced Hb).

Because it is important to saturate hemoglobin with oxygen fully, what are the factors that affect achievement of oxygen saturation? To begin with, it should be clear by now that the P O₂ of blood is especially important. Then, too, the temperature of the blood, the pH (acidity) of the blood, and the amount of carbon dioxide in the blood play a role in the percentage saturation of hemoglobin. To understand these relationships better, it is helpful to consider them singly and collectively using the oxyhemoglobin dissociation curve.

**Oxyhemoglobin (HbO₂) Dissociation Curve**

The oxyhemoglobin dissociation curve is an S-shaped curve that represents the percent saturation of hemoglobin in relation to oxygen pressure. The right y-axis shows the quantity of oxygen carried in each 100 mL of blood under normal resting conditions (i.e., with blood pH of 7.4 and with a temperature of 37°C). The x-axis shows the P O₂ (mmHg) in solution. Note that the arterial blood P O₂ is 100 mmHg. This occurs at the alveoli–capillary level during the time the blood moves through the capillaries. At a P O₂ of 100 mmHg, the 15 g of Hb per 100 mL of blood is fully saturated with oxygen. That means the arterial blood is transporting 20 mL of oxygen for each 100 mL of blood to the tissues. At the cell level, the P O₂ is 40 mmHg at rest. The pressure difference of 60 mmHg causes the oxygen to dissociate from hemoglobin to move into the cell. This means that 5 mL of oxygen (or 5 mL O₂ · dL⁻¹) went into the muscle, or 25% of the arterial oxygen per 100 mL of blood was consumed for metabolic purposes. The remaining difference is 15 mL of oxygen per 100 mL of blood (or 15 mL O₂ · dL⁻¹), which corresponds to 75% saturation of hemoglobin in the venous blood. The 5 mL of oxygen per 100 mL of blood is referred to as the arteriovenous oxygen difference (a-vO₂diff). That is, a-vO₂diff is the difference between the amount of oxygen carried in the arterial blood and the amount of oxygen returned in the venous blood. Thus, it represents the amount of oxygen released (dissociated) from the red blood cells (also called the coefficient of oxygen utilization) that is used by the tissues to support cellular metabolism (Figure 2-5).
Whereas the large change in $P_O_2$ shown by the shallow, upper part of the curve is associated with a small change in the amount of oxygen held by hemoglobin, the smaller change in $P_O_2$ shown by the steep middle and lower portions of the curve is associated with a large change in the amount of oxygen held by hemoglobin, reflecting a greater cellular need for oxygen. From about a $P_O_2$ of 50 mmHg, a small change in $P_O_2$ is associated with a large change in hemoglobin saturation. For example, if tissue $P_O_2$ decreases from 40 to 20 mmHg, $S_bO_2$% decreases from 75 to 20%. This is an additional a-vo$_2$ diff of 11 mL of oxygen consumed at the cell level in addition to the original 5 mL of oxygen, or a total of 16 mL of oxygen per 100 mL of blood. The challenge in consumption of oxygen exists at the cell level. Oxygen cannot be consumed if the mitochondria are not using the oxygen in the first place. If the mitochondria can use the oxygen, given the level of intensity of muscle contraction, then the $P_O_2$ within the muscle cell can decrease. This cellular adjustment allows for an increased dissociation of oxygen from hemoglobin. More oxygen means more energy for sustaining or increasing aerobic performance.

As mentioned earlier, the oxyhemoglobin dissociation curve is also under the influence of increases in blood acidity (which decreases pH), temperature, and carbon dioxide. Each of the three can cause a shift of the curve to the right, thus decreasing the tendency for oxygen to remain bound to hemoglobin. This is known as the Bohr effect after its discoverer, Christian Bohr. The influence of these three factors is particularly important during exercise, in which there is an increase in carbon dioxide production, an increase in lactic acid, which decreases the blood pH, and an increase in body temperature due to elevated temperatures resulting from increased metabolism. Hence, at a given $P_O_2$, a shift of the oxygen–hemoglobin curve to the right makes more oxygen available to the tissues for use in cellular metabolism. The increase in oxygen could be as high as 75–85%, which would represent an arteriovenous oxygen difference of 15–17 mL of oxygen per 100 mL of blood (or 15–17 mL $O_2 \cdot dL^{-1}$).

![Oxyhemoglobin saturation and blood oxygen content.](image)
Another factor that influences hemoglobin's affinity for oxygen is the anaerobic metabolite 2,3-diphosphoglycerate (2,3-DPG; formerly called diphosphoglycerate). This erythrocyte constituent is also referred to as 2,3-bisphosphoglycerate (BPG). It is produced in the red blood cell as a by-product of glycolysis because the red blood cell lacks a nucleus and mitochondria, thus it cannot use oxygen. An increase in 2,3-DPG shifts the oxygen hemoglobin dissociation curve to the right: It facilitates oxygen dissociation by combining with subunits of hemoglobin to decrease the affinity of hemoglobin for oxygen (just as it increases in CO₂ and decreases in pH). The end result is that more oxygen is unloaded as the blood flows through the tissues. With more oxygen at the cell level, there is an increase in aerobic performance.

Today, it is common practice for endurance athletes to use a combination of high-altitude living and low-altitude training (known as Hi-Lo training) to increase RBC mass and the RBC's content of 2,3-DPG. The 2,3-DPG binds with the Hb molecule to reduce the affinity of Hb for oxygen while also decreasing RBC pH. Both conditions cause a rightward shift in the dissociation, which promotes oxygen unloading at the active muscles and theoretically increases the oxygen utilization curve. The exact mechanisms of improvement in athletic performance are yet to be fully understood, especially as some athletes do not respond to the Hi-Lo training.

Myoglobin and Storage of Oxygen

Like hemoglobin, the molecule myoglobin (Mb) is an iron–protein compound that combines with oxygen. It is found in cardiac muscle cells and skeletal muscle fibers, especially in the slow-twitch fibers (i.e., high aerobic capacity). Its purpose is to help with the delivery of oxygen to the mitochondria once the oxygen is released from hemoglobin at the tissues. Because myoglobin has a higher affinity for oxygen than that of hemoglobin, it encourages the unloading of oxygen from hemoglobin. The binding of oxygen to myoglobin (MbO₂) acts as a temporary storage of oxygen in the muscle cell, especially under PO₂ conditions in which there is already an adequate supply of oxygen to the cell. Otherwise, when the PO₂ of the cell reaches very low values (e.g., 10 or 5 mmHg) during vigorous exercise, myoglobin unloads its oxygen to the mitochondria within the muscle fiber. Also, an increase in myoglobin increases mitochondrial respiration, particularly during intermittent periods of low PO₂ in the arterial blood.

Carbon Dioxide Transport in the Blood

The arterial blood transports approximately 49 mL CO₂ · dL⁻¹ (or 49 mL per 100 mL of blood), whereas the venous blood transports approximately 54 mL CO₂ · dL⁻¹. As the end product of oxidative metabolism, carbon dioxide is transported in three ways in the blood: (1) dissolved in physical solution; (2) as bicarbonate; and (3) as carbamino compounds (Figure 2-6). These three forms of CO₂ are in equilibrium with one another, and it is the dissolved fraction in physical solution (plasma) that exerts the partial pressure measured as PaCO₂. Normal PaCO₂ ranges between 36 and 44 mmHg, whereas the mixed venous partial pressure of carbon dioxide (PvCO₂) is approximately 6 mmHg higher. Unlike oxygen, where the partial pressure at rest is high in the arterial blood (PO₂ of 100 mmHg) and low in the venous blood (PO₂ of 40 mmHg), the partial pressure of carbon dioxide is higher in the venous blood (PCO₂ of 46 mmHg) than in the arterial blood (PCO₂ of 40 mmHg).
In Solution

The amount of dissolved CO$_2$ in the venous blood is small but larger than that of oxygen because it is more soluble than oxygen in plasma. Thus, a greater proportion of the total CO$_2$ than of O$_2$ is dissolved in the blood. Dissolved CO$_2$ represents a range of 10% of the total carbon dioxide transported from the cells to the lungs.

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In the blood, carbon dioxide reacts with water to form a weak acid, carbonic acid (H₂CO₃). What is important about the dissolved CO₂ is that the amount of CO₂ physically dissolved in the plasma depends on the Pₐ₃.

**As Carbaminohemoglobin**

Given the higher carbon dioxide concentration in the tissues resulting from energy metabolism versus the Pₐ₃ in the blood flow to the muscles, carbon dioxide diffuses into the venous blood. Once carbon dioxide enters the blood, it is carried in chemical combination with the globin of hemoglobin to form a carbamino compound while releasing a proton: Hb · NH₃ + CO₂ ⇌ Hb · NH · COOH. The carbamino compound formed is called carbaminohemoglobin (HbCO₂). This occurs very rapidly without an enzyme. Reduced Hb combines more CO₂ than HbO₂. It represents approximately 30% of carbon dioxide that is transported to the lungs.

At the lungs, the formation of carbaminohemoglobin is reversed, thus allowing carbon dioxide to diffuse from the pulmonary capillary blood into the alveoli from which the carbon dioxide is exhaled. Simultaneously, as oxygen diffuses from the alveoli into the pulmonary capillaries (thus, oxygenating Hb), it decreases hemoglobin’s capacity to bind carbon dioxide. At the tissues, after hemoglobin has released oxygen, the hemoglobin has an increased ability to pick up carbon dioxide. This cycle of events facilitates the removal of carbon dioxide from the tissues and lungs (termed the Haldane effect).

**As Bicarbonate**

About 60% of the carbon dioxide diffuses from the tissues to red blood cells to be transported to the lungs in a chemical combination with sodium in the plasma, as sodium bicarbonate. In the red blood cells, carbon dioxide reacts with water inside the red blood cell to form carbonic acid (CO₂ + H₂O → H₂CO₃). An enzyme called carbonic anhydrase located in red blood cells causes the reaction of water and carbon dioxide to form carbonic acid (H₂CO₃) 12,000 times faster than it would take place without the enzyme (such as in the blood plasma). As fast as carbonic acid is formed, it dissociates into a hydrogen ion (H⁺) and a bicarbonate ion (HCO₃⁻), where most of the carbon dioxide is located.

Because the H⁺ ions inside the cell will increase the acidity of the venous blood, especially during exercise, which increases the proton load by a factor of about 20, the hydrogen ion concentration must be buffered. This is done by hemoglobin rather than oxyhemoglobin because Hb is a better buffer. The H⁺ binds to Hb (H⁺ + Hb → HHb). This prevents a change in pH while the HCO₃⁻ diffuses into the plasma. To counteract the loss of negative charges, chloride ions (Cl⁻) move from the plasma to the RBC. When oxygen dissociates from hemoglobin and diffuses into the tissues, the buffering of H⁺ ions is increased along with an increase in HCO₃⁻ ions. The end result is an increase in the transport of carbon dioxide while the blood is kept from becoming too acidic.

As the concentration of HCO₃⁻ is increased in the red blood cells, it diffuses into the plasma. In the plasma, sodium chloride (NaCl) dissociates, leaving sodium to react with the HCO₃⁻ ions, forming NaHCO₃. This is the primary way in which carbon dioxide is transported to the lungs. The trade-off is that the chloride ions (Cl⁻) diffuse from the plasma into the red blood cells to form potassium chloride. This is termed the chloride shift, which helps to maintain the ionic (electrical) balance between the red blood cells and the plasma. Here, it is important to point out that the reaction CO₂ + H₂O → H₂CO₃ is in reverse. This means that as the reaction
moves to the right, carbon dioxide diffuses into the venous blood to be transported to the lungs. The reverse of the events occurs in the lungs. When the reaction moves to the left, carbon dioxide diffuses from the red blood cells into the alveoli.

**Diffusing Capacity and Transit Time**

Because the surface area for gas exchange at the alveolar–capillary interface is large in healthy subjects, diffusion and gas equilibration are not a problem. The *diffusing capacity* (transfer factor) is a test of the integrity of the alveolar–capillary membrane for gas transfer. It is performed by measuring the volume of gas that diffuses through each minute for a pressure difference of 1 mmHg. At rest, this value is about 21 mL·min⁻¹·mmHg⁻¹ and 400 mL·min⁻¹·mmHg⁻¹ for oxygen and carbon dioxide, respectively. During exercise, the oxygen and carbon dioxide values are increased to approximately 65 mL·min⁻¹·mmHg⁻¹ and 1200 mL·min⁻¹·mmHg⁻¹, respectively. Diffusing capacity is likely to be high if lung disease is not present, and if there is more surface area available for the transfer of oxygen and carbon dioxide (i.e., *ventilation–perfusion ratio*).

Whereas diffusing capacity does not limit healthy subjects, *transit time* has the potential to have a negative effect on athletic performance at very high workloads. Red blood cells spend approximately 0.75 s in the pulmonary capillaries, which is more than twice the time to oxygenate the blood (0.3 s). With exercise, the increased participation of pulmonary capillaries and their alveoli accommodates the increased cardiac output without a major increase in blood flow velocity. Thus, an optimal transit time is maintained for gas exchange. If this were not the case, blood flow through the capillaries would be increased (i.e., decreased transit time) to a point of failing to saturate the hemoglobin fully.

**Ventilation–Perfusion Ratio**

Ventilation and perfusion are processes that should be closely matched in the normal lung. This means the ratio would be in the vicinity of 1.0 if all parts of the lungs are equally ventilated and perfused, thus leading to the concept of *ventilation–perfusion matching* (or an optimal gas exchange). Conversely, *ventilation–perfusion mismatch* is the term used when the ventilation and the perfusion of a gas exchange are not matched. In other words, it is possible that an alveolus can be ventilated but not matched with an adequate blood flow, thus gas exchange does not take place as it should. The ventilation–perfusion ratio (or *V/Q ratio*) is used to assess the efficiency and adequacy of gas exchange (the air that reaches the lungs) and pulmonary perfusion (the blood that reaches the lungs).

The impact of gravity on pulmonary perfusion, especially at the apex of the lungs, can result in a pressure that is insufficient for developing a flow. This suggests that the variation in blood flow between the upper and lower parts of the lungs in the upright posture accounts for the whole of the ventilation–perfusion ratio inequality in the normal lungs. This is why the *V/Q* ratio is less than ideal. The apex of the lung may be highly ventilated relative to blood flow, which results in poor gas exchange. For the whole lung, the ventilation–perfusion ratio is the alveolar ventilation (*VA*) divided by the pulmonary blood flow (*Q*, cardiac output), thus the following calculation:

\[
\frac{V_A}{Q} \text{ ratio} \quad \text{where} \quad V_A = 4.2 \text{ L·min}^{-1} \quad \text{and} \quad Q = 5 \text{ L·min}^{-1} \quad \text{then} \quad \frac{V_A}{Q} = 0.84.
\]

When *VA* and *Q* are approximately equal, the alveolar and arterial oxygen tension (*PO₂*) values are about 100 mmHg. But, if the *V/A* ratio is decreased either by decreasing alveolar ventilation or increasing blood flow, the alveolar oxygen tension (*PAO₂*) decreases, while the arterial oxygen tension (*PaO₂*) value
The converse is true if the $V_A/Q$ ratio is increased by increasing alveolar ventilation or by decreasing the blood flow; then the $P_{AO_2}$ increases toward the inspired oxygen tension ($P_{I0_2}$). The point is that the alveolar oxygen tension reflects the rate of oxygen delivered to the alveoli and the volume of oxygen transferred to the pulmonary blood and consumed by the tissues. Thus, oxygen delivery depends on both alveolar ventilation and inspired oxygen tension.

**Oxygen Delivery and Utilization**

The volume of oxygen available to the tissues per minute (oxygen delivery; $D_O_2$) is a product of cardiac output ($Q$) and arterial content of oxygen ($C_aO_2$). The blood flow to the tissues is directly related to the integrity of the myocardium to produce the blood flow (i.e., $Q$, cardiac output = $HR \times SV$, stroke volume) that is appropriate for adequate oxygenation of the tissues. The volume of oxygen consumed (i.e., oxygen utilization) at the tissue level is termed oxygen consumption ($VO_2$). It is the product of cardiac output and arteriovenous oxygen difference ($Q \times C_aO_2 - C_vO_2$).

At rest, given the normal hemoglobin level of 15 g per 100 mL of blood (or 150 g of Hb per liter of blood) and a normal arterial oxygen saturation the equivalent of 98% at arterial oxygen content of 20 mL of oxygen (15 g per 100 mL x 1.34 mL of oxygen per gram of Hb = 20.1) per each 100 mL of blood (or 20 volumes percent), then, if the cardiac output ($Q$) is 5.0 L·min$^{-1}$, the calculation is $D_O_2 = 1.34 \times 150 \times 5.0 \times 98 + 100 = 984.9$ mL·min$^{-1}$ (or essentially 1000 mL·min$^{-1}$). This is a typical resting oxygen delivery ($D_O_2$) value for an adult subject. Note that 1.34 is used to represent the physiological oxygen binding capacity rather than the theoretical value of 1.39 mL of oxygen binding capacity of Hb. The reason is that 4% of the binding sites cannot combine with oxygen because they are occupied by carbon monoxide and methemoglobin.

If the venous content of oxygen ($C_vO_2$) is 15 mL of O$_2$ per each 100 mL of blood, the arteriovenous oxygen difference ($a-vO_2$) would be 5 mL of oxygen per 100 mL of blood. Given that there is 10 x 100 mL of blood per liter of blood, then 5 x 10 equals 50 mL of oxygen utilized at the tissues per liter of blood. Following through with the calculation of the total body oxygen utilization steps: $VO_2 = Q \times a-vO_2$, diff, therefore 250 mL·min$^{-1}$ = 5 L·min$^{-1}$ x 50 mL·L$^{-1}$. Note that the 250 mL·min$^{-1}$ consumed at the tissues equals essentially 25% of the oxygen delivered to the tissues ($D_O_2$). Thus, 1000 mL·min$^{-1}$ minus 250 mL·min$^{-1}$ equals the volume of oxygen remaining in the venous blood (i.e., 740 mL·min$^{-1}$). This is consistent with the 75% saturation of the hemoglobin in the venous blood ($S_vO_2$) for the body as a whole at rest.

A variation on this thinking is consistent with the concept of an oxygen extraction ratio ($O_2$ER) whereby $O_2$ER equals oxygen utilization, which ultimately equals $VO_2$. For example, $O_2$ER = $VO_2 + D_O_2 \times 100$, thus 250 mL·min$^{-1}$ + 1000 mL·min$^{-1}$ x 100 = 25%. Normal oxygen extraction ratios range from 25 to 30%. Twenty-five percent of 1000 mL·min$^{-1}$ is 250 mL·min$^{-1}$, or, in this case, resting $VO_2$. It is important that oxygen is present in sufficient amounts in the mitochondria to maintain effective concentrations of ATP in the electron transport system.

In general, $VO_2$ reflects metabolic demands and remains relatively independent of $D_O_2$. During heavy exercise, the increase in cellular metabolism can require 15 times the resting oxygen consumption, or 15 x 250 mL·min$^{-1}$ = 3750 mL·min$^{-1}$. A Q of 25 L·min$^{-1}$ is required to match the $VO_2$ requirement. A concomitant rise in $D_O_2$ is a function of the increase in Q. The rise in $D_O_2$ is smaller in magnitude than the increase in exercise $VO_2$, leading to the increase in the oxygen extraction ratio as well as a progressive increase in the $a-vO_2$ diff. This improved ability to extract oxygen is directly a function of the capacity of tissues to consume oxygen.

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**Oxygen delivery** The collective function of the lungs, heart, and arterial system that sustains aerobic cellular metabolism throughout the body is required to deliver oxygen.

**Oxygen utilization** Defined as the muscles’ ability to extract (use) oxygen to sustain aerobic power within seconds to minutes of a vigorous exercise, depending on the availability of oxygen, optimal distribution of blood flow in the exercising muscles, and a limitation in the rate of oxygen extraction.

**Oxygen extraction ratio** Defined by the slope of the relation between oxygen transport ($D_O_2$) and oxygen uptake ($VO_2$): $O_2$ Extraction Ratio = ($C_aO_2 - C_vO_2$)/$C_aO_2$. 

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Study Questions

1. How does minute ventilation differ from alveolar ventilation?
2. In what way is the upper respiratory system designed to carry out its functions?
3. How does internal respiration differ from external respiration?
4. During strenuous exercise, what additional muscles help with respiration?
5. What are the static measures of lung volume and capacity?
6. What is anatomical dead space?
7. What is the difference between anatomical and physiologic dead space?
8. What is the role of myoglobin in facilitating oxygen transfer to the mitochondria during strenuous exercise?
9. When alveolar ventilation (in liters of air per minute) and alveolar capillary blood flow (in liters of blood per minute) are approximately equal. What is the effect on oxygen equilibration across the alveolar capillary membrane?
10. What is the significance of the different static lung volumes?
11. What is the Bohr effect? How is it related to blood carbon dioxide?
12. What is the Haldane effect?
13. Where and why does the chloride shift take place?
14. What determines whether oxygen and hemoglobin are combined or dissociated (separated)?
15. Why does hemoglobin combine with oxygen in the lungs and release oxygen at the tissues?
16. How would a high V/Q ratio affect gas exchange in the lungs?
17. Discuss the ways in which CO₂ is transported in the blood.

Suggested Readings


References
