chapter 4

Respiratory Physiology

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)

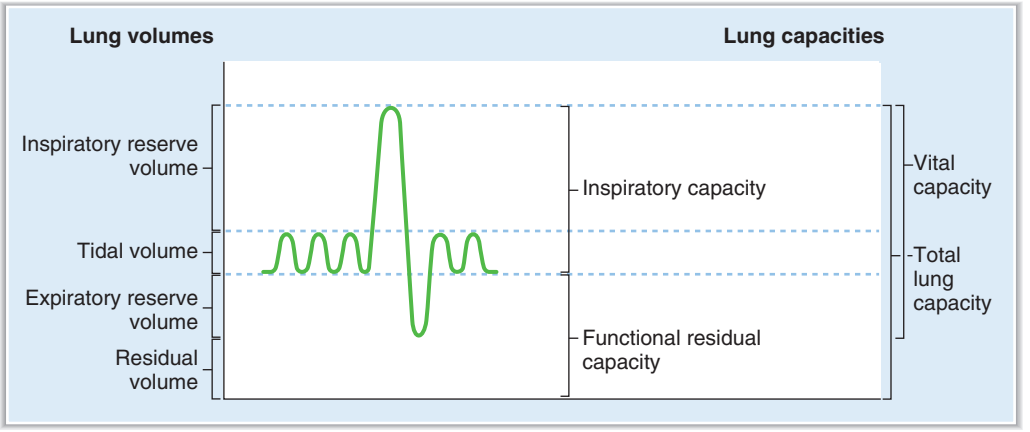


FIGURE 4-1 Lung volumes and capacities.

- In words, the equation states that physiologic dead space is tidal volume multiplied by a fraction. The fraction represents the dilution of alveolar P_{CO_2} by dead-space air, which does not participate in gas exchange and does not therefore contribute CO_2 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:

$$\text{Alveolar ventilation} = \left(\text{Tidal volume} - \text{Dead space}\right) \times \text{Breaths/min}$$

- **Sample problem:** A person with a tidal volume (V_T) of 0.5 L is breathing at a rate of 15 breaths/min. The P_{CO_2} of his arterial blood is 40 mm Hg, and the P_{CO_2} of his expired air is 36 mm Hg. What is his rate of alveolar ventilation?

$$\begin{aligned}
\text{Dead space} &= V_T \times \frac{P_{A_{CO_2}} - P_{E_{CO_2}}}{P_{A_{CO_2}}} \\
&= 0.5\,\text{L} \times \frac{40\,\text{mm Hg} - 36\,\text{mm Hg}}{40\,\text{mm Hg}} \\
&= 0.05\,\text{L} \\
\text{Alveolar ventilation} &= \left(\text{Tidal volume} - \text{Dead space}\right) \times \text{Breaths/min} \\
&= \left(0.5\,\text{L} - 0.05\,\text{L}\right) \times 15\,\text{Breaths/min} \\
&= 6.75\,\text{L/min}
\end{aligned}$$

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.**

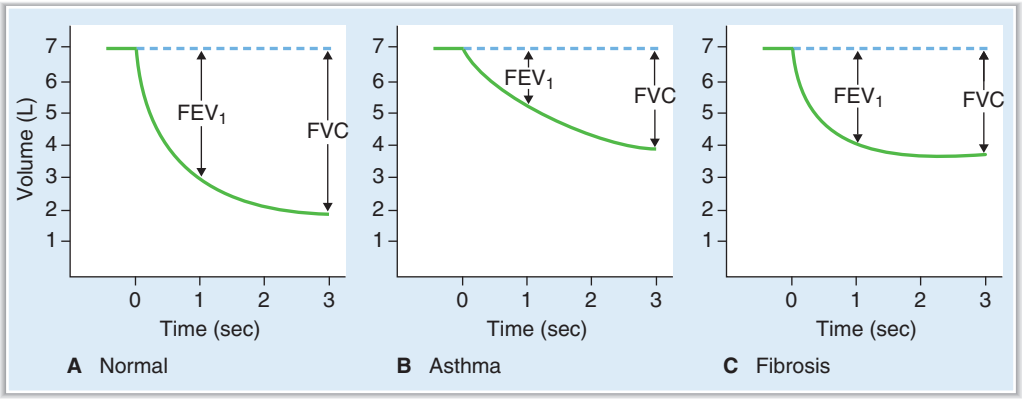


FIGURE 4-2 Forced vital capacity (FVC) and FEV_1 in normal subjects and in patients with lung disease. FEV_1 = volume expired in first second of forced maximal expiration.

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 (FEV_1) [Figure 4-2]

- FEV_1 is the volume of air that can be expired in the first second of a forced maximal expiration.
- FEV_1 is **normally 80% of the forced vital capacity**, which is expressed as:

$$FEV_1/FVC = 0.8$$

- In obstructive lung disease, such as **asthma**, FEV_1 is reduced more than FVC so that **FEV_1/FVC is decreased.**
- In restrictive lung disease, such as **fibrosis**, both FEV_1 and FVC are reduced and FEV_1/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:

$$\mathbf{C = V/P}$$

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.

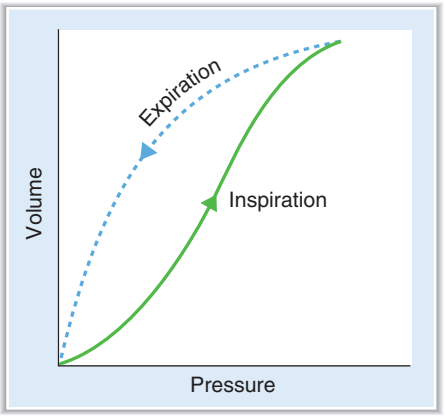


FIGURE 4-3 Compliance of the lungs. Different curves are followed during inspiration and expiration (hysteresis).

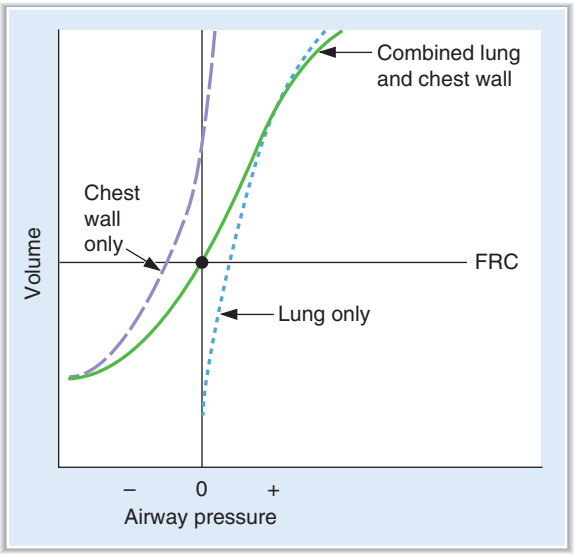


FIGURE 4-4 Compliance of the lungs and chest wall separately and together. FRC = functional residual capacity.

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.

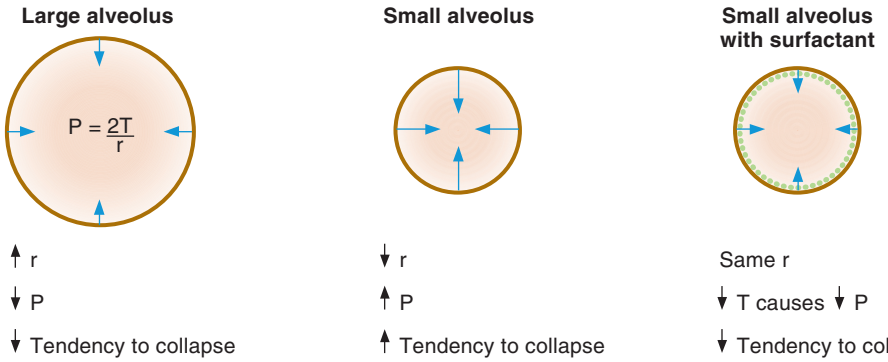


FIGURE 4-5 Effect of alveolar size and surfactant on the pressure that tends to collapse the alveoli. P = pressure; r = radius; T = surface tension.

- 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:

$$\mathbf{P = \frac{2T}{r}}$$

where:
P = collapsing pressure on alveolus (or pressure required to keep alveolus open) [dynes/cm^2]
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)
ΔP = pressure gradient (cm H_2O)
R = airway resistance (cm H_2O/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
η = 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 **β_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.

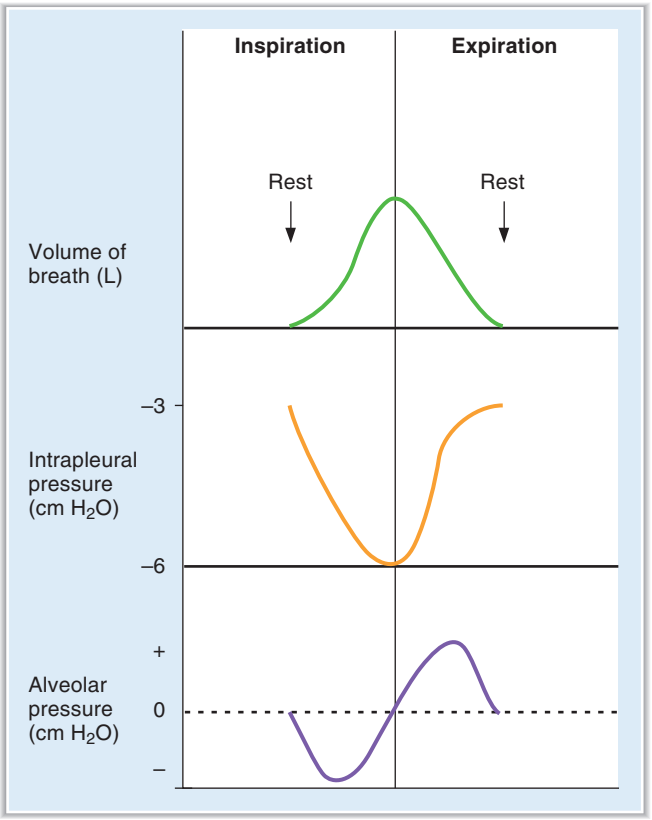


FIGURE 4-6 Volumes and pressures during the breathing cycle.

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 FEV_1, and **decreased FEV_1/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 FEV_1, and **decreased FEV_1/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 P_{CO_2}).

b. "Blue bloaters" (primarily bronchitis) have **severe hypoxemia** with cyanosis and, because they do not maintain alveolar ventilation, **hypercapnia** (increased P_{CO_2}). 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 FEV_1 is decreased less than FVC, **FEV_1/FVC is increased** (or may be normal).

table 4-1 Characteristics of Lung Diseases

Disease	FEV_1	FVC	FEV_1/FVC	FRC
Asthma	↓↓	↓	↓	↑
COPD	↓↓	↓	↓	↑
Fibrosis	↓	↓↓	↑ (or normal)	↓

COPD = chronic obstructive pulmonary disease; FEV_1 = 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_2 can be calculated as follows. Assume that total pressure is atmospheric and the fractional concentration of O_2 is 0.21.

$$\begin{aligned} P_{O_2} &= 760\ \text{mm Hg} \times 0.21 \\ &= 160\ \text{mm Hg} \end{aligned}$$

2. **In humidified tracheal air** at 37°C, the calculation is modified to correct for the partial pressure of H_2O, which is 47 mm Hg.

$$\begin{aligned} P_{Total} &= 760\ \text{mm Hg} - 47\ \text{mm Hg} \\ &= 713\ \text{mm Hg} \\ P_{O_2} &= 713\ \text{mm Hg} \times 0.21 \\ &= 150\ \text{mm Hg} \end{aligned}$$

B. Partial pressures of O_2 and CO_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 P_{O_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_2 in arterial blood as an **example:**

$$\begin{aligned} \textbf{Dissolved}[O_2] &= \mathbf{P_{O_2} \times \text{Solubility of } O_2 \text{ in blood}} \\ &= \mathbf{100\ \text{mm Hg} \times 0.03\ \text{mL } O_2/\text{L/mm Hg}} \\ &= \mathbf{0.3\ \text{mL } O_2/100\ \text{mL blood}} \end{aligned}$$

where:
$[O_2]$ = O_2 concentration in blood
P_{O_2} = Partial pressure of O_2 in blood
0.03 mL O_2/L/mm Hg = Solubility of O_2 in blood

D. Diffusion of gases such as O_2 and CO_2

- The diffusion rates of O_2 and CO_2 depend on the **partial pressure differences** across the membrane and the area available for diffusion.
- **For example**, the diffusion of O_2 from alveolar air into the pulmonary capillary depends on the partial pressure difference for O_2 between alveolar air and pulmonary capillary blood. Normally, capillary blood equilibrates with alveolar gas; when the partial pressures of O_2 become equal (see Table 4-2), then there is no more net diffusion of O_2.

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

1. Perfusion-limited exchange

- is illustrated by **N_2O** and by **O_2 under normal conditions.**

table 4-2 Partial Pressures of O_2 and CO_2 (mm Hg)

Gas	Dry Inspired Air	Humidified Tracheal Air	Alveolar Air	Systemic Arterial Blood	Mixed Venous Blood
P_{O_2}	160	150 Addition of H_2O decreases P_{O_2}	100 O_2 has diffused from alveolar air into pulmonary capillary blood, decreasing the P_{O_2} of alveolar air	100* Blood has equilibrated with alveolar air (is "arterialized")	40 O_2 has diffused from arterial blood into tissues, decreasing the P_{O_2} of venous blood
P_{CO_2}	0	0	40 CO_2 has been added from pulmonary capillary blood into alveolar air	40 Blood has equilibrated with alveolar air	46 CO_2 has diffused from the tissues into venous blood, increasing the P_{CO_2} of venous blood

*Actually, slightly <100 mm Hg because of the "physiologic shunt."

- 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 **O_2 during strenuous exercise.**
- is also illustrated in disease states. In **fibrosis**, the diffusion of O_2 is restricted because thickening of the alveolar membrane increases diffusion distance. In **emphysema**, the diffusion of O_2 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

- O_2 is carried in blood in two forms: dissolved or bound to hemoglobin (most important).
- Hemoglobin, at its normal concentration, increases the O_2-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 **(Fe^{2+})**, which binds O_2.

table 4-3 Perfusion-limited and Diffusion-limited Gas Exchange

Perfusion-limited	Diffusion-limited
O_2 (normal conditions)	O_2 (emphysema, fibrosis, exercise)
CO_2	CO
N_2O	

- 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 $\alpha_2\beta_2$.

2. Fetal hemoglobin [hemoglobin F (HbF)]

- In **fetal hemoglobin**, the **β chains are replaced by γ chains**; thus, fetal hemoglobin is called $\alpha_2\gamma_2$.
- The O_2 affinity of fetal hemoglobin is higher than the O_2 affinity of adult hemoglobin **(left-shift)** because 2,3-diphosphoglycerate (DPG) binds less avidly.
- Because the O_2 affinity of fetal hemoglobin is higher than the O_2 affinity of adult hemoglobin, O_2 movement from mother to fetus is facilitated (see IV C 2 b).

3. Methemoglobin

- Iron is in the Fe^{3+} state.
- Does not bind O_2.

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. O_2-binding capacity of blood

- is the maximum amount of O_2 that can be bound to hemoglobin in blood.
- is dependent on the **hemoglobin concentration** in blood.
- limits the amount of O_2 that can be carried in blood.
- is measured at 100% saturation.

6. O_2 content of blood

- is the total amount of O_2 carried in blood, including bound and dissolved O_2.
- depends on the hemoglobin concentration, the P_{O_2}, and the P_{50} of hemoglobin.
- is given by the following equation:

$$\textbf{O}_2\textbf{ content} = (\textbf{O}_2\textbf{-binding capacity} \times \textbf{\% saturation}) + \textbf{Dissolved O}_2$$

where:

O_2 content = amount of O_2 in blood (mL O_2/100 mL blood)
O_2-binding capacity = maximal amount of O_2 bound to hemoglobin at 100% saturation (mL O_2/100 mL blood)
% saturation = % of heme groups bound to O_2 (%)
Dissolved O_2 = unbound O_2 in blood (mL O_2/100 mL blood)

B. Hemoglobin–O_2 dissociation curve (Figure 4-7)

1. Hemoglobin combines rapidly and reversibly with O_2 to form **oxyhemoglobin.**
2. The hemoglobin–O_2 dissociation curve is a plot of percent saturation of hemoglobin as a function of PO_2.
   - **a. At a P_{O_2} of 100 mm Hg** (e.g., arterial blood)
     - hemoglobin is 100% saturated; O_2 is bound to all four heme groups on all hemoglobin molecules.
   - **b. At a P_{O_2} 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 O_2 bound.
   - **c. At a P_{O_2} of 25 mm Hg**
     - hemoglobin is 50% saturated.

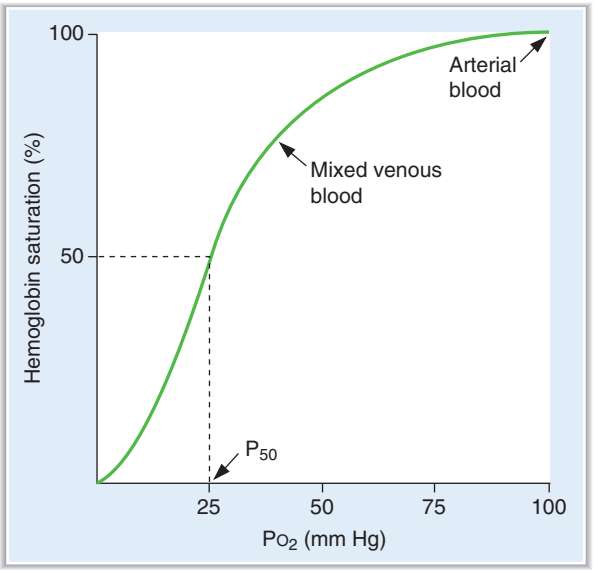


FIGURE 4-7 Hemoglobin–O_2 dissociation curve.

- The P_{O_2} at 50% saturation is the **P_{50}**. Fifty percent saturation means that, on average, two of the four heme groups of each hemoglobin molecule have O_2 bound.

3. The **sigmoid shape** of the curve is the result of a change in the affinity of hemoglobin as each successive O_2 molecule binds to a heme site (called **positive cooperativity**).

- Binding of the first O_2 molecule increases the affinity for the second O_2 molecule, and so forth.
- The **affinity for the fourth O_2 molecule is the highest.**
- This change in affinity facilitates the loading of O_2 in the lungs (flat portion of the curve) and the unloading of O_2 at the tissues (steep portion of the curve).

a. In the lungs

- Alveolar gas has a P_{O_2} of 100 mm Hg.
- Pulmonary capillary blood is "arterialized" by the diffusion of O_2 from alveolar gas into blood, so that the P_{O_2} of pulmonary capillary blood also becomes 100 mm Hg.
- The very high affinity of hemoglobin for O_2 at a P_{O_2} of 100 mm Hg facilitates the diffusion process. By tightly binding O_2, the free O_2 concentration and O_2 partial pressure are kept low, thus maintaining the partial pressure gradient (that drives the diffusion of O_2).
- The curve is almost **flat when the P_{O_2} is between 60 and 100 mm Hg.** Thus, humans can tolerate changes in atmospheric pressure (and P_{O_2}) without compromising the O_2-carrying capacity of hemoglobin.

b. In the peripheral tissues

- O_2 diffuses from arterial blood to the cells.
- The gradient for O_2 diffusion is maintained because the cells consume O_2 for aerobic metabolism, keeping the tissue P_{O_2} low.
- The lower affinity of hemoglobin for O_2 in this steep portion of the curve facilitates the unloading of O_2 to the tissues.

C. Changes in the hemoglobin–O_2 dissociation curve (Figure 4-8)

1. Shifts to the right

- occur when the **affinity of hemoglobin for O_2 is decreased.**

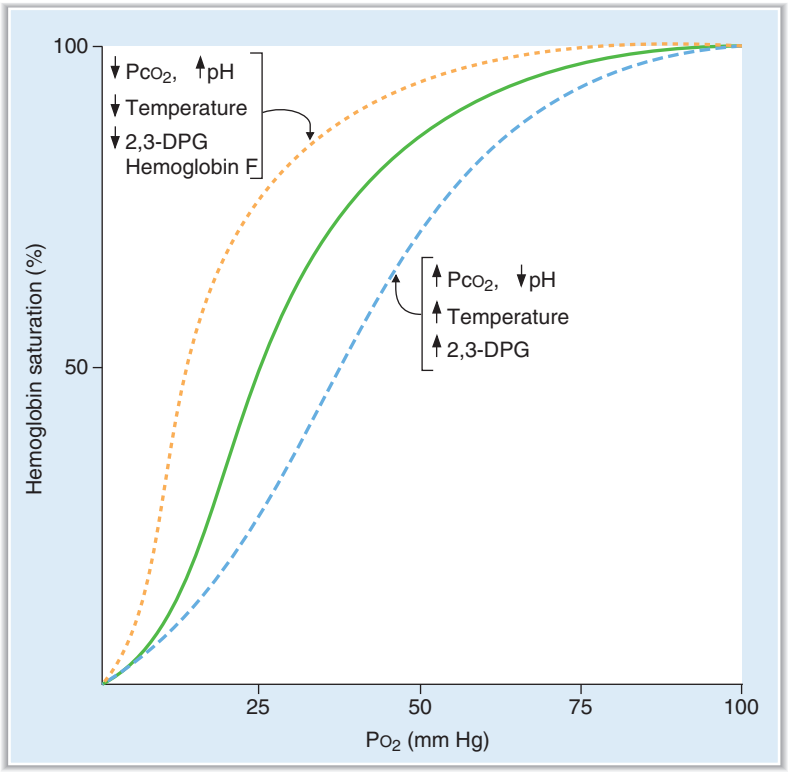


FIGURE 4-8 Changes in the hemoglobin–O_2 dissociation curve. Effects of P_{CO_2}, pH, temperature, 2,3-diphosphoglycerate (DPG), and fetal hemoglobin (hemoglobin F) on the hemoglobin–O_2 dissociation curve.

- 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 β 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.

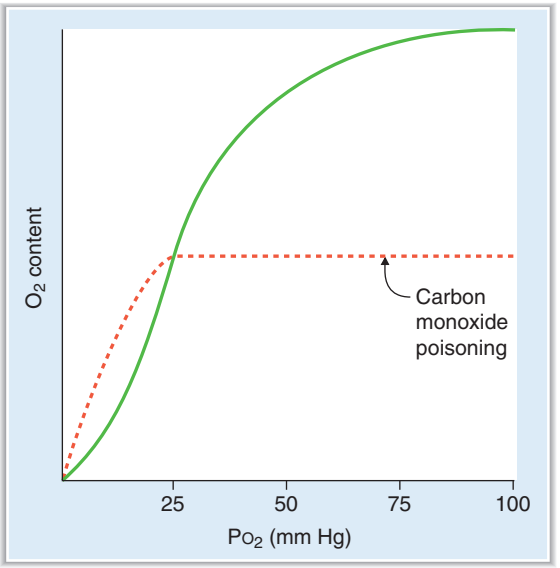


FIGURE 4-9 Effect of carbon monoxide on the hemoglobin–O_2 dissociation curve.

- For any level of P_{O_2}, 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 P_{CO_2}, 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 O_2, decreased P_{50}, and a **shift of the curve to the left.**

c. Carbon monoxide (CO) poisoning (Figure 4-9)

- CO competes for O_2-binding sites on hemoglobin. The affinity of hemoglobin for CO is 200 times its affinity for O_2.
- CO occupies O_2-binding sites on hemoglobin, thus **decreasing the O_2 content of blood.**
- In addition, binding of CO to hemoglobin increases the affinity of remaining sites for O_2, 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 P_{O_2}.**
- **A–a gradient** can be used to compare causes of hypoxemia, and is described by the following equation:

$$\textbf{A–a gradient} = P_{A_{O_2}} - Pa_{O_2}$$

where:

A–a gradient = difference between alveolar P_{O_2} and arterial P_{O_2}

P_{AO2} = alveolar P_{O_2} (calculated from the alveolar gas equation)

Pa_{O2} = arterial P_{O_2} (measured in arterial blood)

table 4-4 Causes of Hypoxemia

Cause	Pa_{O_2}	A–a Gradient
High altitude (↓ P_B)	Decreased	Normal
Hypoventilation (↓ $P_{A_{O_2}}$)	Decreased	Normal
Diffusion defect (e.g., fibrosis)	Decreased	Increased
V/Q defect	Decreased	Increased
Right-to-left shunt	Decreased	Increased

A–a gradient = difference in P_{O_2} between alveolar gas and arterial blood; P_B = barometric pressure; $P_{A_{O2}}$ = alveolar P_{O_2}; Pa_{O2} = arterial P_{O_2}; V/Q = ventilation/perfusion ratio.

- Alveolar P_{O_2} is calculated from the **alveolar gas equation** as follows:

$$\mathbf{P_{A_{O_2}} = P_{I_{O_2}} - P_{A_{CO_2}}/R}$$

where:

P_{AO2} = alveolar P_{O_2}
P_{IO2} = inspired P_{O_2}
P_{ACO2} = alveolar P_{CO_2} = arterial P_{CO_2} (measured in arterial blood)
R = respiratory exchange ratio or respiratory quotient (CO_2 production/O_2 consumption)

- The **normal A–a gradient is < 10 mm Hg.** Since O_2 normally equilibrates between alveolar gas and arterial blood, P_{AO2} is approximately equal to Pa_{O2}.
- The **A–a gradient is increased** (>10 mm Hg) if O_2 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 O_2 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 P_{O_2}).
- Thus, hypoxia can be caused by decreased cardiac output, decreased O_2-binding capacity of hemoglobin, or decreased arterial P_{O_2}.

V. CO_2 TRANSPORT

A. Forms of CO_2 in blood

- CO_2 is produced in the tissues and carried to the lungs in the venous blood in three forms:

1. Dissolved CO_2 (small amount), which is free in solution

table 4-5 Causes of Hypoxia

Cause	Mechanisms
↓ Cardiac output	↓ Blood flow
Hypoxemia	↓ Pa_{O_2} causes ↓ % saturation of hemoglobin
Anemia	↓ Hemoglobin concentration causes ↓ O_2 content of blood
Carbon monoxide poisoning	↓ O_2 content of blood
Cyanide poisoning	↓ O_2 utilization by tissues

Pa_{O2} = arterial P_{O_2}.

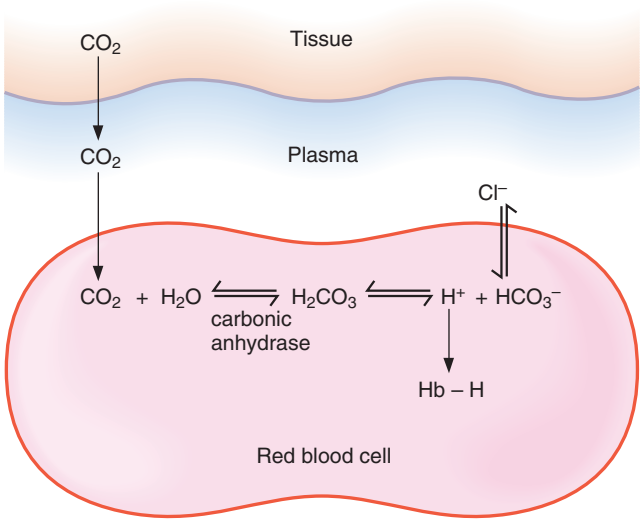


FIGURE 4-10 Transport of CO_2 from the tissues to the lungs in venous blood. H^+ is buffered by hemoglobin (Hb–H).

2. Carbaminohemoglobin (small amount), which is CO_2 bound to hemoglobin
3. **HCO_3^-** (from hydration of CO_2 in the RBCs), which is the **major form (90%)**

B. Transport of CO_2 as HCO_3^- (Figure 4-10)

1. **CO_2 is generated in the tissues** and diffuses freely into the venous plasma and then into the RBCs.
2. In the RBCs, CO_2 combines with H_2O to form H_2CO_3, a reaction that is catalyzed by **carbonic anhydrase.** H_2CO_3 dissociates into H^+ and HCO_3^-.
3. **HCO_3^-** leaves the RBCs in exchange for Cl^- **(chloride shift)** and is transported to the lungs in the plasma. HCO_3^- is the major form in which CO_2 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 CO_2 is being added).
5. **In the lungs**, all of the above reactions occur in reverse. HCO_3^- enters the RBCs in exchange for Cl^-. HCO_3^- recombines with H^+ to form H_2CO_3, which decomposes into CO_2 and H_2O. Thus, CO_2, 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 Po_2** 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% O_2 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.

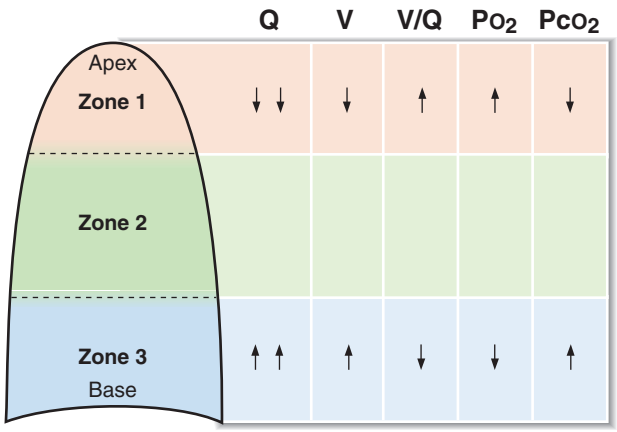


FIGURE 4-11 Regional variations in the lung of perfusion (blood flow [Q]), ventilation (V), V/Q, P_{O_2}, and P_{CO_2}.

- are usually caused by congenital abnormalities (e.g., **patent ductus arteriosus**) or traumatic injury.
- ***do not* result in a decrease in arterial P_{O_2}.** Instead, P_{O_2} 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_{O_2} of 100 mm Hg and an arterial P_{CO_2} 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_{O_2} and P_{CO_2}. Regional differences for P_{O_2} are greater than those for P_{CO_2}.
   a. **At the apex** (higher V/Q), P_{O_2} is highest and P_{CO_2} is lower because gas exchange is more efficient.
   b. **At the base** (lower V/Q), P_{O_2} is lowest and P_{CO_2} 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.**

table 4-6 V/Q Characteristics of Different Areas of the Lung

Area of Lung	Blood Flow	Ventilation	V/Q	Regional Arterial P_{O_2}	Regional Arterial P_{CO_2}
Apex	Lowest	Lower	Higher	Highest	Lower
Base	Highest	Higher	Lower	Lowest	Higher

V/Q = ventilation/perfusion ratio.

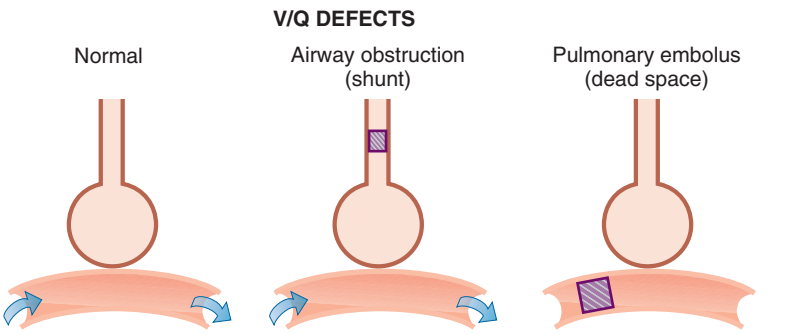
- There is ***no* gas exchange** in a lung that is perfused but not ventilated. The **P_{O_2} and P_{CO_2} of pulmonary capillary blood** (and, therefore, of systemic arterial blood) **will approach their values in mixed venous blood.**
- There is an **increased A–a gradient.**

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.



V/Q	0.8	0	∞
$P_{A_{O_2}}$	100 mm Hg	–	150 mm Hg
$P_{A_{CO_2}}$	40 mm Hg	–	0 mm Hg
Pa_{O_2}	100 mm Hg	40 mm Hg	–
Pa_{CO_2}	40 mm Hg	46 mm Hg	–

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. $P_{A_{O2}}$ = alveolar P_{O_2}; $P_{A_{CO2}}$ = alveolar P_{CO_2}; Pa_{O2} = arterial P_{O_2}; Pa_{CO2} = arterial P_{CO_2}.

A. Central control of breathing (brain stem and cerebral cortex)

1. Medullary respiratory center

- is located in the **reticular formation.**

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_{CO_2} and decrease in P_{O_2}. A previous period of hyperventilation extends the period of breath-holding.

B. Chemoreceptors for CO_2, H^+, and O_2 (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 Co_2 does.

a. Co_2 diffuses from arterial blood into the CSF because Co_2 is lipid-soluble and readily crosses the blood–brain barrier.

table 4-7 Comparison of Central and Peripheral Chemoreceptors

Type of Chemoreceptor	Location	Stimuli that Increase Breathing Rate
Central	Medulla	↓ pH ↑ (P_{CO_2})
Peripheral	Carotid and aortic bodies	↓ P_{O_2} (if < 60 mm Hg) ↑ P_{CO_2} ↓ pH

b. In the CSF, CO_2 combines with H_2O to produce H^+ and HCO_3^-. The resulting **H^+ acts directly on the central chemoreceptors.**

c. Thus, increases in P_{CO_2} and $[H^+]$ stimulate breathing, and decreases in P_{CO_2} and $[H^+]$ inhibit breathing.

d. The resulting hyperventilation or hypoventilation then returns the arterial P_{CO_2} toward normal.

2. Peripheral chemoreceptors in the carotid and aortic bodies

- The carotid bodies are located at the bifurcation of the common carotid arteries.
- The aortic bodies are located above and below the aortic arch.

a. Decreases in arterial P_{O_2}

- stimulate the peripheral chemoreceptors and **increase breathing rate.**
- P_{O_2} must decrease to low levels **(<60 mm Hg)** before breathing is stimulated. When P_{O_2} is less than 60 mm Hg, breathing rate is exquisitely sensitive to P_{O_2}.

b. Increases in arterial P_{CO_2}

- stimulate peripheral chemoreceptors and **increase breathing rate.**
- potentiate the stimulation of breathing caused by hypoxemia.
- The response of the peripheral chemoreceptors to CO_2 is less important than the response of the central chemoreceptors to CO_2 (or H^+).

c. Increases in arterial $[H^+]$

- stimulate the carotid body peripheral chemoreceptors directly, independent of changes in P_{CO_2}.
- 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 O_2 consumption and CO_2 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.

table 4-8 Summary of Respiratory Responses to Exercise

Parameter	Response
O_2 consumption	↑
CO_2 production	↑
Ventilation rate	↑ (Matches O_2 consumption/CO_2 production)
Arterial P_{O_2} and P_{CO_2}	No change
Arterial pH	No change in moderate exercise
	↓ In strenuous exercise (lactic acidosis)
Venous P_{CO_2}	↑
Pulmonary blood flow (cardiac output)	↑
V/Q ratios	More evenly distributed in lung

V/Q = ventilation/perfusion ratio.

2. The ***mean* values for arterial P_{O_2} and P_{CO_2} 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 P_{CO_2} increases** during exercise because the excess CO_2 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 P_{O_2} is decreased** at high altitude because the barometric pressure is decreased. As a result, arterial P_{O_2} 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 O_2-carrying capacity of blood, and increased O_2 content of blood.
4. **2,3-DPG concentrations are increased**, shifting the hemoglobin–O_2 dissociation curve to the right. There is a resulting decrease in affinity of hemoglobin for O_2 that facilitates unloading of O_2 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.

table 4-9 Summary of Adaptation to High Altitude

Parameter	Response
Alveolar P_{O_2}	↓ (Resulting from ↓ barometric pressure)
Arterial P_{O_2}	↓ (Hypoxemia)
Ventilation rate	↑ (Hyperventilation due to hypoxemia)
Arterial pH	↑ (Respiratory alkalosis)
Hemoglobin concentration	↑ (Polycythemia)
2,3-DPG concentration	↑
Hemoglobin–O_2 curve	Shift to right; ↓ affinity; ↑ P_{50}
Pulmonary vascular resistance	↑ (Hypoxic vasoconstriction)

DPG = diphosphoglycerate.

Review Test

1. Which of the following lung volumes or capacities can be measured by spirometry?

(A) Functional residual capacity (FRC)
(B) Physiologic dead space
(C) Residual volume (RV)
(D) Total lung capacity (TLC)
(E) Vital capacity (VC)

2. An infant born prematurely in gestational week 25 has neonatal respiratory distress syndrome. Which of the following would be expected in this infant?

(A) Arterial P_{O_2} of 100 mm Hg
(B) Collapse of the small alveoli
(C) Increased lung compliance
(D) Normal breathing rate
(E) Lecithin:sphingomyelin ratio of greater than 2:1 in amniotic fluid

3. In which vascular bed does hypoxia cause vasoconstriction?

(A) Coronary
(B) Pulmonary
(C) Cerebral
(D) Muscle
(E) Skin

Questions 4 and 5

A 12-year-old boy has a severe asthmatic attack with wheezing. He experiences rapid breathing and becomes cyanotic. His arterial P_{O_2} is 60 mm Hg and his P_{CO_2} is 30 mm Hg.

4. Which of the following statements about this patient is most likely to be true?

(A) Forced expiratory volume/forced vital capacity (FEV_1/FVC) is increased
(B) Ventilation/perfusion (V/Q) ratio is increased in the affected areas of his lungs
(C) His arterial P_{CO_2} is higher than normal because of inadequate gas exchange
(D) His arterial P_{CO_2} is lower than normal because hypoxemia is causing him to hyperventilate
(E) His residual volume (RV) is decreased

5. To treat this patient, the physician should administer

(A) an α_1-adrenergic antagonist
(B) a β_1-adrenergic antagonist
(C) a β_2-adrenergic agonist
(D) a muscarinic agonist
(E) a nicotinic agonist

6. Which of the following is true during inspiration?

(A) Intrapleural pressure is positive
(B) The volume in the lungs is less than the functional residual capacity (FRC)
(C) Alveolar pressure equals atmospheric pressure
(D) Alveolar pressure is higher than atmospheric pressure
(E) Intrapleural pressure is more negative than it is during expiration

7. Which volume remains in the lungs after a tidal volume (TV) is expired?

(A) Tidal volume (TV)
(B) Vital capacity (VC)
(C) Expiratory reserve volume (ERV)
(D) Residual volume (RV)
(E) Functional residual capacity (FRC)
(F) Inspiratory capacity
(G) Total lung capacity

8. A 35-year-old man has a vital capacity (VC) of 5 L, a tidal volume (TV) of 0.5 L, an inspiratory capacity of 3.5 L, and a functional residual capacity (FRC) of 2.5 L. What is his expiratory reserve volume (ERV)?

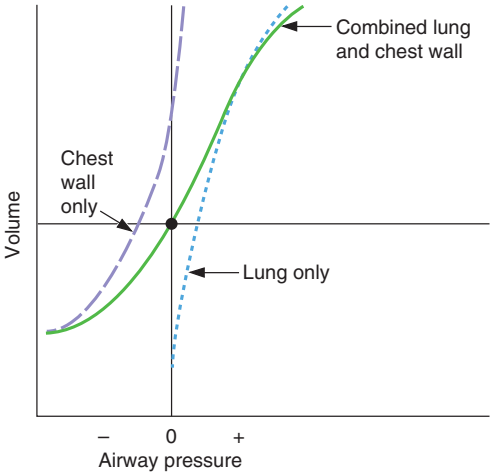
(A) 4.5 L
(B) 3.9 L
(C) 3.6 L
(D) 3.0 L
(E) 2.5 L
(F) 2.0 L
(G) 1.5 L

9. When a person is standing, blood flow in the lungs is

(A) equal at the apex and the base
(B) highest at the apex owing to the effects of gravity on arterial pressure

(C) highest at the base because that is where the difference between arterial and venous pressure is greatest
(D) lowest at the base because that is where alveolar pressure is greater than arterial pressure

10. Which of the following is illustrated in the graph showing volume versus pressure in the lung–chest wall system?



(A) The slope of each of the curves is resistance
(B) The compliance of the lungs alone is less than the compliance of the lungs plus chest wall
(C) The compliance of the chest wall alone is less than the compliance of the lungs plus chest wall
(D) When airway pressure is zero (atmospheric), the volume of the combined system is the functional residual capacity (FRC)
(E) When airway pressure is zero (atmospheric), intrapleural pressure is zero

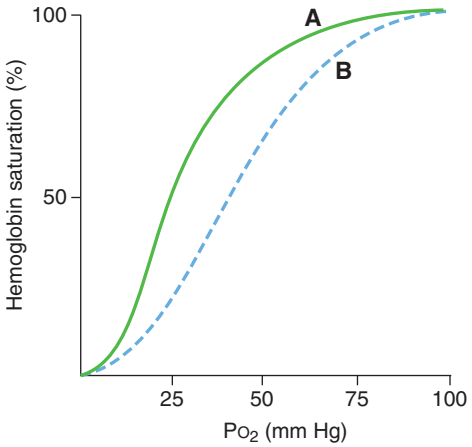
11. Which of the following is the site of highest airway resistance?

(A) Trachea
(B) Largest bronchi
(C) Medium-sized bronchi
(D) Smallest bronchi
(E) Alveoli

12. A 49-year-old man has a pulmonary embolism that completely blocks blood flow to his left lung. As a result, which of the following will occur?

(A) Ventilation/perfusion (V/Q) ratio in the left lung will be zero
(B) Systemic arterial P_{O_2} will be elevated
(C) V/Q ratio in the left lung will be lower than in the right lung
(D) Alveolar P_{O_2} in the left lung will be approximately equal to the P_{O_2} in inspired air
(E) Alveolar P_{O_2} in the right lung will be approximately equal to the P_{O_2} in venous blood

Questions 13 and 14



13. In the hemoglobin–O_2 dissociation curves shown above, the shift from curve A to curve B could be caused by

(A) increased pH
(B) decreased 2,3-diphosphoglycerate (DPG) concentration
(C) strenuous exercise
(D) fetal hemoglobin (HbF)
(E) carbon monoxide (CO) poisoning

14. The shift from curve A to curve B is associated with

(A) increased P_{50}
(B) increased affinity of hemoglobin for O_2
(C) impaired ability to unload O_2 in the tissues
(D) increased O_2-carrying capacity of hemoglobin
(E) decreased O_2-carrying capacity of hemoglobin

15. Which volume remains in the lungs after a maximal expiration?

(A) Tidal volume (TV)
(B) Vital capacity (VC)
(C) Expiratory reserve volume (ERV)
(D) Residual volume (RV)
(E) Functional residual capacity (FRC)

(F) Inspiratory capacity
(G) Total lung capacity

16. Compared with the systemic circulation, the pulmonary circulation has a

(A) higher blood flow
(B) lower resistance
(C) higher arterial pressure
(D) higher capillary pressure
(E) higher cardiac output

17. A healthy 65-year-old man with a tidal volume (TV) of 0.45 L has a breathing frequency of 16 breaths/min. His arterial P_{CO_2} is 41 mm Hg, and the P_{CO_2} of his expired air is 35 mm Hg. What is his alveolar ventilation?

(A) 0.066 L/min
(B) 0.38 L/min
(C) 5.0 L/min
(D) 6.14 L/min
(E) 8.25 L/min

18. Compared with the apex of the lung, the base of the lung has

(A) a higher pulmonary capillary P_{O_2}
(B) a higher pulmonary capillary P_{CO_2}
(C) a higher ventilation/perfusion (V/Q) ratio
(D) the same V/Q ratio

19. Hypoxemia produces hyperventilation by a direct effect on the

(A) phrenic nerve
(B) J receptors
(C) lung stretch receptors
(D) medullary chemoreceptors
(E) carotid and aortic body chemoreceptors

20. Which of the following changes occurs during strenuous exercise?

(A) Ventilation rate and O_2 consumption increase to the same extent
(B) Systemic arterial P_{O_2} decreases to about 70 mm Hg
(C) Systemic arterial P_{CO_2} increases to about 60 mm Hg
(D) Systemic venous P_{CO_2} decreases to about 20 mm Hg
(E) Pulmonary blood flow decreases at the expense of systemic blood flow

21. If an area of the lung is not ventilated because of bronchial obstruction, the pulmonary capillary blood serving that area will have a P_{O_2} that is

(A) equal to atmospheric P_{O_2}
(B) equal to mixed venous P_{O_2}
(C) equal to normal systemic arterial P_{O_2}
(D) higher than inspired P_{O_2}
(E) lower than mixed venous P_{O_2}

22. In the transport of CO_2 from the tissues to the lungs, which of the following occurs in venous blood?

(A) Conversion of CO_2 and H_2O to H^+ and HCO_3^- in the red blood cells (RBCs)
(B) Buffering of H^+ by oxyhemoglobin
(C) Shifting of HCO_3^- into the RBCs from plasma in exchange for Cl^-
(D) Binding of HCO_3^- to hemoglobin
(E) Alkalinization of the RBCs

23. Which of the following causes of hypoxia is characterized by a decreased arterial P_{O_2} and an increased A–a gradient?

(A) Hypoventilation
(B) Right-to-left cardiac shunt
(C) Anemia
(D) Carbon monoxide poisoning
(E) Ascent to high altitude

24. A 42-year-old woman with severe pulmonary fibrosis is evaluated by her physician and has the following arterial blood gases: pH = 7.48, Pa_{O_2} = 55 mm Hg, and Pa_{CO_2} = 32 mm Hg. Which statement best explains the observed value of Pa_{CO_2}?

(A) The increased pH stimulates breathing via peripheral chemoreceptors
(B) The increased pH stimulates breathing via central chemoreceptors
(C) The decreased Pa_{O_2} inhibits breathing via peripheral chemoreceptors
(D) The decreased Pa_{O_2} stimulates breathing via peripheral chemoreceptors
(E) The decreased Pa_{O_2} stimulates breathing via central chemoreceptors

25. A 38-year-old woman moves with her family from New York City (sea level) to Leadville Colorado (10,200 feet above sea level). Which of the following will occur as a result of residing at high altitude?

(A) Hypoventilation
(B) Arterial P_{O_2} greater than 100 mm Hg
(C) Decreased 2,3-diphosphoglycerate (DPG) concentration

(D) Shift to the right of the hemoglobin–O_2 dissociation curve
(E) Pulmonary vasodilation
(F) Hypertrophy of the left ventricle
(G) Respiratory acidosis

26. The pH of venous blood is only slightly more acidic than the pH of arterial blood because

(A) CO_2 is a weak base
(B) there is no carbonic anhydrase in venous blood
(C) the H^+ generated from CO_2 and H_2O is buffered by HCO_3^- in venous blood
(D) the H^+ generated from CO_2 and H_2O is buffered by deoxyhemoglobin in venous blood
(E) oxyhemoglobin is a better buffer for H^+ than is deoxyhemoglobin

27. In a maximal expiration, the total volume expired is

(A) tidal volume (TV)
(B) vital capacity (VC)
(C) expiratory reserve volume (ERV)
(D) residual volume (RV)
(E) functional residual capacity (FRC)
(F) inspiratory capacity
(G) total lung capacity

28. A person with a ventilation/perfusion (V/Q) defect has hypoxemia and is treated with supplemental O_2. The supplemental O_2 will be *most* helpful if the person's predominant V/Q defect is

(A) dead space
(B) shunt
(C) high V/Q
(D) low V/Q
(E) V/Q = 0
(F) V/Q = ×

29. Which person would be expected to have the largest A–a gradient?

(A) Person with pulmonary fibrosis
(B) Person who is hypoventilating due to morphine overdose
(C) Person at 12,000 feet above sea level
(D) Person with normal lungs breathing 50% O_2
(E) Person with normal lungs breathing 100% O_2

Answers and Explanations

1. **The answer is E** [I A 4, 5, B 2, 3, 5]. Residual volume (RV) cannot be measured by spirometry. Therefore, any lung volume or capacity that includes the RV cannot be measured by spirometry. Measurements that include RV are functional residual capacity (FRC) and total lung capacity (TLC). Vital capacity (VC) does not include RV and is, therefore, measurable by spirometry. Physiologic dead space is not measurable by spirometry and requires sampling of arterial P_{CO_2} and expired CO_2.

2. **The answer is B** [II D 2]. Neonatal respiratory distress syndrome is caused by lack of adequate surfactant in the immature lung. Surfactant appears between the 24th and the 35th gestational week. In the absence of surfactant, the surface tension of the small alveoli is too high. When the pressure on the small alveoli is too high ($P = 2T/r$), the small alveoli collapse into larger alveoli. There is decreased gas exchange with the larger, collapsed alveoli, and ventilation/perfusion (V/Q) mismatch, hypoxemia, and cyanosis occur. The lack of surfactant also decreases lung compliance, making it harder to inflate the lungs, increasing the work of breathing, and producing dyspnea (shortness of breath). Generally, lecithin:sphingomyelin ratios greater than 2:1 signify mature levels of surfactant.

3. **The answer is B** [VI C]. Pulmonary blood flow is controlled locally by the P_{O_2} of alveolar air. Hypoxia causes pulmonary vasoconstriction and thereby shunts blood away from unventilated areas of the lung, where it would be wasted. In the coronary circulation, hypoxemia causes vasodilation. The cerebral, muscle, and skin circulations are not controlled directly by P_{O_2}.

4. **The answer is D** [VIII B 2 a]. The patient's arterial P_{CO_2} is lower than the normal value of 40 mm Hg because hypoxemia has stimulated peripheral chemoreceptors to increase his breathing rate; hyperventilation causes the patient to blow off extra CO_2 and results in respiratory alkalosis. In an obstructive disease, such as asthma, both forced expiratory volume (FEV_1) and forced vital capacity (FVC) are decreased, with the larger decrease occurring in FEV_1. Therefore, the FEV_1/FVC ratio is decreased. Poor ventilation of the affected areas decreases the ventilation/perfusion (V/Q) ratio and causes hypoxemia. The patient's residual volume (RV) is increased because he is breathing at a higher lung volume to offset the increased resistance of his airways.

5. **The answer is C** [II E 3 a (2)]. A cause of airway obstruction in asthma is bronchiolar constriction. β_2-adrenergic stimulation (β_2-adrenergic agonists) produces relaxation of the bronchioles.

6. **The answer is E** [II F 2]. During inspiration, intrapleural pressure becomes *more negative* than it is at rest or during expiration (when it returns to its less negative resting value). During inspiration, air flows into the lungs when alveolar pressure becomes lower (due to contraction of the diaphragm) than atmospheric pressure; if alveolar pressure were not lower than atmospheric pressure, air would not flow inward. The volume in the lungs during inspiration is the functional residual capacity (FRC) *plus* one tidal volume (TV).

7. **The answer is E** [I B 2]. During normal breathing, the volume inspired and then expired is a tidal volume (TV). The volume remaining in the lungs after expiration of a TV is the functional residual capacity (FRC).

8. **The answer is G** [I A 3; Figure 4-1]. Expiratory reserve volume (ERV) equals vital capacity (VC) minus inspiratory capacity. [Inspiratory capacity includes tidal volume (TV) and inspiratory reserve volume (IRV)].

9. **The answer is C** [VI B]. The distribution of blood flow in the lungs is affected by gravitational effects on arterial hydrostatic pressure. Thus, blood flow is highest at the base, where arterial hydrostatic pressure is greatest and the difference between arterial and venous pressure is also greatest. This pressure difference drives the blood flow.

10. **The answer is D** [II C 2; Figure 4-3]. By convention, when airway pressure is equal to atmospheric pressure, it is designated as zero pressure. Under these equilibrium conditions, there is no airflow because there is no pressure gradient between the atmosphere and the alveoli, and the volume in the lungs is the functional residual capacity (FRC). The slope of each curve is compliance, not resistance; the steeper the slope is, the greater the volume change is for a given pressure change, or the greater compliance is. The compliance of the lungs alone or the chest wall alone is greater than that of the combined lung–chest wall system (the slopes of the individual curves are steeper than the slope of the combined curve, which means higher compliance). When airway pressure is zero (equilibrium conditions), intrapleural pressure is negative because of the opposing tendencies of the chest wall to spring out and the lungs to collapse.

11. **The answer is C** [II E 4]. The medium-sized bronchi actually constitute the site of highest resistance along the bronchial tree. Although the small radii of the alveoli might predict that they would have the highest resistance, they do not because of their parallel arrangement. In fact, early changes in resistance in the small airways may be "silent" and go undetected because of their small overall contribution to resistance.

12. **The answer is D** [VII B 2]. Alveolar P_{O_2} in the left lung will equal the P_{O_2} in inspired air. Because there is no blood flow to the left lung, there can be no gas exchange between the alveolar air and the pulmonary capillary blood. Consequently, O_2 is not added to the capillary blood. The ventilation/perfusion (V/Q) ratio in the left lung will be infinite (not zero or lower than that in the normal right lung) because Q (the denominator) is zero. Systemic arterial P_{O_2} will, of course, be decreased because the left lung has no gas exchange. Alveolar P_{O_2} in the right lung is unaffected.

13. **The answer is C** [IV C 1; Figure 4-8]. Strenuous exercise increases the temperature and decreases the pH of skeletal muscle; both effects would cause the hemoglobin–O_2 dissociation curve to shift to the right, making it easier to unload O_2 in the tissues to meet the high demand of the exercising muscle. 2,3-Diphosphoglycerate (DPG) binds to the β chains of adult hemoglobin and reduces its affinity for O_2, shifting the curve to the right. In fetal hemoglobin, the β chains are replaced by γ chains, which do not bind 2,3-DPG, so the curve is shifted to the left. Because carbon monoxide (CO) increases the affinity of the remaining binding sites for O_2, the curve is shifted to the left.

14. **The answer is A** [IV C 1; Figure 4-7]. A shift to the right of the hemoglobin–O_2 dissociation curve represents decreased affinity of hemoglobin for O_2. At any given P_{O_2}, the percent saturation is decreased, the P_{50} is increased (read the P_{O_2} from the graph at 50% hemoglobin saturation), and unloading of O_2 in the tissues is facilitated. The O_2-carrying capacity is determined by the hemoglobin concentration and is unaffected by the shift from curve A to curve B.

15. **The answer is D** [I A 3]. During a forced maximal expiration, the volume expired is a tidal volume (TV) plus the expiratory reserve volume (ERV). The volume remaining in the lungs is the residual volume (RV).

16. **The answer is B** [VI A]. Blood flow (or cardiac output) in the systemic and pulmonary circulations is nearly equal; pulmonary flow is slightly less than systemic flow because about 2% of the systemic cardiac output bypasses the lungs. The pulmonary circulation is characterized by both lower pressure and lower resistance than the systemic circulation, so flows through the two circulations are approximately equal (flow = pressure/resistance).

17. **The answer is D** [I A 5 b, 6 b]. Alveolar ventilation is the difference between tidal volume (TV) and dead space multiplied by breathing frequency. TV and breathing frequency are given, but dead space must be calculated. Dead space is TV multiplied by the difference

between arterial P_{CO_2} and expired P_{CO_2} divided by arterial P_{CO_2}. Thus: dead space = 0.45 × (41 – 35/41) = 0.066 L. Alveolar ventilation is then calculated as: (0.45 L – 0.066 L) × 16 breaths/min = 6.14 L/min.

18. The answer is B [VII C; Figure 4-10; Table 4-5]. Ventilation and perfusion of the lung are not distributed uniformly. Both are lowest at the apex and highest at the base. However, the differences for ventilation are not as great as for perfusion, making the ventilation/perfusion (V/Q) ratios higher at the apex and lower at the base. As a result, gas exchange is more efficient at the apex and less efficient at the base. Therefore, blood leaving the apex will have a higher P_{O_2} and a lower P_{CO_2} because it is better equilibrated with alveolar air.

19. The answer is E [VIII B 2]. Hypoxemia stimulates breathing by a direct effect on the peripheral chemoreceptors in the carotid and aortic bodies. Central (medullary) chemoreceptors are stimulated by CO_2 (or H^+). The J receptors and lung stretch receptors are not chemoreceptors. The phrenic nerve innervates the diaphragm, and its activity is determined by the output of the brain stem breathing center.

20. The answer is A [IX A]. During exercise, the ventilation rate increases to match the increased O_2 consumption and CO_2 production. This matching is accomplished without a change in mean arterial P_{O_2} or P_{CO_2}. Venous P_{CO_2} increases because extra CO_2 is being produced by the exercising muscle. Because this CO_2 will be blown off by the hyperventilating lungs, it does not increase the arterial P_{CO_2}. Pulmonary blood flow (cardiac output) increases manyfold during strenuous exercise.

21. The answer is B [VII B 1]. If an area of lung is not ventilated, there can be no gas exchange in that region. The pulmonary capillary blood serving that region will not equilibrate with alveolar P_{O_2}, but will have a P_{O_2} equal to that of mixed venous blood.

22. The answer is A [V B; Figure 4-9]. CO_2 generated in the tissues is hydrated to form H^+ and HCO_3^- in red blood cells (RBCs). H^+ is buffered inside the RBCs by deoxyhemoglobin, which *acidifies* the RBCs. HCO_3^- leaves the RBCs in exchange for Cl^- and is carried to the lungs in the plasma. A small amount of CO_2 (not HCO_3^-) binds directly to hemoglobin (carbaminohemoglobin).

23. The answer is B [IV A 4; IV D; Table 4-4; Table 4-5]. Hypoxia is defined as decreased O_2 delivery to the tissues. It occurs as a result of decreased blood flow or decreased O_2 content of the blood. Decreased O_2 content of the blood is caused by decreased hemoglobin concentration (anemia), decreased O_2-binding capacity of hemoglobin (carbon monoxide poisoning), or decreased arterial P_{O_2} (hypoxemia). Hypoventilation, right-to-left cardiac shunt, and ascent to high altitude all cause hypoxia by decreasing arterial P_{O_2}. Of these, only right-to-left cardiac shunt is associated with an increased A–a gradient, reflecting a lack of O_2 equilibration between alveolar gas and systemic arterial blood. In right-to-left shunt, a portion of the right heart output, or pulmonary blood flow, is not oxygenated in the lungs and thereby "dilutes" the P_{O_2} of the normally oxygenated blood. With hypoventilation and ascent to high altitude, both alveolar and arterial P_{O_2} are decreased, but the A–a gradient is normal.

24. The answer is D [VIII B; Table 4-7]. The patient's arterial blood gases show increased pH, decreased Pa_{O_2}, and decreased Pa_{CO_2}. The decreased Pa_{O_2} causes hyperventilation (stimulates breathing) via the peripheral chemoreceptors, but not via the central chemoreceptors. The decreased Pa_{CO_2} results from hyperventilation (increased breathing) and causes increased pH, which *inhibits* breathing via the peripheral and central chemoreceptors.

25. The answer is D [IX B; Table 4-9]. At high altitudes, the P_{O_2} of alveolar air is decreased because barometric pressure is decreased. As a result, arterial P_{O_2} is decreased (<100 mm Hg), and hypoxemia occurs and causes hyperventilation by an effect on peripheral chemoreceptors. Hyperventilation leads to respiratory alkalosis. 2,3-Diphosphoglycerate (DPG) levels increase adaptively; 2,3-DPG binds to hemoglobin and causes the hemoglobin–O_2 dissociation curve to shift to the right to improve unloading of O_2 in the tissues. The pulmonary

vasculature vasoconstricts in response to alveolar hypoxia, resulting in increased pulmonary arterial pressure and hypertrophy of the right ventricle (not the left ventricle).

26. The answer is D [V B]. In venous blood, CO_2 combines with H_2O and produces the weak acid H_2CO_3, catalyzed by carbonic anhydrase. The resulting H^+ is buffered by deoxyhemoglobin, which is such an effective buffer for H^+ (meaning that the pK is within 1.0 unit of the pH of blood) that the pH of venous blood is only slightly more acid than the pH of arterial blood. Oxyhemoglobin is a less effective buffer than deoxyhemoglobin.

27. The answer is B [I B 3]. The volume expired in a forced maximal expiration is forced vital capacity, or vital capacity (VC).

28. The answer is D [VII]. Supplemental O_2 (breathing inspired air with a high P_{O_2}) is most helpful in treating hypoxemia associated with a ventilation/perfusion (V/Q) defect if the predominant defect is low V/Q. Regions of low V/Q have the highest blood flow. Thus, breathing high P_{O_2} air will raise the P_{O_2} of a large volume of blood and have the greatest influence on the total blood flow leaving the lungs (which becomes systemic arterial blood). Dead space (i.e., $V/Q = \infty$ has no blood flow, so supplemental O_2 has no effect on these regions. Shunt (i.e., $V/Q = 0$) has no ventilation, so supplemental O_2 has no effect. Regions of high V/Q have little blood flow, thus raising the P_{O_2} of a small volume of blood will have little overall effect on systemic arterial blood.

29. The answer is A [IV D]. Increased A–a gradient signifies lack of O_2 equilibration between alveolar gas (A) and systemic arterial blood (a). In pulmonary fibrosis, there is thickening of the alveolar/pulmonary capillary barrier and increased diffusion distance for O_2, which results in lack of equilibration of O_2, hypoxemia, and increased A–a gradient. Hypoventilation and ascent to 12,000 feet also cause hypoxemia, because systemic arterial blood is equilibrated with a lower alveolar P_{O_2} (normal A–a gradient). Persons breathing 50% or 100% O_2 will have elevated alveolar P_{O_2}, and their arterial P_{O_2} will equilibrate with this higher value (normal A–a gradient).