23

Ventilation, Perfusion, and Ventilation/Perfusion Relationships

LEARNING OBJECTIVES

Upon completion of this chapter, the student should be able to answer the following questions:

1. What are the two types of dead space ventilation, and how does dead space ventilation change with changes in tidal volume?
2. What is the composition of gas in ambient air, the trachea, and the alveolus? How does this composition change when oxygen fraction (FiO_2) is increased? How does a change in barometric pressure change gas composition?
3. How is the alveolar air equation, used to calculate the alveolar-arterial difference for oxygen ($AaDo_2$), useful in the evaluation of hypoxemia?
4. What effect does a change in alveolar ventilation have on alveolar carbon dioxide?
5. At rest, how well does the distribution of pulmonary blood flow match the distribution of ventilation? What happens during exercise?
6. What are the four categories of hypoxia and the six causes of hypoxic hypoxia?
7. How does providing 100% inspired O_2 help determine the cause of hypoxic hypoxia?
8. What are the two causes of hypercapnia, and how are they different from each other?

The major determinant of normal gas exchange and thus the level of Po_2 and Pco_2 in blood is the relationship between ventilation ($\dot{V}$) and perfusion ($\dot{Q}$). This relationship is called the ventilation/perfusion ($\dot{V}/\dot{Q}$) ratio.

Ventilation

Ventilation is the process by which air moves in to and out from the lungs. The incoming air is composed of a volume that fills the conducting airways (dead space ventilation) and a portion that fills the alveoli (alveolar ventilation). Minute (or total) ventilation ($\dot{V}_E$) is the volume of air that enters or leaves the lung per minute:

Equation 23.1

$$\dot{V}_E = f \times V_T$$

where f is the frequency or number of breaths per minute and V_T (also known as TV) is the tidal volume, or volume of air inspired (or exhaled) per breath. Tidal volume varies with age, sex, body position, and metabolic activity. In an average-sized adult at rest, tidal volume is 500 mL. In children, it is 3 to 5 mL/kg. As metabolic activity increases, minute ventilation increases.

Dead Space Ventilation: Anatomical and Physiological

Anatomical Dead Space

Dead space ventilation is ventilation to airways that do not participate in gas exchange. There are two types of dead space: anatomical dead space and physiological dead space. **Anatomical dead space** (V_D) is composed of the volume of gas that fills the conducting airways:

Equation 23.2

$$V_T = V_D + V_A$$

where V refers to volume and the subscripts T, D, and A refer to tidal, dead space, and alveolar. A "dot" above V denotes a volume per unit of time (n):

Equation 23.3

$$V_T \times n = (V_D \times n) + (V_A \times n)$$

or

Equation 23.4

$$\dot{V}_E = \dot{V}_D + \dot{V}_A$$

where $\dot{V}_E$ is the total volume of gas in liters expelled from the lungs per minute (also called exhaled minute volume), $\dot{V}_D$ is the dead space ventilation per minute, and $\dot{V}_A$ is alveolar ventilation per minute.

In a healthy adult, the volume of gas contained in the conducting airways at functional residual capacity (FRC) is approximately 100 to 200 mL, in comparison with the 3 L of gas in an entire lung. The ratio of the volume of the

conducting airways (dead space) to tidal volume represents the fraction of each breath that is "wasted" in filling the conducting airways. This volume is related to tidal volume (V_T) and to exhaled minute ventilation $\dot{V}_E$ in the following way:

Equation 23.5

$$\dot{V}_D = \frac{V_D}{V_T} \times \dot{V}_E$$

IN THE CLINIC

If the dead space volume is 150 mL and tidal volume increases from 500 to 600 mL for the same exhaled minute ventilation, what is the effect on dead space ventilation?

$$V_T = 500 \text{ mL}$$
$$V_D = \left(\frac{150 \text{ mL}}{500 \text{ mL}}\right) \times \dot{V}_E$$
$$V_D = 0.3 \times \dot{V}_E$$

and, similarly,

$$V_T = 600 \text{ mL}$$
$$V_D = \left(\frac{150 \text{ mL}}{600 \text{ mL}}\right) \times \dot{V}_E$$
$$V_D = 0.25 \times \dot{V}_E$$

Increasing tidal volume is an effective way to increase alveolar ventilation. This might occur during exercise or periods of metabolic stress. As tidal volume increases, the fraction of the dead space ventilation decreases for the same exhaled minute ventilation.

Dead space ventilation (V_D) varies inversely with tidal volume (V_T). The larger the tidal volume, the smaller the proportion of dead space ventilation. Normally, V_D/V_T is 20% to 30% of exhaled minute ventilation. Changes in dead space are important contributors to work of breathing. If the dead space increases, the individual must inspire a larger tidal volume to maintain normal levels of alveolar ventilation. This adds to the work of breathing and can contribute to respiratory muscle fatigue and respiratory failure. If metabolic demands increase (e.g., during exercise or with fever), individuals with lung disease may not be able to increase tidal volume sufficiently. This can be observed at the beach when using a snorkel to extend the airway to the surface of the water, when swimming under water. This device increases "anatomic" dead space, such that increased tidal volume is needed to maintain adequate alveolar ventilation. Due to increased water pressure when under water, the mechanical work of breathing increases. Snorkel devices are manufactured with relatively short tubes to decrease the risk of underwater hypoventilation and CO_2 accumulation.

Physiological Dead Space

The second type of dead space is physiological dead space. Often in diseased lungs, some alveoli are perfused but not ventilated. The **total** volume of gas in each breath that does not participate in gas exchange is called the **physiological dead space.** This volume includes the anatomical dead space and the dead space secondary to perfused but unventilated alveoli. The physiological dead space is always at least as large as the anatomical dead space, and in the presence of lung disease it may be considerably larger.

Both anatomical and physiological dead space can be measured, but they are not measured routinely in the course of patient care.

IN THE CLINIC

In individuals with certain types of chronic obstructive pulmonary disease (COPD), such as emphysema, physiological dead space is increased. If dead space doubles, tidal volume must increase in order to maintain the same level of alveolar ventilation. If tidal volume is 500 mL and V_D/V_T is 0.25, then:

$$V_T = V_D + V_A$$
$$500 \text{ mL} = 125 \text{ mL} + 375 \text{ mL}$$

If V_D increases from 125 mL to 250 mL in this example, tidal volume (V_T) must increase to 625 mL to maintain a normal alveolar ventilation (i.e., V_A = 375 mL):

$$V_T = 250 \text{ mL} + 375 \text{ mL}$$
$$V_T = 625 \text{ mL}$$

Alveolar Ventilation

Composition of Air

Inspiration brings ambient or atmospheric air to the alveoli, where O_2 is taken up and CO_2 is removed. Ambient air is a gas mixture composed of N_2 and O_2, with minute quantities of CO_2, argon, and inert gases. The composition of this gas mixture can be described in terms of either gas fractions or the corresponding partial pressure.

Ambient air is a gas, so gas laws can be applied. This provides two important principles. First when the components of a gas mixture are viewed in terms of gas fractions (F), the sum of the individual gas fractions must equal one.

Equation 23.6

$$1.0 = F_{N_2} = F_{O_2} + F_{\text{argon and other gases}}$$

The sum of the **partial pressures** (in millimeters of mercury) of individual gas components in a mixture, also known as the gas **tension** (in torr), must be equal to the total pressure of the entire gas mixture. Thus at sea level, where atmospheric pressure (also known as barometric pressure [P_b]) is 760 mm Hg, the partial pressures of the gases in air are as follows:

Equation 23.7

$$P_b = P_{N_2} + P_{O_2} + P_{CO_2} + P_{H_2O} + P_{(\text{OTHER GLASES})}$$

Three important gas laws govern ambient air and alveolar ventilation. According to **Boyle's law,** when temperature is constant, pressure (P) and volume (V) are inversely related; that is, $P_1V_1 = P_2V_2$. Boyle's law is used in the measurement

of lung volumes (see Fig. 21.4). **Dalton's law** is that the partial pressure of a gas in a gas mixture is the pressure that the gas would exert if it occupied the total volume of the mixture in the absence of the other components. Eq. 23.7 is an example of how Dalton's law is used in the lung. According to **Henry's law,** the concentration of a gas dissolved in a liquid is proportional to its partial pressure.

The second important principle is that the partial pressure of a gas (P_{gas}) is equal to the fraction of that gas in the gas mixture (F_{gas}) multiplied by the atmospheric (barometric) pressure:

Equation 23.8

$$P_{gas} = F_{gas} \times P_b$$

Ambient air is composed of approximately 21% O_2 and 79% N_2. (The contribution of CO_2, <0.01%, is typically excluded.) Therefore, the partial pressure of O_2 in inspired ambient air (Po_2) is calculated as follows:

Equation 23.9

$$Po_2 = Fio_2 \times P_b$$
$$Po_2 = 0.21 \times 760 \text{ mm Hg}$$
$$Po_2 = 159 \text{ mm Hg or } 159 \text{ torr}$$

where (Fio_2) is the fraction of oxygen in inspired air. The partial pressure of O_2, or oxygen tension, in ambient air at the mouth at the start of inspiration is therefore 159 mm Hg, or 159 torr. The O_2 tension at the mouth can be altered in one of two ways: by changing the fraction of O_2 in inspired air (Fio_2) or by changing barometric pressure. Thus ambient O_2 tension can be increased through the administration of supplemental O_2 or by increasing air pressure. At high altitude, the FiO_2 is unchanged, but atmospheric pressure is decreased and as a result, the partial pressure of oxygen is decreased.

IN THE CLINIC

The partial pressure of O_2 in ambient air varies with altitude. The highest and lowest points in the contiguous United States are Mount Whitney in Sequoia National Park/Inyo National Forest (14,505 feet above sea level; barometric pressure, 437 mm Hg) and Badwater Basin in Death Valley National Park (282 feet below sea level; barometric pressure, 768 mm Hg). On Mount Whitney, the partial pressure of O_2 in ambient air is calculated as follows:

$$Po_2 = 0.21 \times 437 \text{ mm Hg} = 92 \text{ mm Hg}$$

whereas in Death Valley Badwater Basin, the partial pressure of oxygen is calculated as follows:

$$Po_2 = 0.21 \times 768 \text{ mm Hg} = 161 \text{ mm Hg}$$

If supplemental oxygen were used on Mount Whitney to bring Fio_2 from 0.21 to 0.40, $Po_2 = 0.40 \times 437$ mm Hg = 175 mm Hg. Note that the Fio_2 does not vary at different altitudes; only the barometric pressure varies. These differences in oxygen tension have profound effects on arterial blood gas values.

As inspiration begins, ambient air is brought into the nasopharynx and laryngopharynx, where it becomes warmed to body temperature and humidified. Inspired air becomes saturated with water vapor by the time it reaches the glottis. Water vapor exerts a partial pressure and dilutes the total pressure in which the other gases are distributed. Water vapor pressure at body temperature is 47 mm Hg. To calculate the partial pressures of O_2 and N_2 in a humidified mixture, the water vapor partial pressure must be subtracted from the total barometric pressure. Thus in the conducting airways, which begin in the trachea, the partial pressure of O_2 is calculated as follows

Equation 23.10

$$P_{trachea}O_2 = (P_b - PH_2O) \times Fio_2$$
$$= (760 \text{ mm Hg} - 47 \text{ mm Hg}) \times 0.21$$
$$= 150 \text{ mm Hg}$$

and the partial pressure of N_2 is calculated similarly

Equation 23.11

$$P_{trachea}N_2 = (P_b - PH_2O) \times FiN_2$$
$$= (760 \text{ mm Hg} - 47 \text{ mm Hg}) \times 0.79$$
$$= 563 \text{ mm Hg}$$

Note that the total pressure remains constant at 760 mm Hg (150 + 563 + 47 mm Hg) and that the fractions of O_2 and N_2 are unchanged. Water vapor pressure, however, reduces the partial pressures of O_2 and N_2. Note also that in the calculation of the partial pressure of ambient air (Eq. 23.9), water vapor is ignored, and ambient air is considered "dry." The conducting airways do not participate in gas exchange. The partial pressures of O_2, N_2, and water vapor remain unchanged in the airways until the air reaches the alveolus.

Alveolar Gas Composition

When the inspired air reaches the alveolus, O_2 diffuses across the alveolar membrane into the capillary bed, and CO_2 diffuses from the capillary bed into the alveolus. The process by which this occurs is described in Chapter 24. At the end of inspiration and with the glottis open, the total pressure in the alveolus is atmospheric. The sum of partial pressures of the gases in the alveolus must equal the total pressure, which in this case is atmospheric. The composition of the gas mixture, however, is changed and can be described as follows:

Equation 23.12

$$1.0 = FO_2 + FN_2 + FH_2O + F_{argon} + F \text{ other gases}$$

where N_2 and argon are inert gases; the fraction of these gases in the alveolus does not change from ambient fractions. The fraction of water vapor also does not change because the inspired gas is already fully saturated with water vapor and is at body temperature. As a consequence of gas exchange, however, the fraction of O_2 in the alveolus decreases, and the fraction of CO_2 in the alveolus increases. Because of changes in the fractions of O_2 and CO_2, the partial pressures exerted by these gases also change. The partial pressure of O_2 in the alveolus (PAo_2) is given by the **alveolar gas equation,** which is also called the **ideal alveolar oxygen equation:**

Equation 23.13

$$P_{AO_2} = P_{IO_2} - \frac{P_{ACO_2}}{R}$$
$$= \left[F_{IO_2} \times (P_b - P_{H_2O})\right] - \frac{P_{ACO_2}}{R}$$

where P_{IO_2} is the partial pressure of inspired O_2, which is equal to the fraction of O_2 (F_{IO_2}) multiplied by the barometric pressure (P_b) minus water vapor pressure (P_{H_2O}); P_{ACO_2} is the partial pressure of alveolar CO_2; and R is the respiratory exchange ratio, or **respiratory quotient.** The respiratory quotient is the ratio of the amount of CO_2 excreted ($\dot{V}_{CO_2}$) to the amount of O_2 taken up ($\dot{V}_{O_2}$) by the lungs. This quotient is the amount of CO_2 produced in relation to the amount of O_2 consumed by metabolism, and is to some extent dependent on the metabolic calorie source. The respiratory quotient varies between 0.7 and 1.0; it is 0.7 in states of exclusive fatty acid metabolism and 1.0 in states of exclusive carbohydrate metabolism. Under normal dietary conditions, the respiratory quotient is assumed to be 0.8. Thus the quantity of O_2 taken up exceeds the quantity of CO_2 that is released in the alveoli. The partial pressures of O_2, CO_2, and N_2 from ambient air to the alveolus at sea level are shown in Table 23.1.

A similar approach can be used to calculate the estimated P_{ACO_2}. The fraction of CO_2 in the alveolus is a function of the rate of CO_2 production by the cells during metabolism and the rate at which the CO_2 is eliminated from the alveolus. This process of elimination of CO_2 is known as **alveolar ventilation.** The relationship between CO_2 production and alveolar ventilation is defined by the **alveolar carbon dioxide equation:**

Equation 23.14

$$\dot{V}_{CO_2} = \dot{V}_A \times F_{ACO_2}$$
or
$$F_{ACO_2} = \dot{V}_{CO_2} / \dot{V}_A$$

where $\dot{V}_{CO_2}$ is the rate of CO_2 production by the body, $\dot{V}_A$ is alveolar ventilation per minute, and F_{ACO_2} is the fraction of CO_2 in dry alveolar gas. This relationship demonstrates that the rate of elimination of CO_2 from the alveolus is related to alveolar ventilation and to the fraction of CO_2 in the alveolus. Like the partial pressure of any other gas (see Eq. 23.8), P_{ACO_2} is defined by the following:

Equation 23.15

$$P_{ACO_2} = F_{ACO_2} \times (P_b - P_{H_2O})$$

Substituting for F_{ACO_2} in the previous equation yields the following relationship:

Equation 23.16

$$P_{ACO_2} = \frac{\left[\dot{V}_{CO_2} \times (P_b - P_{H_2O})\right]}{\dot{V}_A}$$

This equation demonstrates several important relationships. First, there is an inverse relationship between the partial pressure of CO_2 in the alveolus (P_{ACO_2}) and alveolar ventilation per minute ($\dot{V}_A$), regardless of the exhaled CO_2. Specifically, if ventilation is doubled, P_{ACO_2} decreases by 50%. Conversely, if ventilation is decreased by half, the P_{ACO_2} doubles. Second, at a constant alveolar ventilation per minute ($\dot{V}_A$), doubling of the metabolic production of CO_2 ($\dot{V}_{CO_2}$) causes the P_{ACO_2} to double. The relationship between $\dot{V}_A$ and P_{ACO_2} is depicted in Fig. 23.1.

Arterial Gas Composition

In normal lungs, P_{aCO_2} is tightly regulated by the brain stem respiratory center, and maintained at 40 ± 2 mm Hg. Increases or decreases in P_{aCO_2}, particularly when associated with changes in arterial pH, have profound effects on cell function, including enzyme and protein activity. Specialized chemoreceptors monitor P_{aCO_2} in the brainstem (Chapter 25), and exhaled minute ventilation (Eq. 23.1) varies in accordance with the level of P_{aCO_2}.

An acute increase in P_{aCO_2} results in **respiratory acidosis** (pH < 7.35), whereas an acute decrease in P_{aCO_2} results in **respiratory alkalosis** (pH > 7.45). **Hypercapnia** is defined as an elevation in P_{aCO_2}, and it occurs when CO_2 production exceeds alveolar ventilation (hypoventilation). Conversely, hyperventilation occurs when alveolar ventilation exceeds CO_2 production, and it decreases P_{aCO_2} **(hypocapnia).**

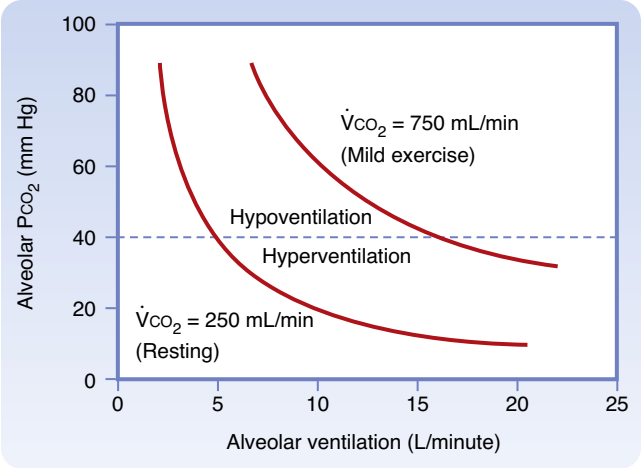
TABLE 23.1 Total and Partial Pressure Kres of Respiratory Gases in Ideal Alveolar Gas and Blood at Sea Level (760 mm Hg)

Parameter	Ambient Air (Dry)	Moist Tracheal Air	Alveolar Gas (R = 0.8)	Systemic Arterial Blood	Mixed Venous Blood
P_{O_2}	159	150	102	90	40
P_{CO_2}	0	0	40	40	46
P_{H_2O}, 37°C	0	47	47	47	47
P_{N_2}	601	563	571[a]	571	571
P_{total}	760	760	760	748	704[b]

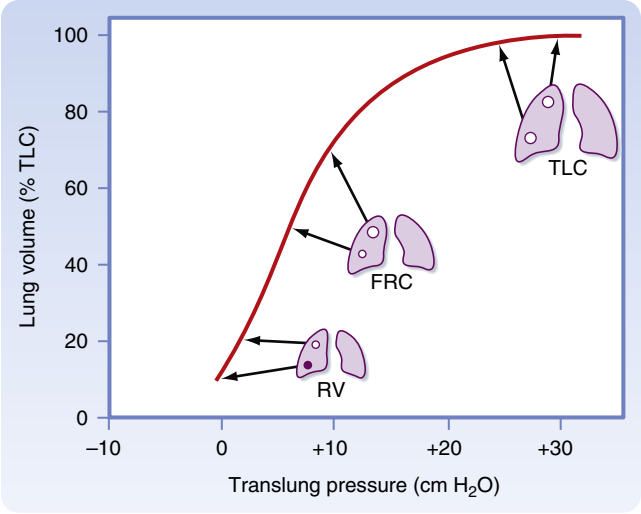
[a] P_{N_2} is increased in alveolar gas by 1% because R is normally less than 1.

[b] P_{total} is less in venous than in arterial blood because P_{O_2} has decreased more than P_{CO_2} has increased.

P_{CO_2}, Partial pressure of carbon dioxide; *P_{H_2O}*, partial pressure of water; *P_{N_2}*, partial pressure of nitrogen; *P_{O_2}*, partial pressure of oxygen; *P_{total}*, partial pressure of all parameters; *R*, respiratory quotient.



• **Fig. 23.1** The alveolar partial pressure of carbon dioxide (P_{CO_2}; *y-axis*) as a function of alveolar ventilation per minute ($\dot{V}_A$; *x-axis*) in the lung. Each line corresponds to a given metabolic rate associated with a constant production of CO_2 ($\dot{V}_{CO_2}$ *isometabolic line*). Normally, alveolar ventilation is controlled to maintain an alveolar P_{CO_2} of approximately 40 mm Hg. Thus at rest, when $\dot{V}_{CO_2}$ is approximately 250 mL/minute, alveolar ventilation of 5 L/minute results in an alveolar P_{CO_2} of 40 mm Hg. A 50% decrease in ventilation at rest (i.e., from 5 to 2.5 L/minute) results in doubling of alveolar P_{CO_2}. During exercise, CO_2 production is increased ($\dot{V}_{CO_2}$ = 750 mL/minute), and to maintain normal alveolar P_{CO_2}, ventilation must increase (in this case, to 15 L/minute). Again, however, a 50% reduction in ventilation (from 15 to 7.5 L/minute) results in doubling of the alveolar P_{CO_2}.



• **Fig. 23.2** Regional distribution of lung volume, including alveolar size *(Circles)* and location on the pressure-volume curve of the lung at different lung volumes. Because the lungs are suspended in the upright position, the pleural pressure (P_{pl}) and translung pressure (P_L) of lung units at the apex are greater than those at the base. These lung units are larger at any lung volume than are those at the base. The effect is greatest at residual volume *(RV)*, less so at functional residual capacity *(FRC)*, and absent at total lung capacity *(TLC)*. Note also that because of their "location" on the pressure-volume curve, inspired air is differentially distributed to these lung units; those at the apex are less compliant and receive a smaller proportion of the inspired air than do the lung units at the base, which are more compliant (i.e., are represented at a steeper part of the pressure-volume curve).

Distribution of Ventilation

Ventilation is not uniformly distributed in the lung, largely because of the effects of gravity. In the upright position, at most lung volumes, alveoli near the apex of the lung are more expanded than are alveoli at the base. Gravity pulls the lung downward and away from the chest wall. As a result, pleural pressure is lower (i.e., more negative) at the apex than at the base of the lung, and static translung pressure ($P_L = P_A - P_{pl}$) is increased; this results in an increase in alveolar volume at the apex. Because of the difference in alveolar volume at the apex and at the base of the lung (Fig. 23.2), alveoli at the lung base are represented along the steep portion of the pressure-volume curve, and they receive more of the ventilation (i.e., they have greater compliance). In contrast, the alveoli at the apex are represented closer to the top or flat portion of the pressure-volume curve. They have lower compliance and thus receive proportionately less of the tidal volume. The effect of gravity is less pronounced when a person is supine rather than upright, and it is less when a person is supine rather than prone. This is because the diaphragm is pushed in a cephalad direction when a person is supine, and it affects the size of all of the alveoli.

In addition to gravitational effects on the distribution of ventilation, ventilation in alveoli is not uniform. The reason for this is variable airway resistance (R) or compliance (C), and it is described quantitatively by the **time constant** (τ):

Equation 23.17

$$\tau = R \times C$$

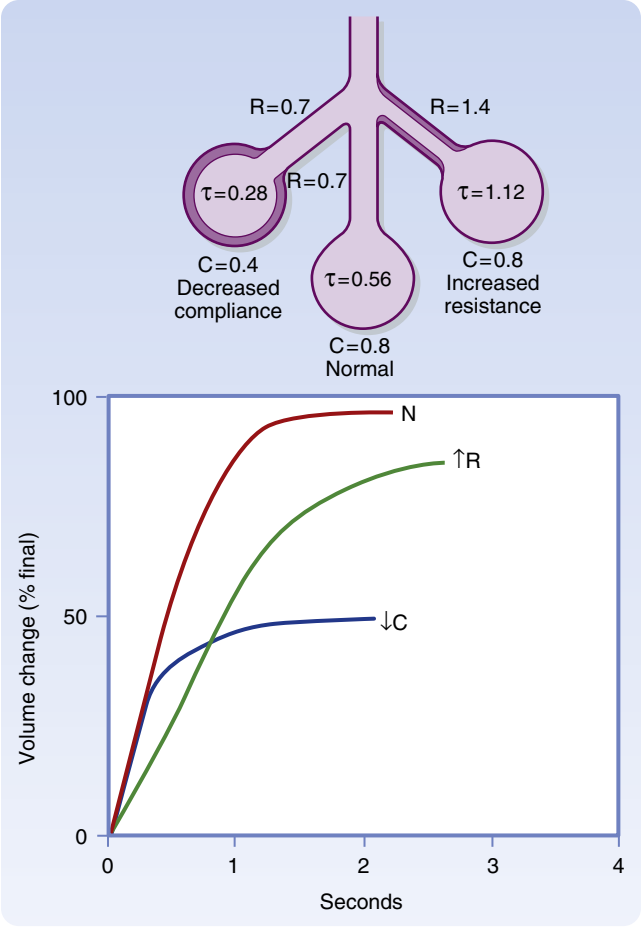
Alveolar units with long time constants fill and empty slowly. Thus an alveolar unit with increased airway resistance or increased compliance takes longer to fill and longer to empty. In adults, the normal respiratory rate is approximately 12 breaths per minute, the inspiratory time is approximately 2 seconds, and the expiratory time is approximately 3 seconds. In normal lungs, this time is sufficient to approach volume equilibrium (Fig. 23.3). In the presence of increased resistance or increased compliance, however, volume equilibrium is not reached.

IN THE CLINIC

Adults with COPD have a very long time constant as a result of an increase in resistance and, in the case of individuals with emphysema, an increase in compliance. As a result, such affected adults tend to breathe at a low respiratory rate. When individuals with COPD exert themselves (e.g. climbing a flight of stairs), the increased respiratory rate does not allow sufficient time for a full exhalation, and a process called *dynamic hyperinflation* occurs (Fig. 23.4). Lung volumes, which are already increased, increase further. The hyperinflated lung becomes less compliant, and the work of breathing (which is already elevated compared to healthy individuals) increases further.

Pulmonary Vascular Resistance

Blood flow in the pulmonary circulation is pulsatile and influenced by pulmonary vascular resistance (PVR), gravity, alveolar pressure, and the arterial-to-venous pressure



• **Fig. 23.3** Examples of local regulation of ventilation as a result of variation in the resistance *(R)* or compliance *(C)* of individual lung units. *Top,* The individual resistance and compliance values of three different lung units are illustrated. *Bottom,* The graph illustrates the volume of these three lung units as a function of time. In the upper schema, the normal lung (N) has a time constant *(τ)* of 0.56 second. This lung unit reaches 97% of final volume equilibrium in 2 seconds, which is the normal inspiratory time. The lung unit at the right (↑R) has a twofold increase in resistance; hence its time constant is doubled. That lung unit fills more slowly and reaches only 80% volume equilibrium during a normal inspiratory time (see graph); thus this lung unit is underventilated. The lung unit on the left (↓C) has decreased compliance (is "stiff"), which acts to reduce its time constant. This lung unit fills quickly, reaching its maximum volume within 1 second, but **receives only half the ventilation of a normal lung** unit.

gradient. PVR is calculated as the change in pressure from the pulmonary artery (P_{PA}) to the left atrium (P_{LA}), divided by the flow (Q_T), which is cardiac output:

Equation 23.18

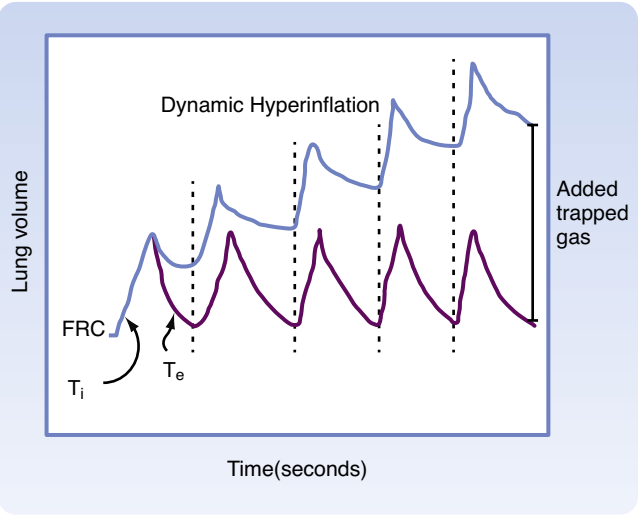
$$PVR = \frac{P_{PA} - P_{LA}}{Q_T}$$

Under normal circumstances,

Equation 23.19

$$PVR = \frac{14\ \text{mm Hg} - 8\ \text{mm Hg}}{6\ \text{L/minute}} = 1.00\ \text{mm Hg/L/minute}$$

This resistance is about 10 times less than that in the systemic circulation. The pulmonary circulation has two unique



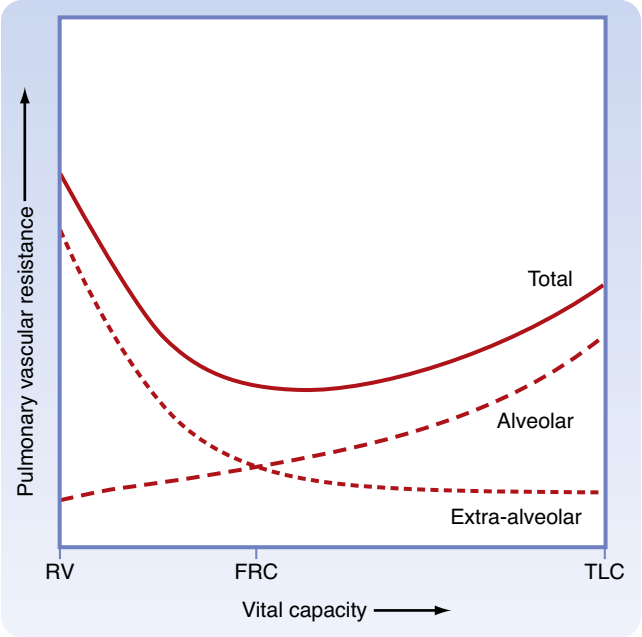
• **Fig. 23.4** Dynamic hyperinflation. The total time for respiration (T_{tot}) is composed of the time for inspiration *(T_i)* and the time for exhalation *(T_e)*. When the respiratory rate increases (e.g., during exercise), T_{tot} decreases. In individuals with chronic obstructive pulmonary disease (COPD), the effect of the increase in T_{tot} on Te may not allow for complete emptying of the alveoli with a long time constant, and with each succeeding breath, there is an increase in the lung volume (air trapping). This increase in lung volume eventually results in such a degree of hyperinflation that the affected person is no longer able to do the work needed to overcome the decreased compliance of the lung at this high lung volume. In such individuals, it is a major cause of shortness of breath with activity. *FRC*, Functional residual capacity.

features that allow increased blood flow on demand without an increase in pressure: (1) With increased demand, as during exercise, pulmonary vessels that are normally closed are recruited; and (2) the blood vessels in the pulmonary circulation are highly distensible, and their diameter increases with only a minimal increase in pulmonary arterial pressure.

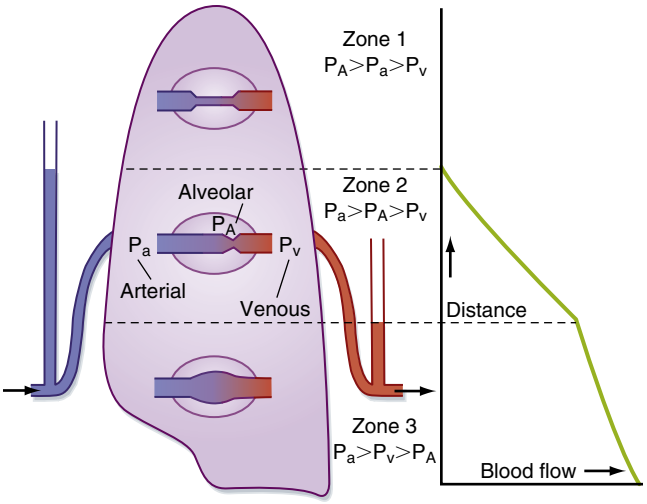
Lung volume affects PVR through its influence on alveolar capillaries (Fig. 23.5). At end inspiration, the air-filled alveoli compress the alveolar capillaries and increase PVR. In contrast to the capillary beds in the systemic circulation, the capillary beds in the lungs account for approximately 40% of PVR. The diameters of the larger extra-alveolar vessels increase at end inspiration because of radial traction and elastic recoil, and their PVR is lower at higher lung volume. During exhalation, the deflated alveoli apply the least resistance to the alveolar capillaries and their PVR is diminished, whereas the higher pleural pressure during exhalation increases the PVR of extra-alveolar vessels. As a result of these opposite effects of lung volume on PVR, total PVR in the lung is lowest at FRC.

Distribution of Pulmonary Blood Flow

Because the pulmonary circulation is a low-pressure/low-resistance system, it is influenced by gravity much more dramatically than is the systemic circulation. This gravitational effect contributes to an uneven distribution of blood flow in the lungs. In normal upright persons at rest, the volume of blood flow increases from the apex of the lung to the base of



• **Fig. 23.5** Schematic representation of the effects of changes in vital capacity on total pulmonary vascular resistance and the contributions to the total afforded by alveolar and extra-alveolar vessels. During inflation from residual volume *(RV)* to total lung capacity *(TLC)*, resistance to blood flow through alveolar vessels increases, whereas resistance through extra-alveolar vessels decreases. Thus changes in total pulmonary vascular resistance are plotted as a U-shaped curve during lung inflation, with the nadir at functional residual capacity *(FRC)*.



• **Fig. 23.6** Model to explain the uneven distribution of blood flow in the lung according to the pressures affecting the capillaries. P_A, Pulmonary alveolar pressure; P_a, pulmonary arterial pressure; P_v, pulmonary venous pressure. (From West JB, Dollery CT, Naimark A. *J Appl Physiol.* 1964;19:713.)

the lung, where blood flow is greatest. Similarly, in a supine individual, blood flow is least in the uppermost (anterior) regions and greatest in the lower (posterior) regions. Under conditions of stress, such as exercise, the difference in blood flow in the apex and base of the lung in upright persons becomes smaller, mainly because of the increase in arterial pressure.

On leaving the pulmonary artery, blood must travel against gravity to the apex of the lung in upright people. For every 1-cm increase in location of a pulmonary artery segment above the heart, there is a corresponding decrease in hydrostatic pressure equal to 0.74 mm Hg. Thus the pressure in a pulmonary artery segment that is 10 cm above the heart is 7.4 mm Hg less than the pressure in a segment at the level of the heart. Conversely, a pulmonary artery segment 5 cm below the heart has a 3.7-mm Hg increase in pulmonary arterial pressure. This effect of gravity on blood flow affects arteries and veins equally and results in wide variations in arterial and venous pressure from the apex to the base of the lung. These variations influence both flow and ventilation/perfusion relationships.

In addition to the pulmonary arterial pressure (P_a) to pulmonary venous pressure (P_v) gradients, differences in pulmonary alveolar pressure (P_A) also influence blood flow in the lung. Classically, the lung has been thought to be divided into three functional zones (Fig. 23.6). Zone 1 represents the lung apex, where P_a is so low that it can be exceeded by P_A. The capillaries collapse because of the greater external P_A, and blood flow ceases. Under normal conditions, this zone does not exist; however, this state could be reached during positive-pressure mechanical ventilation or if P_a decreases sufficiently (such as might occur with a marked decrease in circulating blood volume). In zone 2, or the upper third of the lung, P_a is greater than P_A, which is in turn is greater than P_v. Because P_A is greater than P_v, the greater external P_A partially collapses the capillaries and causes a "damming" effect decreasing overall blood flow in this zone. This phenomenon is often referred to as the *waterfall effect.* In zone 3, P_a is greater than P_v, which is greater than P_A, and blood flows in this area in accordance with the pressure gradients. Pulmonary blood flow is greater in the base of the lung because the increased transmural pressure distends the vessels and lowers the resistance.

Active Regulation of Blood Flow

Blood flow in the lung is regulated primarily by the passive mechanisms described previously. There are, however, several active mechanisms that regulate blood flow. Although the smooth muscle around pulmonary vessels is much thinner than that around systemic vessels, it is sufficient to affect vessel caliber and thus PVR. Oxygen levels have a major effect on blood flow. **Hypoxic vasoconstriction** occurs in arterioles in response to decreased PAo_2. The response is local, and the result is the shifting of blood flow from hypoxic areas to areas of the lung that are better oxygenated in an effort to enhance gas exchange. Isolated, local hypoxia does not alter PVR; approximately 20% of the vessels must be hypoxic before a change in PVR can be measured. Low inspired O_2 levels as a result of high altitude have a greater effect on PVR because all vessels are affected. High levels of inspired O_2 can dilate pulmonary vessels and decrease PVR. Other factors and some hormones (Box 23.1) can also

• Box 23.1 Factors and Hormones That Regulate Pulmonary Blood Flow

Pulmonary Vasoconstrictors

Low PA_{O_2}
Thromboxane A_2
α-Adrenergic catecholamines
Angiotensin
Leukotrienes
Neuropeptides
Serotonin
Endothelin
Histamine
Prostaglandins
High CO_2

Pulmonary Vasodilators

High PA_{O_2}
Prostacyclin
Nitric oxide
Acetylcholine
Bradykinin
Dopamine
β-Adrenergic catecholamines

PA_{O_2}, Partial pressure of O_2 in the alveolus.

influence vessel caliber, but their effects are usually local, brief, and important only in pathological conditions. Pulmonary capillaries lack smooth muscle and are thus not affected by these mechanisms. In some individuals, pulmonary artery vascular resistance and subsequently pulmonary artery pressures rise **(pulmonary arterial hypertension).** There are many pathophysiologic causes for pulmonary arterial hypertension, including chronic hypoxia, connective tissue diseases, certain drugs and toxins, and chronic pulmonary emboli. In some cases (idiopathic pulmonary arterial hypertension) the cause cannot be determined.

AT THE CELLULAR LEVEL

Endothelin-1 is an amino acid peptide that is produced by the vascular endothelium. Endothelin regulates the tone of pulmonary arteries and is a potent vasoconstrictor. Increased expression of endothelin-1 has been found in individuals with pulmonary arterial hypertension. Endothelin-1 also decreases endothelial expression of nitric oxide synthase. Nitric oxide is a vasodilator, so as nitric oxide levels decrease, there is less vasodilation. Endothelin-1 antagonists (*e.g.,* bosentan, ambrisentan, sitaxentan) have been produced and are important drugs in the treatment of pulmonary arterial hypertension. Phosphodiesterase inhibitors (*e.g.,* sildenafil, tadalafil) increase the effectiveness of nitric oxide leading to greater vasodilatory effect.

Ventilation/Perfusion Relationships

Both ventilation ($\dot{V}$) and lung perfusion ($\dot{Q}$) are essential components of normal gas exchange, but a normal relationship between the two components is insufficient to ensure normal gas exchange. The ventilation/perfusion ratio (also referred to as the $\dot{V}/\dot{Q}$ ratio) is defined as the ratio of ventilation to blood flow. This ratio can be defined for a single alveolus, for a group of alveoli, or for the entire lung. At the level of a single alveolus, the ratio is defined as alveolar ventilation per minute ($\dot{V}_A$) divided by capillary flow ($\dot{Q}_c$). At the level of the lung, the ratio is defined as total alveolar ventilation divided by cardiac output. In normal lungs, alveolar ventilation is approximately 4.0 L/minute, whereas pulmonary blood flow is approximately 5.0 L/minute. Thus in a normal lung, the overall ventilation/perfusion ratio is approximately 0.8, but the range of $\dot{V}/\dot{Q}$ ratios varies widely in different lung units. When ventilation exceeds perfusion, the ventilation/perfusion ratio is greater than 1 ($\dot{V}/\dot{Q} > 1$), and when perfusion exceeds ventilation, the ventilation/perfusion ratio is less than 1 ($\dot{V}/\dot{Q} < 1$). Mismatching of pulmonary blood flow and ventilation results in impaired O_2 and CO_2 transfer. In individuals with cardiopulmonary disease, mismatching of pulmonary blood flow and alveolar ventilation is the most frequent cause of systemic arterial **hypoxemia** (reduced Pa_{O_2}). In general, $\dot{V}/\dot{Q}$ ratios greater than 1 are not associated with hypoxemia.

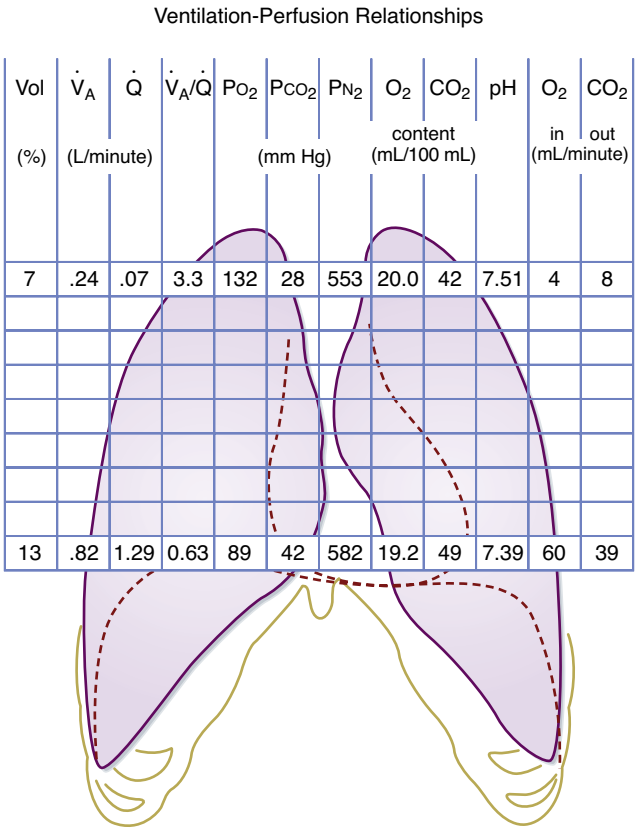
A normal ventilation/perfusion ratio does not mean that ventilation and perfusion of that lung unit are normal; it simply means that the relationship between ventilation and perfusion is normal. For example, in lobar pneumonia, ventilation to the affected lobe is decreased. If perfusion to this area remains unchanged, perfusion would exceed ventilation; that is, the ventilation/perfusion ratio would be less than 1 ($\dot{V}/\dot{Q} < 1$). However, the decrease in ventilation to this area leads to hypoxic vasoconstriction in the pulmonary arterial bed supplying this lobe. This results in a decrease in perfusion to the affected area and a more "normal" ventilation/perfusion ratio. Nonetheless, neither the ventilation nor the perfusion to this area is normal (both are decreased), but the relationship between the two could approach the normal range.

Regional Differences in Ventilation/Perfusion Ratios

The ventilation/perfusion ratio varies in different areas of the lung. In an upright individual, although both ventilation and perfusion increase from the apex to the base of the lung, the increase in ventilation is less than the increase in blood flow. As a result, the normal $\dot{V}/\dot{Q}$ ratio at the apex of the lung is much greater than 1 (ventilation exceeds perfusion), whereas the $\dot{V}/\dot{Q}$ ratio at the base of the lung is much less than 1 (perfusion exceeds ventilation). The relationship between ventilation and perfusion from the apex to the base of the lung is depicted in Fig. 23.7.

Alveolar-Arterial Difference for Oxygen

PA_{CO_2} and Pa_{CO_2} are equal because of the solubility properties of CO_2 (see Chapter 24). The same is not true for alveolar and arterial O_2. Even in individuals with normal lungs, PA_{O_2} is slightly greater than Pa_{O_2}. The difference



• **Fig. 23.7** Ventilation/perfusion relationships in a normal lung in the *upright* position. Only the apical and basal values are shown for clarity. In each column, the *number* on *top* represents values at the apex of the lung, and the *number* on the *bottom* represents values at the base. P_{CO_2}, Partial pressure of carbon dioxide; P_{N_2}, partial pressure of nitrogen; P_{O_2}, partial pressure of oxygen; $\dot{Q}$, perfusion per minute; $\dot{V}_A$, alveolar ventilation per minute.

between PA_{O_2} and Pa_{O_2} is called *the alveolar-arterial difference for oxygen* ($AaDo_2$). An increase in the $AaDo_2$ is a hallmark of abnormal O_2 exchange. This small difference in healthy individuals is not caused by "imperfect" gas exchange, but by the small number of veins that bypass the lung and empty directly into the arterial circulation. The thebesian vessels of the left ventricular myocardium drain directly into the left ventricle (rather than into the coronary sinus in the right atrium), and some bronchial and mediastinal veins drain into the pulmonary veins. This results in venous admixture and a decrease in Pa_{O_2}. (This is an example of an anatomical shunt; see the section "Anatomical Shunts.") Approximately 2% to 3% of the cardiac output is **shunted** in this way.

To measure the clinical effectiveness of gas exchange in the lung, Pa_{O_2} and Pa_{CO_2} are measured. PA_{O_2} is calculated from the alveolar air equation (Eq. 23.13). The difference between the calculated PA_{O_2} and the measured Pa_{O_2} is the $AaDo_2$. In individuals with normal lungs who are breathing room air, the $AaDo_2$ is less than 15 mm Hg. The mean value rises approximately 3 mm Hg per decade of life after 30 years of age. Hence, an $AaDo_2$ lower than 25 mm Hg is considered the upper limit of normal.

IN THE CLINIC

An individual with pneumonia is receiving 30% supplemental O_2 by face mask. Arterial blood gas pH is 7.40, Pa_{CO_2} is 44 mm Hg, and Pa_{O_2} is 70 mm Hg. What is the patient's $AaDo_2$? (Assume that the patient is at sea level and the patient's respiratory quotient is 0.8.) According to the alveolar air equation (Eq. 23.13),

$$PA_{O_2} = \left[Fi_{O_2} \times (P_b - P_{H_2O})\right] - \frac{PA_{CO_2}}{R}$$

$$PA_{O_2} = \left[0.3 \times (760 - 47)\right] - \frac{44}{0.8}$$

$$= 159 \text{ mm Hg}$$

Therefore,

$$AaDo_2 = PA_{O_2} - Pa_{O_2}$$

$$= 159 - 70 = 89 \text{ mm Hg}$$

This high $AaDo_2$ suggests that the patient has lung disease (in this case, pneumonia).

Abnormalities in Pa_{O_2} can occur with or without an elevation in $AaDo_2$. Hence, the relationship between Pa_{O_2} and $AaDo_2$ is useful in determining the cause of an abnormal Pa_{O_2} and in predicting the response to therapy (particularly to supplemental O_2 administration). Causes of a reduction in Pa_{O_2} (arterial hypoxemia) and their effect on $AaDo_2$ are listed in Table 23.2. Each of these causes is discussed in greater detail in the following sections.

TABLE 23.2 Causes of Hypoxic Hypoxia

Cause	Pa_{O_2}	$AaDo_2$	Pa_{O_2} Response to 100% O_2
Anatomical shunt	Decreased	Increased	No significant change
Physiological shunt	Decreased	Increased	Decreased
Decreased Fi_{O_2}	Decreased	Normal	Increased
Low ventilation/perfusion ratio	Decreased	Increased	Increased
Diffusion abnormality	Decreased	Increased	Increased
Hypoventilation	Decreased	Normal	Increased

$AaDo_2$, Alveolar-arterial difference for oxygen; *Fio_2*, fraction of inspired oxygen; *Pao_2*, partial pressure of arterial oxygen.

Arterial Blood Hypoxemia, Hypoxia, and Hypercarbia

Arterial hypoxemia is defined as a Pao_2 lower than 80 mm Hg in an adult who is breathing room air at sea level. **Hypoxia** is defined as insufficient O_2 to carry out normal metabolic functions; hypoxia often occurs when the Pao_2 is less than 60 mm Hg. There are four major categories of hypoxia. The first, *hypoxic hypoxia,* is the most common. The six main pulmonary conditions associated with hypoxic hypoxia—anatomical shunt, physiological shunt, decreased Fio_2, $\dot{V}/\dot{Q}$ mismatching, diffusion abnormalities, and hypoventilation—are described in the following sections and in Table 23.2. A second category is *anemic hypoxia,* which is caused by a decrease in the amount of functioning hemoglobin as a result of too little hemoglobin, abnormal hemoglobin, or interference with the chemical combination of oxygen and hemoglobin (e.g., carbon monoxide poisoning; see the following "In the Clinic" box). The third category is *hypoperfusion hypoxia,* which results from low blood flow (e.g., decreased cardiac output) and reduced oxygen delivery to the tissues. *Histotoxic hypoxia,* the fourth category of hypoxia, occurs when the cellular machinery that uses oxygen to produce energy is poisoned, as in cyanide poisoning. In this situation, arterial and venous PO_2 are normal or increased because oxygen is not being utilized.

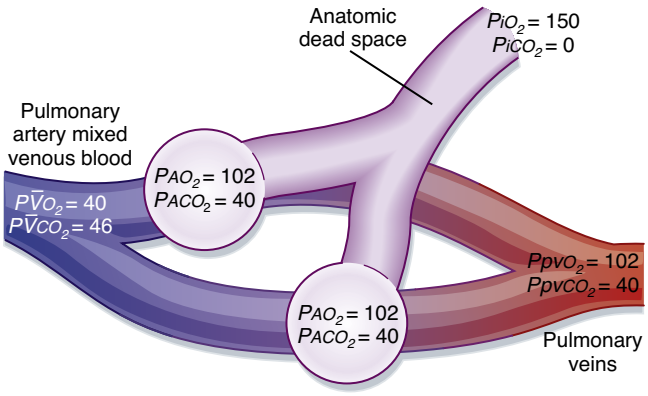
IN THE CLINIC

Carbon monoxide is a combustion by-product, and can be generated from a variety of sources such as a fuel burning space heater, car exhaust, or from a burning building. Individuals exposed to increased levels of carbon monoxide experience headache, nausea, and dizziness. If the exposure is severe, exposed individuals may die. In carbon monoxide poisoning, the lips often have a cherry-red appearance, and oxygen saturation as measured by pulse oximeter can be falsely elevated. Even on an arterial blood gas, the PAo_2 may be normal. However, as CO is tightly bound to the hemoglobin molecule, there is little available hemoglobin to bind to and transport oxygen. This results in tissue hypoxemia. Thus it is imperative that the clinician recognize a potential case of carbon monoxide poisoning and order an oxygen saturation measurement with the use of a carbon monoxide oximeter (CO-oximeter) or by arterial blood gas analysis. If a patient has carbon monoxide poisoning, there will be a marked difference between the measurement of oxygen saturation by oximetry and that measured with a carbon monoxide oximeter. Arterial blood gas analysis will confirm elevation of CO-hemoglobin.

Ventilation/Perfusion Abnormalities and Shunts

Anatomical Shunts

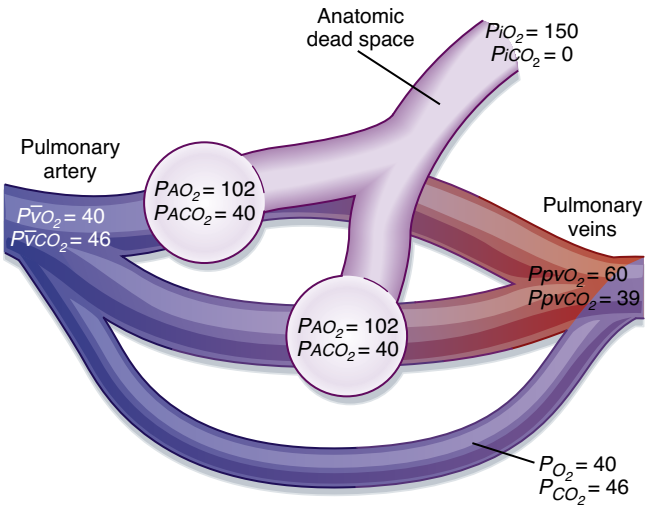
A useful way to examine the relationship between ventilation and perfusion is with the hypothetical two–lung unit model (Fig. 23.8). Two alveoli "lung units" are ventilated, and each is supplied by blood from the heart. When ventilation is uniform, half the inspired gas goes to each alveolus, and when perfusion is uniform, half the cardiac output goes to each alveolus. In this normal unit, the ventilation/perfusion ratio in each of the alveoli is the same and is equal to 1. The alveoli are perfused by mixed venous blood that is deoxygenated and contains increased $Paco_2$. PAo_2 is higher than mixed venous O_2, and this provides a gradient for movement of O_2 into blood. In contrast, mixed venous CO_2 is greater than $PAco_2$, and this provides a gradient for movement of CO_2 into the alveolus. Note that in this ideal model, alveolar-arterial O_2 values do not differ.



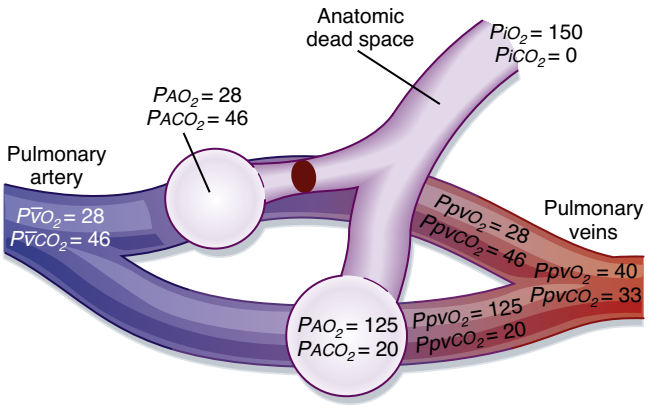
• **Fig. 23.8** Simplified lung model of two normal parallel lung units. Both units receive equal volumes of air and blood flow for their size. The blood and alveolar gas partial pressures are normal values in a resting person at sea level. $PAco_2$, Partial pressure of alveolar carbon dioxide; PAo_2, partial pressure of alveolar oxygen; $Pico_2$, partial pressure of inspired carbon dioxide; Pio_2, partial pressure of inspired oxygen; $Ppvco_2$, partial pressure of carbon dioxide in pulmonary venous blood; $Ppvo_2$, partial pressure of oxygen in pulmonary venous blood; $P\bar{v}CO_2$, partial pressure of carbon dioxide in mixed venous blood; $P\bar{v}O_2$, partial pressure of oxygen in mixed venous blood.

An anatomical shunt occurs when mixed venous blood bypasses the gas-exchange unit and goes directly into the arterial circulation (Fig. 23.9). Alveolar ventilation, the distribution of alveolar gas, and the composition of alveolar gas are normal, but the distribution of cardiac output is changed. Some of the cardiac output goes through the pulmonary capillary bed that supplies the gas-exchange units, but the rest of it bypasses the gas-exchange units and goes directly into the arterial circulation. The blood that bypasses the gas-exchange unit is thus *shunted,* and because the blood is deoxygenated, this type of bypass is called a **right-to-left shunt.** Most anatomical shunts develop within the heart, and they develop when deoxygenated blood from the right atrium or ventricle crosses the septum and mixes with blood from the left atrium or ventricle. The effect of this right-to-left shunt is to mix deoxygenated blood with oxygenated blood, and it results in varying degrees of arterial hypoxemia.

An important feature of an anatomical shunt is that if an affected individual is given 100% O_2 to breathe, there is only a minimal increase in oxygen saturation.



• **Fig. 23.9** Right-to-left shunt. Alveolar ventilation is normal, but a portion of the cardiac output bypasses the lung and mixes with oxygenated blood. Pa_{O_2} varies according to the size of the shunt. P_{ACO_2}, Partial pressure of alveolar carbon dioxide; P_{AO_2}, partial pressure of alveolar oxygen; P_{ICO_2}, partial pressure of inspired carbon dioxide; P_{IO_2}, partial pressure of inspired oxygen; P_{pvCO_2}, partial pressure of carbon dioxide in pulmonary venous blood; P_{pvO_2}, partial pressure of oxygen in pulmonary venous blood; $P\bar{V}CO_2$, partial pressure of carbon dioxide in mixed venous blood; $P\bar{V}O_2$, partial pressure of oxygen in mixed venous blood.



• **Fig. 23.10** Schema of a physiological shunt (venous admixture). Notice the marked decrease in Pa_{O_2} in comparison to Pc_{O_2}. The alveolar-arterial difference for oxygen (AaD_{O_2}) in this example is 85 mm Hg. P_{ACO_2}, Partial pressure of alveolar carbon dioxide; P_{AO_2}, partial pressure of alveolar oxygen; P_{ICO_2}, partial pressure of inspired carbon dioxide; P_{IO_2}, partial pressure of inspired oxygen; P_{pvCO_2}, partial pressure of carbon dioxide in pulmonary venous blood; P_{pvO_2}, partial pressure of oxygen in pulmonary venous blood; $P\bar{V}CO_2$, partial pressure of carbon dioxide in mixed venous blood; $P\bar{V}O_2$, partial pressure of oxygen in mixed venous blood. Note differing Ppv_{O_2} and Ppv_{CO_2} levels in pulmonary veins draining the unventilated lung unit (top) and fully ventilated lung unit (bottom.) The resulting mixed Ppv_{O_2} is substantially lower than the Ppv_{O_2} from fully ventilated lung unit.

The blood that bypasses the gas-exchanging units is never exposed to the enriched O_2, and thus it continues to be deoxygenated. The PO_2 in the blood that is not being shunted increases and it mixes with the deoxygenated blood. Thus the degree of persistent hypoxemia in response to 100% O_2 varies with the volume of the shunted blood. Normally, the hemoglobin in the blood that perfuses the ventilated alveoli is almost fully saturated. Therefore, most of the added O_2 is in the form of dissolved O_2 (see Chapter 24).

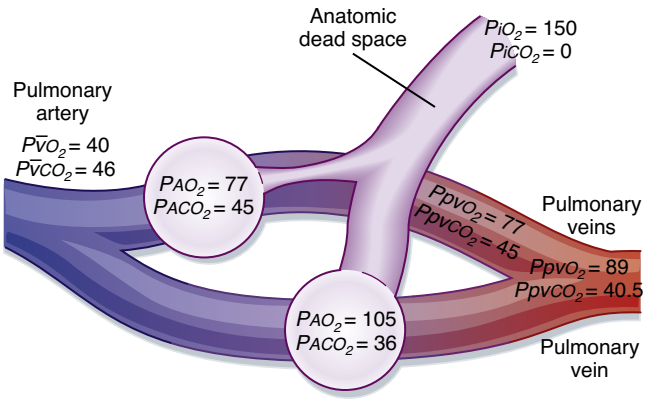
The Pa_{CO_2} in an anatomical shunt is not usually increased, even though the shunted blood has an elevated level of CO_2. The reason for this is that the central chemoreceptors (see Chapter 25) respond to any elevation in CO_2 with an increase in ventilation and reduce Pa_{CO_2} to the normal range. If the hypoxemia is severe, the increased respiratory drive secondary to the hypoxemia increases the ventilation and can decrease Pa_{CO_2} to below the normal range.

Physiological Shunts

A physiological shunt (also known as *venous admixture*) can develop when ventilation to lung units is absent in the presence of continuing perfusion (Fig. 23.10). In this situation, in the two–lung unit model, all the ventilation goes to the other lung unit, whereas perfusion is equally distributed between both lung units. The lung unit without ventilation but with perfusion has a $\dot{V}/\dot{Q}$ ratio of 0. The blood perfusing this unit is mixed venous blood; because there is no ventilation, no gas is exchanged in the unit, and the blood leaving this unit continues to resemble mixed venous blood. The effect of a physiological shunt on oxygenation is similar to the effect of an anatomical shunt; that is, deoxygenated blood bypasses a gas-exchanging unit and admixes with arterial blood. Clinically, **atelectasis** (in which a portion of the lung becomes deflated or deaerated) is an example of a situation in which the lung region has a $\dot{V}/\dot{Q}$ of 0, as there is no ventilation to the atelectatic lung units. Causes of atelectasis include mucous plugs, airway edema, foreign bodies, and tumors in the airway. Decreased inspiratory effort following surgery is a common cause of atelectasis.

Low Ventilation/Perfusion

Mismatching between ventilation and perfusion is the most frequent cause of arterial hypoxemia in individuals with respiratory disorders. In the most common example, the composition of mixed venous blood, total blood flow (cardiac output), and the distribution of blood flow are normal. However, when alveolar ventilation is distributed unevenly between the two gas-exchange units (Fig. 23.11) and blood flow is equally distributed, the unit with decreased ventilation has a $\dot{V}/\dot{Q}$ ratio of less than 1, whereas the unit with the increased ventilation has a $\dot{V}/\dot{Q}$ of greater than 1. This causes the alveolar and end-capillary gas compositions to vary. Both the arterial O_2 content and CO_2 content are abnormal in the blood that has come from the unit with the decreased ventilation ($\dot{V}/\dot{Q}$, <1). The unit with the increased ventilation ($\dot{V}/\dot{Q}$, >1) has a lower CO_2 content and a higher O_2 content because it is being overventilated. The actual Pa_{O_2} and Pa_{CO_2} vary, depending on the relative contribution of each of these units to arterial blood. The alveolar-arterial O_2 gradient (AaD_{O_2}) is increased because the relative



• **Fig. 23.11** Effects of ventilation/perfusion mismatching on gas exchange. The decrease in ventilation to the one lung unit could be due to mucus obstruction, airway edema, bronchospasm, a foreign body, or a tumor. P_{ACO_2}, Partial pressure of alveolar carbon dioxide; P_{AO_2}, partial pressure of alveolar oxygen; P_{ICO_2}, partial pressure of inspired carbon dioxide; P_{IO_2}, partial pressure of inspired oxygen; P_{pvCO_2}, partial pressure of carbon dioxide in pulmonary venous blood; P_{pvO_2}, partial pressure of oxygen in pulmonary venous blood; $P\bar{v}CO_2$, partial pressure of carbon dioxide in mixed venous blood; $P\bar{v}O_2$, partial pressure of oxygen in mixed venous blood.

overventilation of one unit does not fully compensate (either by the addition of extra O_2 or by the removal of extra CO_2) for underventilation of the other unit. The failure to compensate is greater for O_2 than for CO_2, as indicated by the flatness of the upper part of the oxyhemoglobin dissociation curve, in contrast to the slope of the CO_2 dissociation curve (see Chapter 24). In other words, increased ventilation increases P_{AO_2}, but it adds little extra O_2 content to the blood because hemoglobin is close to being 100% saturated in the overventilated areas. This is not the case for CO_2, for which the steeper slope of the CO_2 curve indicates removal of more CO_2 when ventilation increases. Thus inasmuch as CO_2 moves by diffusion, then as long as a CO_2 gradient is maintained, CO_2 diffusion will occur.

Alveolar Hypoventilation

The P_{AO_2} is determined by a balance between the rate of O_2 uptake and the rate of O_2 replenishment by ventilation. Oxygen uptake depends on blood flow through the lung and the metabolic demands of the tissues. If ventilation decreases, P_{AO_2} decreases, and P_{aO_2} subsequently decreases. In addition, V_A and P_{ACO_2} are directly but inversely related. When ventilation is halved, the P_{ACO_2} doubles, and thus so does the P_{aCO_2} (see Eq. 23.16). Ventilation insufficient to maintain normal levels of CO_2 is called **hypoventilation.** Hypoventilation always decreases P_{aO_2} and increases P_{aCO_2}.

One of the hallmarks of hypoventilation is a normal $A_aD_{O_2}$. Hypoventilation reduces P_{AO_2}, which in turn results in a decrease in P_{aO_2}. Because gas exchange is normal, the $A_aD_{O_2}$ remains normal. Hypoventilation accompanies diseases associated with decreased central drive to breathe, weakness of the respiratory muscles, and is also associated with drugs that reduce respiratory drive. In the presence of hypoventilation, however, regions of the lung may become deaerated (atelectatic) and in these regions the $\dot{V}/\dot{Q}$ ratio is 0. When this occurs, the $A_aD_{O_2}$ rises.

Diffusion Abnormalities

Abnormalities in diffusion of O_2 across the alveolar-capillary barrier could potentially result in arterial hypoxia. Equilibration between alveolar and capillary O_2 and CO_2 content occurs rapidly: in a fraction of the time that it takes for red blood cells to transit the pulmonary capillary network. Hence, diffusion equilibrium almost always occurs in normal people, even during exercise, when the transit time of red blood cells through the lung increases significantly. An increased $A_aD_{O_2}$ attributable to incomplete diffusion **(diffusion disequilibrium)** has been observed in normal persons only during exercise at high altitude (≥10,000 feet). Even in individuals with an abnormal diffusion capacity, diffusion disequilibrium at rest is unusual but can occur during periods of increased metabolic demand such as exercise or illness, or when at high altitude. **Alveolar-capillary block,** or thickening of the air-blood barrier, is an uncommon cause of hypoxemia. Even when the alveolar wall is thickened, there is usually sufficient time for gas diffusion unless the red blood cell transit time is increased. Carbon dioxide diffuses nearly 20 times more rapidly than oxygen. Impaired CO_2 diffusion rarely clinically relevant.

Mechanisms of Hypercapnia

Two major mechanisms account for the development of **hypercapnia** (elevated P_{CO_2}): hypoventilation and increases in dead space ventilation. As noted previously, alveolar ventilation and alveolar CO_2 are inversely related. When ventilation is halved, P_{ACO_2} and P_{aCO_2} double. Hypoventilation always decreases P_{aO_2} and increases P_{aCO_2} and thereby results in a hypoxemia that responds to an enriched source of O_2. Dead space ventilation increased when pulmonary blood flow is interrupted in the presence of normal ventilation. This is sometimes referred to as "wasted ventilation." This is most often caused by a blood clot (pulmonary embolus) obstructing blood flow in a region of the pulmonary circulation. The embolus halts blood to pulmonary areas with normal ventilation ($\dot{V}/\dot{Q} = \infty$). In this situation, the ventilation is wasted because it fails to oxygenate any of the mixed venous blood, and that region becomes physiologic dead space. The remaining perfused regions of the lung receive all of the blood flow (regional perfusion is increased) and normal ventilation (regional ventilation is unchanged.) As a result, there is relative "hypoventilation" as the $\dot{V}/\dot{Q}$ ratio is decreased. If compensation does not occur, P_{aCO_2} increases and P_{aO_2} decreases. Compensation after a pulmonary embolus, however, begins almost immediately; local bronchoconstriction occurs, and the distribution of ventilation

shifts to the areas being perfused. As a result, changes in arterial CO_2 and O_2 content are minimized.

Effect of 100% Oxygen on Arterial Blood Gas Abnormalities

One of the ways that a right-to-left shunt can be distinguished from other causes of hypoxemia is for the individual to breathe 100% O_2 through a nonrebreathing face mask for approximately 15 minutes. When the individual breathes 100% O_2, all of the N_2 in the alveolus is replaced by O_2. Thus the PAO_2, according to the alveolar air equation (Eq. 23.13), is calculated as follows:

Equation 23.20

$$\begin{aligned} PAO_2 &= [1.0 \times (P_b - PH_2O)] - PaCO_2/0.8 \\ &= [1.0 \times (760 - 47)] - 40/0.8 \\ &= 713 - 50 \\ &= 663 \text{ mm Hg} \end{aligned}$$

In a normal lung, the PAO_2 rapidly increases, and it provides the gradient for transfer of O_2 into capillary blood. This is associated with a marked increase in PaO_2 (see Table 23.2). Similarly, during the 15-minutes of breathing 100% O_2, even areas with very low $\dot{V}/\dot{Q}$ ratios develop high alveolar O_2 pressure as the N_2 is replaced by O_2. In the presence of normal perfusion to these areas, there is a gradient for gas exchange, and the end-capillary blood is highly enriched with O_2. In contrast, in the presence of a right-to-left shunt, oxygenation is not corrected because mixed venous blood continues to flow through the shunt and mix with blood that has perfused normal units. The poorly oxygenated blood from the shunt lowers the arterial O_2 content and maintains the $AaDO_2$. An elevated $AaDO_2$ during a properly conducted study with 100% O_2 signifies the presence of a shunt (anatomical or physiological); the magnitude of the $AaDO_2$ can be used to quantify the proportion of the cardiac output that is being shunted.

Regional Differences

The regional differences in ventilation and perfusion and the relationship between ventilation and perfusion were discussed earlier in this chapter. The effects of various physiological abnormalities (e.g., shunt, $\dot{V}/\dot{Q}$ mismatch, and hypoventilation) on arterial O_2 and CO_2 levels were also described. In addition, however, it should be noted that because the $\dot{V}/\dot{Q}$ ratio varies in different regions of the lung, the end-capillary blood coming from these regions has different O_2 and CO_2 levels. These differences are shown in Fig. 23.7, and they demonstrate the complexity of the lung. First, recall that the volume of the lung at the apex is less than the volume at the base. As previously described, ventilation and perfusion are less at the apex than at the base, but the differences in perfusion are greater than the differences in ventilation. Thus the $\dot{V}/\dot{Q}$ ratio is high at the apex and low at the base. This difference in ventilation/perfusion ratios is associated with a difference in alveolar O_2 and CO_2 content between the apex and the base. The PAO_2 is higher and the $PACO_2$ is lower in the apex than in the base. This results in differences in end-capillary contents for these gases. End-capillary PO_2 is lower, and, as a consequence, the O_2 content is lower in end-capillary blood at the lung base than at the apex. In addition, there is significant variation in blood pH in the end capillaries in these regions because of the variation in CO_2 content. During exercise, blood flow to the apex increases and becomes more uniform in the lung; as a result, the difference between the content of gases in the apex and in the base of the lung diminishes with exercise.

Key Points

1. The volume of air in the conducting airways is called the *anatomical dead space.* Dead space ventilation varies inversely with tidal volume. The total volume of gas in each breath that does not participate in gas exchange is called the *physiological dead space.* It includes both the anatomical dead space and the dead space secondary to ventilated but unperfused alveoli.
2. The sum of the partial pressures of a gas is equal to the total pressure. The partial pressure of a gas (P_{gas}) is equal to the fraction of the gas in the gas mixture (F_{gas}) multiplied by the total pressure (P_{total}). The conducting airways do not participate in gas exchange. Therefore, the partial pressures of O_2, N_2, and water vapor in humidified air remain unchanged in the airways until the gas reaches the alveolus.
3. The partial pressure of O_2 in the alveolus is given by the alveolar air equation (Eq. 23.13). This equation is used to calculate the $AaDO_2$, a useful measurement of abnormal arterial O_2.
4. The relationship between CO_2 production and alveolar ventilation is defined by the alveolar carbon dioxide equation (Eq. 23.14). There is an inverse relationship between the $PACO_2$ and V_A, regardless of the exhaled quantity of CO_2. In normal lungs, $PaCO_2$ is tightly regulated by the brainstem respiratory center to remain constant at around 40 mm Hg.
5. Because of the effects of gravity, there are regional differences in ventilation and perfusion. The ventilation/perfusion ($\dot{V}/\dot{Q}$) ratio is defined as the ratio of ventilation to blood flow. In a normal lung, the overall ventilation/perfusion ratio is approximately 0.8. When ventilation exceeds perfusion, the ventilation/perfusion ratio is greater than 1 ($\dot{V}/\dot{Q} > 1$), and when perfusion exceeds ventilation, the ventilation/perfusion ratio is less than 1 ($\dot{V}/\dot{Q} < 1$). The $\dot{V}/\dot{Q}$ ratio at the apex of the lung is high (ventilation is increased in relation to very little blood flow), whereas the $\dot{V}/\dot{Q}$ ratio at the base of the lung is

low. In individuals with normal lungs who are breathing room air, the $AaDo_2$ is less than 15 mm Hg; the upper limit of normal is 25 mm Hg.

6. The pulmonary circulation is a low-pressure, low-resistance system. Recruitment of new capillaries and dilation of arterioles without an increase in pressure are unique features of the lung and allow for adjustments during stress, as in the case of exercise. Pulmonary vascular resistance is the change in pressure from the pulmonary artery (P_{PA}) to the left atrium (P_{LA}), divided by cardiac output (Q_T). This resistance is about 10 times less than in the systemic circulation.
7. There are four categories of hypoxia (hypoxic hypoxia, anemic hypoxia, diffusion hypoxia, and histotoxic hypoxia) and six mechanisms of hypoxic hypoxia and hypoxemia (anatomical shunt, physiological shunt, decreased Fio_2, $\dot{\mathbf{V}}/\dot{\mathbf{Q}}$ mismatching, diffusion abnormalities, and hypoventilation.)
8. There are two mechanisms of the development of hypercapnia: increase in dead space ventilation and hypoventilation.