CHAPTER

23

Respiratory Physiology & Anesthesia

KEY CONCEPTS

1. The trachea serves as a conduit for ventilation and the clearance of tracheal and bronchial secretions and has an average length of 10–13 cm. The trachea bifurcates at the carina into the right and left main stem bronchi. The right main stem bronchus lies in a more vertical orientation relative to the trachea, whereas the left main stem bronchus lies in a more horizontal orientation.
2. The periodic exchange of alveolar gas with the fresh gas from the upper airway reoxygenates desaturated blood and eliminates CO_2. This exchange is brought about by small cyclic pressure gradients established within the airways. During spontaneous ventilation, these gradients are secondary to variations in intrathoracic pressure; during mechanical ventilation, they are produced by intermittent positive pressure in the upper airway.
3. The lung volume at the end of a normal exhalation is called functional residual capacity (FRC). At this volume, the inward elastic recoil of the lung approximates the outward elastic recoil of the chest (including resting diaphragmatic tone).
4. Closing capacity is normally well below FRC, but it rises steadily with age. This increase is probably responsible for the normal age-related decline in arterial O_2 tension.
5. Whereas both forced expiratory volume in 1 sec (FEV_1) and forced vital capacity (FVC) are effort dependent, forced midexpiratory flow ($FEF_{25–75\%}$) is more effort independent and may be a more reliable measure of obstruction.
6. Changes in lung mechanics due to general anesthesia occur shortly after induction. The supine position reduces the FRC by 0.8–1.0 L, and induction of general anesthesia further reduces the FRC by 0.4–0.5 L. FRC reduction is a consequence of alveolar collapse and compression atelectasis due to loss of inspiratory muscle tone, change in chest wall rigidity, and upward shift of the diaphragm.
7. Local factors are more important than the autonomic system in influencing pulmonary vascular tone. Hypoxia is a powerful stimulus for pulmonary vasoconstriction (the opposite of its systemic effect).
8. Because alveolar ventilation ($\dot{V}_A$) is normally about 4 L/min and pulmonary capillary perfusion ($\dot{Q}$) is 5 L/min, the overall $\dot{V}/\dot{Q}$ ratio is about 0.8.
9. Shunting denotes the process whereby desaturated, mixed venous blood from the right heart returns to the left heart without being resaturated with O_2 in the lungs. The overall effect of shunting is to decrease (dilute) arterial O_2 content; this type of shunt is referred to as right-to-left.

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10. General anesthesia commonly increases venous admixture to 5% to 10%, probably as a result of atelectasis and airway collapse in dependent areas of the lung.
11. Note that large increases in $Paco_2$ (>75 mm Hg) readily produce hypoxia (Pao_2 <60 mm Hg) at room air, but not at high inspired O_2 concentrations.
12. The binding of O_2 to hemoglobin seems to be the principal rate-limiting factor in the transfer of O_2 from alveolar gas to blood.
13. The greater the shunt, the less likely the possibility that an increase in the fraction of inspired oxygen (FIO_2) will prevent hypoxemia.
14. A rightward shift in the oxygen–hemoglobin dissociation curve lowers O_2 affinity, displaces O_2 from hemoglobin, and makes more O_2 available to tissues; a leftward shift increases hemoglobin's affinity for O_2, reducing its availability to tissues.
15. Bicarbonate represents the largest fraction of CO_2 in blood.
16. Central chemoreceptors are thought to lie on the anterolateral surface of the medulla and respond primarily to changes in cerebrospinal fluid (CSF) $[H^+]$. This mechanism is effective in regulating $Paco_2$, because the blood–brain barrier is permeable to dissolved CO_2 but not to bicarbonate ions.
17. With increasing depth of anesthesia, the slope of the $Paco_2$/minute ventilation curve decreases, and the apneic threshold increases.

The importance of pulmonary physiology to anesthetic practice is obvious. The most commonly used anesthetics—the inhalation agents—depend on the lungs for uptake and elimination. The most important side effects of both inhalation and intravenously administered anesthetics are primarily respiratory. Moreover, muscle paralysis, unusual positioning during surgery, and techniques such as one-lung anesthesia and cardiopulmonary bypass profoundly alter normal pulmonary physiology.

Much of modern anesthetic practice is based on a thorough understanding of pulmonary physiology and may be considered applied pulmonary physiology. This chapter reviews the basic pulmonary concepts necessary for understanding and applying anesthetic techniques. Although the pulmonary effects of each of the various anesthetic agents are discussed elsewhere in the book, this chapter also reviews the overall effects of general anesthesia on lung function.

FUNCTIONAL RESPIRATORY ANATOMY

1. Rib Cage & Muscles of Respiration

The rib cage contains the two lungs, each surrounded by its own pleura. The apex of the chest is small, allowing only for entry of the trachea, esophagus, and blood vessels, whereas the base is formed by the diaphragm. Contraction of the diaphragm—the principal pulmonary muscle—causes the base of the thoracic cavity to descend 1.5–7 cm and its contents (the lungs) to expand. Diaphragmatic movement normally accounts for 75% of the change in chest volume. Accessory respiratory muscles also increase chest volume (and lung expansion) by their action on the ribs. Each rib (except for the last two) articulates posteriorly with a vertebra and is angulated downward as it attaches anteriorly to the sternum. Upward and outward rib movement expands the chest.

During normal breathing, the diaphragm, and, to a lesser extent, the external intercostal muscles are responsible for inspiration; expiration is generally passive. With increasing effort, the sternocleidomastoid, scalene, and pectoralis muscles can be recruited during inspiration. The sternocleidomastoid muscles assist in elevating the rib cage, whereas the scalene muscles prevent inward displacement of the upper ribs during inspiration. The pectoralis muscles can assist chest expansion when the arms are placed on a fixed support. Expiration is normally passive in the supine position, but becomes active in the upright position and with increased effort. Exhalation may be facilitated by the abdominal muscles (rectus abdominis, external and internal oblique, and transversus) and perhaps the internal intercostal muscles—aiding the downward movement of the ribs.

Although not usually considered respiratory muscles, some pharyngeal muscles are important in maintaining the patency of the airway. Tonic and reflex inspiratory activity in the genioglossus keeps the tongue away from the posterior pharyngeal wall. Tonic activity in the levator palati, tensor palati, palatopharyngeus, and palatoglossus prevents the soft palate from falling back against the posterior pharynx, particularly in the supine position.

2. Tracheobronchial Tree

1 The trachea serves as a conduit for ventilation and the clearance of tracheal and bronchial secretions. The trachea begins at the lower border of the cricoid cartilage and extends to the level of the carina and has an average length of 10–13 cm. It is composed of C-shaped cartilaginous rings, which form the anterior and lateral walls of the trachea and are connected posteriorly by the membranous wall of the trachea. The external diameters of the trachea measure approximately 2.3 cm coronally and 1.8 cm sagitally in men, with corresponding values of 2.0 cm and 1.4 cm, respectively, in women. The cricoid cartilage is the narrowest part of the trachea, with an average diameter of 17 mm in men and 13 mm in women.

The trachea bifurcates at the carina into the right and left main stem bronchi. The tracheal lumen narrows slightly as it progresses toward the carina, with the tracheal bifurcation located at the level of the sternal angle. The right main stem bronchus lies in a more vertical orientation relative to the trachea, whereas the left main stem bronchus lies in a more horizontal orientation. The right main stem bronchus continues as the bronchus intermedius after the take-off of the right upper lobe bronchus. The distance from the tracheal carina to the take-off of the right upper lobe bronchus is an average of 2.0 cm in men and approximately 1.5 cm in women. One in every 250 individuals in the general population may have an abnormal take-off of the right upper lobe bronchus emerging from above the tracheal carina on the right side. The left main stem bronchus is longer than the right main stem bronchus and measures an average of 5.0 cm in men and 4.5 cm in women. The left main stem bronchus divides into the left upper lobe bronchus and the left lower lobe bronchus.

Humidification and filtering of inspired air are functions of the upper airway (nose, mouth, and pharynx). The function of the tracheobronchial tree is to conduct gas flow to and from the alveoli. Dichotomous division (each branch dividing into two smaller branches), starting with the trachea and ending in alveolar sacs, is estimated to involve 23 divisions, or generations (**Figure 23–1**). With each generation, the number of airways is approximately doubled. Each alveolar sac contains, on average, 17 alveoli. An estimated 300 million alveoli provide an enormous membrane (50–100 m^2) for gas exchange in the average adult.

With each successive division, the mucosal epithelium and supporting structures of the airways gradually change. The mucosa makes a gradual transition from ciliated columnar to cuboidal and finally to flat alveolar epithelium. Gas exchange can occur only across the flat epithelium, which begins to appear on respiratory bronchioles (generations 17–19). The wall of the airway gradually loses its cartilaginous support (at the bronchioles) and then its smooth muscle. Loss of cartilaginous support causes the patency of smaller airways to become dependent on radial traction by the elastic recoil of the surrounding tissue; as a corollary, airway diameter becomes dependent on total lung volume.

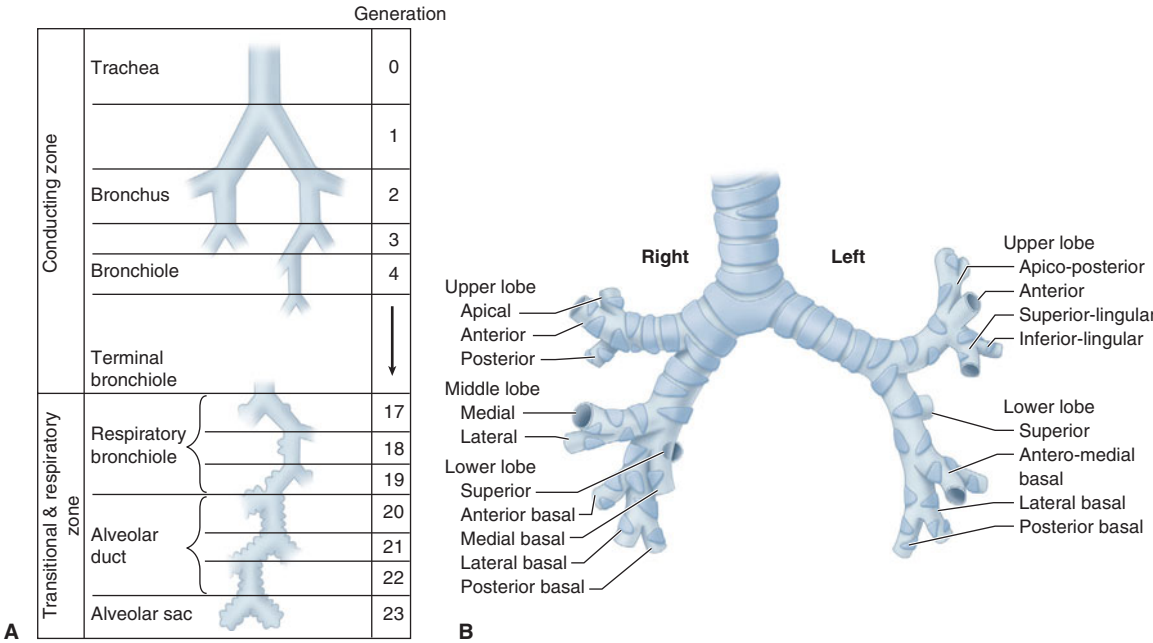

FIGURE 23–1 **A**: Dichotomous division of the airways. (Reproduced, with permission, from Guyton AC: *Textbook of Medical Physiology*, 7th ed. W.B. Saunders, 1986.) **B**: The segmental bronchi. (Reproduced, with permission, from Minnich DJ, Mathisen DJ: Anatomy of the trachea, carina, and bronchi. Thorac Surg Clin 2007 Nov;17(4):571-585.)

Cilia on the columnar and cuboidal epithelium normally beat in a synchronized fashion, such that the mucus produced by the secretory glands lining the airway (and any associated bacteria or debris) moves up toward the mouth.

Alveoli

Alveolar size is a function of both gravity and lung volume. The average diameter of an alveolus is thought to be 0.05–0.33 mm. In the upright position, the largest alveoli are at the pulmonary apex, whereas the smallest tend to be at the base. With inspiration, discrepancies in alveolar size diminish.

Each alveolus is in close contact with a network of pulmonary capillaries. The walls of each alveolus are asymmetrically arranged (**Figure 23–2**). On the thin side, where gas exchange occurs, the alveolar epithelium and capillary endothelium are separated only by their respective cellular and basement membranes; on the thick side, where fluid and solute exchange occurs, the pulmonary interstitial space separates alveolar epithelium from capillary endothelium. The pulmonary interstitial space contains mainly elastin, collagen, and perhaps nerve fibers. Gas exchange occurs primarily on the thin side of the alveolocapillary membrane, which is less than 0.4 μm thick. The thick side (1–2 μm) provides structural support for the alveolus.

The pulmonary epithelium contains at least two cell types. Type I pneumocytes are flat and form tight (1-nm) junctions with one another. These tight junctions are important in preventing the passage of large oncotically active molecules such as albumin into the alveolus. Type II pneumocytes, which are more numerous than type I pneumocytes (but because of their shape occupy less than 10% of the alveolar space), are round cells that contain prominent cytoplasmic inclusions (lamellar bodies). These inclusions contain surfactant, an important substance necessary for normal pulmonary mechanics (see below). Unlike type I cells, type II pneumocytes are capable of cell division and can produce type I

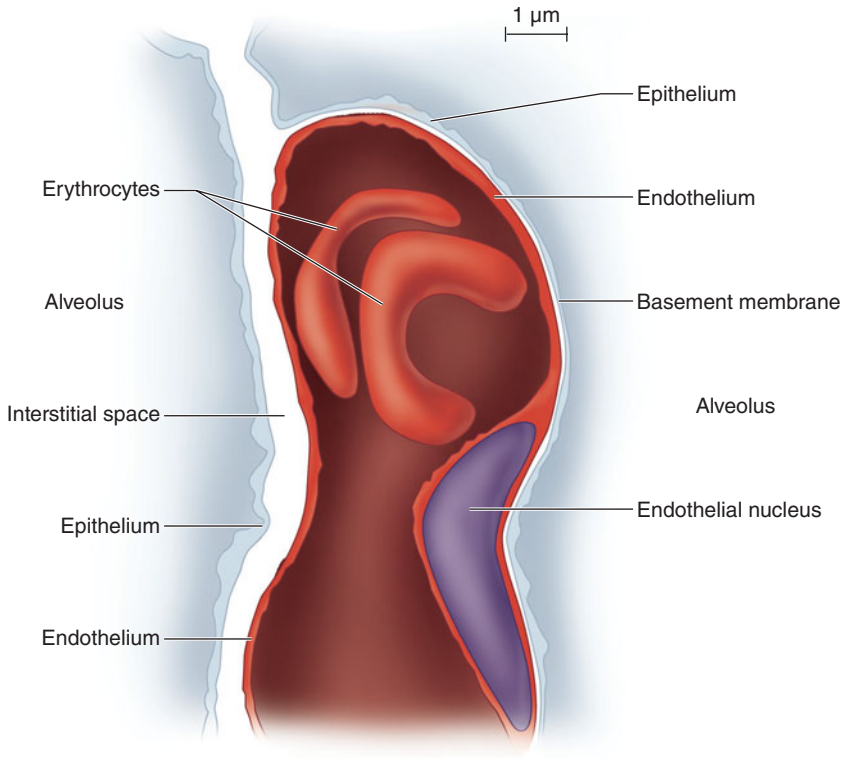

FIGURE 23–2 The pulmonary interstitial space, with a capillary passing between the two alveoli. The capillary is incorporated into the thin (gas-exchanging) side of the alveolus on the right. The interstitial space is incorporated into the thick side of the alveolus on the left. (Reproduced, with permission, from Nunn JF: *Nunn's Applied Physiology*, 4th ed. Butterworth, 2000.)

pneumocytes if the latter are destroyed. They are also resistant to O_2 toxicity.

Other cell types present in the lower airways include pulmonary alveolar macrophages, mast cells, lymphocytes, and amino precursor uptake and decarboxylation (APUD) cells. Neutrophils are also typically present in smokers and patients with acute lung injury.

3. Pulmonary Circulation & Lymphatics

The lungs are supplied by two circulations, pulmonary and bronchial. The bronchial circulation arises from the left heart and sustains the metabolic needs of the tracheobronchial tree. The bronchial circulation provides a small amount of blood flow (ie, less than 4% of the cardiac output). Branches of the bronchial artery supply the wall of the bronchi and follow the airways as far as the terminal bronchioles. Along their courses, the bronchial vessels anastomose with the pulmonary arterial circulation and continue as far as the alveolar duct. Below that level, lung tissue is supported by a combination of the alveolar gas and pulmonary circulation. Except for the main bronchi within the mediastinum, almost all the blood carried by the bronchial arteries enters the pulmonary circulation.

The pulmonary circulation normally receives the total output of the right heart via the pulmonary artery, which divides into right and left branches to supply each lung. Deoxygenated blood passes

through the pulmonary capillaries, where O_2 is taken up and CO_2 is eliminated. The oxygenated blood is then returned to the left heart by four main pulmonary veins (two from each lung). Although flows through the systemic and pulmonary circulations are equal, the lower pulmonary vascular resistance results in pulmonary vascular pressures that are one-sixth of those in the systemic circulation; as a result, both pulmonary arteries and veins normally have thinner walls than systemic vessels with less smooth muscle.

There are connections between the bronchial and the pulmonary circulations. Direct pulmonary arteriovenous communications, bypassing the pulmonary capillaries, are normally insignificant but may become important in certain pathological states. The importance of the bronchial circulation in contributing to the normal venous admixture is discussed below.

Pulmonary Capillaries

Pulmonary capillaries are incorporated into the walls of alveoli. The average diameter of these capillaries (about 10 μm) is barely enough to allow passage of a single red cell. Because each capillary network supplies more than one alveolus, blood may pass through several alveoli before reaching the pulmonary veins. Because of the relatively low pressure in the pulmonary circulation, the amount of blood flowing through a given capillary network is affected by both gravity and alveolar size. Large alveoli have a smaller capillary cross-sectional area and consequently increased resistance to blood flow. In the upright position, apical capillaries tend to have reduced flows, whereas basal capillaries have higher flows.

The pulmonary capillary endothelium has relatively large junctions (5 nm wide), allowing the passage of large molecules such as albumin. As a result, pulmonary interstitial fluid is relatively rich in albumin. Circulating macrophages and neutrophils are able to pass through the endothelium, as well as the smaller alveolar epithelial junctions, with relative ease. Pulmonary macrophages are commonly seen in the interstitial space and inside alveoli; they serve to prevent bacterial infection and to scavenge foreign particles.

Pulmonary Lymphatics

Lymphatic channels in the lung originate in the interstitial spaces of large septa and are close to the bronchial arteries. Bronchial lymphatics return fluids, lost proteins, and various cells that have escaped in the peribronchovascular interstitium into the blood circulation, thus ensuring homeostasis and permitting lung function. Because of the large endothelial junctions, pulmonary lymph has a relatively high protein content, and total pulmonary lymph flow may be as much as 20 mL/hr. Large lymphatic vessels travel upward alongside the airways, forming the tracheobronchial chain of lymph nodes. Lymphatic drainage channels from both lungs communicate along the trachea.

4. Innervation

The diaphragm is innervated by the phrenic nerves, which arise from the C3–C5 nerve roots. Unilateral phrenic nerve block or palsy only modestly reduces most indices of pulmonary function (about 25%) in normal subjects. Although bilateral phrenic nerve palsies produce more severe impairment, accessory muscle activity may maintain adequate ventilation in some patients. Intercostal muscles are innervated by their respective thoracic nerve roots. Cervical cord injuries above C5 are incompatible with spontaneous ventilation because both phrenic and intercostal nerves are affected.

The vagus nerves provide sensory innervation to the tracheobronchial tree. Both sympathetic and parasympathetic autonomic innervation of bronchial smooth muscle and secretory glands is present. Vagal activity mediates bronchoconstriction and increases bronchial secretions via muscarinic receptors. Sympathetic activity (T1–T4) mediates bronchodilation and also decreases secretions via β_2-receptors. The nerve supply of the larynx is reviewed in Chapter 19.

Both α- and β-adrenergic receptors are present in the pulmonary vasculature, but the sympathetic system normally has little effect on pulmonary vascular tone. α_1-Activity causes vasoconstriction; β_2-activity mediates vasodilation. Parasympathetic vasodilatory activity seems to be mediated via the release of nitric oxide.

MECHANISMS OF BREATHING

2 The periodic exchange of alveolar gas with the fresh gas from the upper airway reoxygenates desaturated blood and eliminates CO_2. This exchange is brought about by small cyclic pressure gradients established within the airways. During spontaneous ventilation, these gradients are secondary to variations in intrathoracic pressure; during mechanical ventilation, they are produced by intermittent positive pressure in the upper airway.

Spontaneous Ventilation

Normal pressure variations during spontaneous breathing are shown in Figure 23–3. The pressure within alveoli is always greater than the surrounding (intrathoracic) pressure unless the alveoli are collapsed. Alveolar pressure is normally atmospheric (zero for reference) at end-inspiration and end-expiration. By convention in pulmonary physiology, pleural pressure is used as a measure of intrathoracic pressure. Although it may not be entirely correct to refer to the pressure in a potential space, the concept allows the calculation of transpulmonary pressure. Transpulmonary pressure, or $P_{transpulmonary}$, is then defined as follows:

$$P_{transpulmonary} = P_{alveolar} - P_{intrapleural}$$

At end-expiration, intrapleural pressure normally averages about –5 cm H_2O, and because alveolar pressure is 0 (no flow), transpulmonary pressure is +5 cm H_2O.

Diaphragmatic and intercostal muscle activation during inspiration expands the chest and decreases intrapleural pressure from –5 cm H_2O to –8 or –9 cm H_2O. As a result, alveolar pressure also decreases (between –3 and –4 cm H_2O), and an alveolar–upper airway gradient is established; gas flows from the upper airway into alveoli. At end-inspiration (when gas inflow has ceased), alveolar pressure returns to zero, but intrapleural pressure remains decreased; the new transpulmonary pressure (5 cm H_2O) sustains lung expansion.

During expiration, diaphragmatic relaxation returns intrapleural pressure to –5 cm H_2O. Now the transpulmonary pressure does not support the new lung volume, and the elastic recoil of the lung causes a reversal of the previous alveolar–upper airway gradient; gas flows out of alveoli, and original lung volume is restored.

Mechanical Ventilation

Most forms of mechanical ventilation intermittently apply positive airway pressure at the upper airway. During inspiration, gas flows into alveoli until alveolar pressure reaches that in the upper airway. During the expiratory phase of the ventilator, the positive airway pressure is removed or decreased; the gradient reverses, allowing gas flow out of alveoli.

LUNG MECHANICS

The movement of the lungs is passive and determined by the impedance of the respiratory system, which can be divided into the elastic resistance of tissues and the gas–liquid interface and the nonelastic resistance to gas flow. Elastic resistance governs lung volume and the associated pressures under static conditions (no gas flow). Resistance to gas flow relates to frictional resistance to airflow and tissue deformation. The work necessary to overcome elastic resistance is stored as potential energy, but the work necessary to overcome nonelastic resistance is lost as heat.

1. Elastic Resistance

Both the lungs and the chest have elastic properties. The chest has a tendency to expand outward, whereas the lungs have a tendency to collapse. When the chest is exposed to atmospheric pressure (open pneumothorax), it usually expands about 1 L in adults. In contrast, when the lung is exposed to atmospheric pressure, it collapses completely and all the gas within it is expelled. The recoil properties of the chest are due to structural components that resist deformation and chest wall muscle tone. The elastic recoil of the lungs is due to their high content of elastin fibers, and, even more important, the surface tension forces acting at the air–fluid interface in alveoli.

Surface Tension Forces

The gas–fluid interface lining the alveoli causes them to behave as bubbles. Surface tension forces tend to

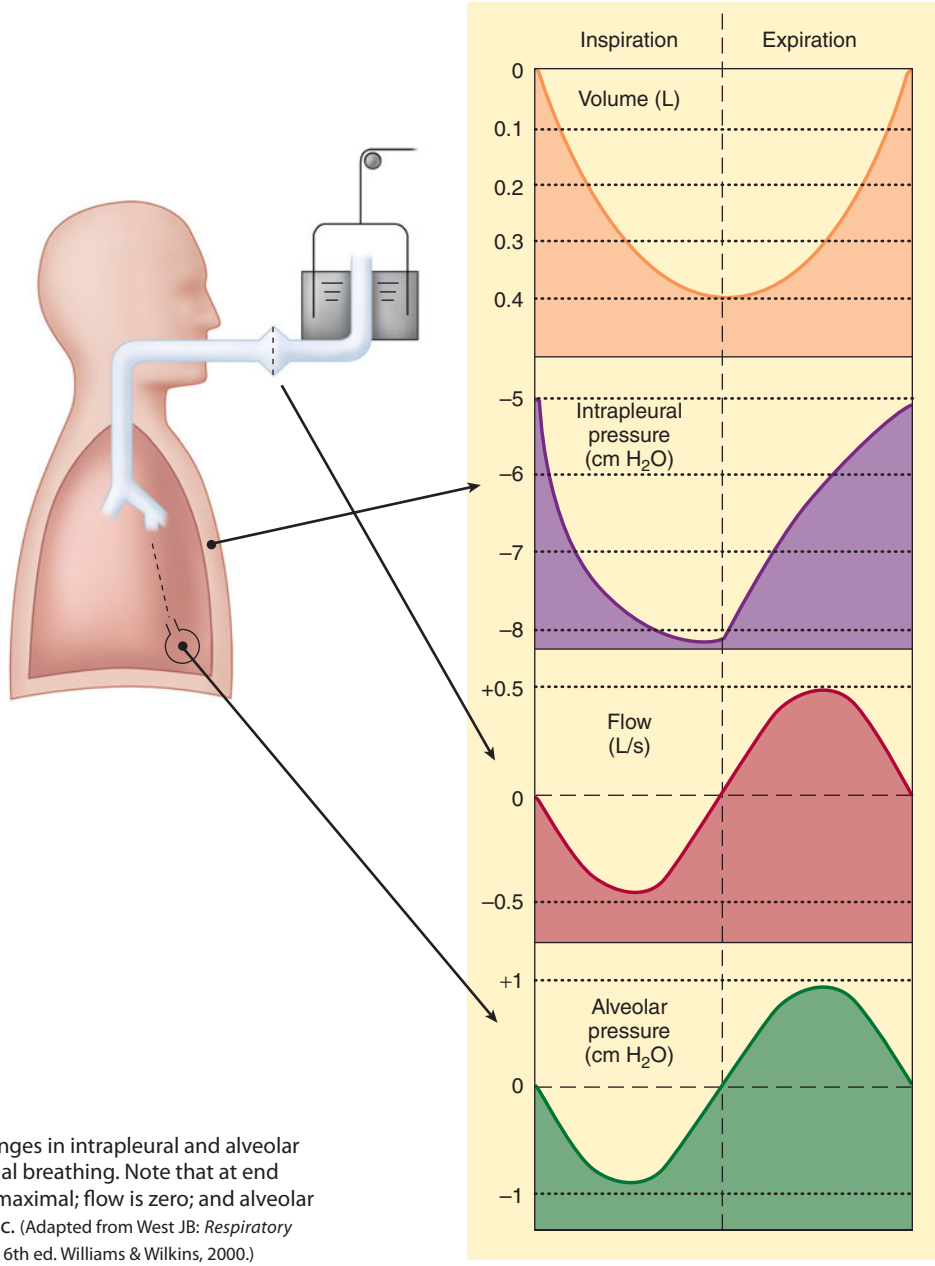

FIGURE 23–3 Changes in intrapleural and alveolar pressures during normal breathing. Note that at end inspiration, volume is maximal; flow is zero; and alveolar pressure is atmospheric. (Adapted from West JB: *Respiratory Physiology—The Essentials*, 6th ed. Williams & Wilkins, 2000.)

reduce the area of the interface and favor alveolar collapse. Laplace's law can be used to quantify these forces:

$$\text{Pressure} = \frac{2 \times \text{Surface tension}}{\text{Radius}}$$

The pressure derived from the equation is that within the alveolus. Alveolar collapse is therefore directly proportional to surface tension. **Fortunately, in contrast to a bubble, pulmonary surfactant decreases alveolar surface tension**. Moreover, the

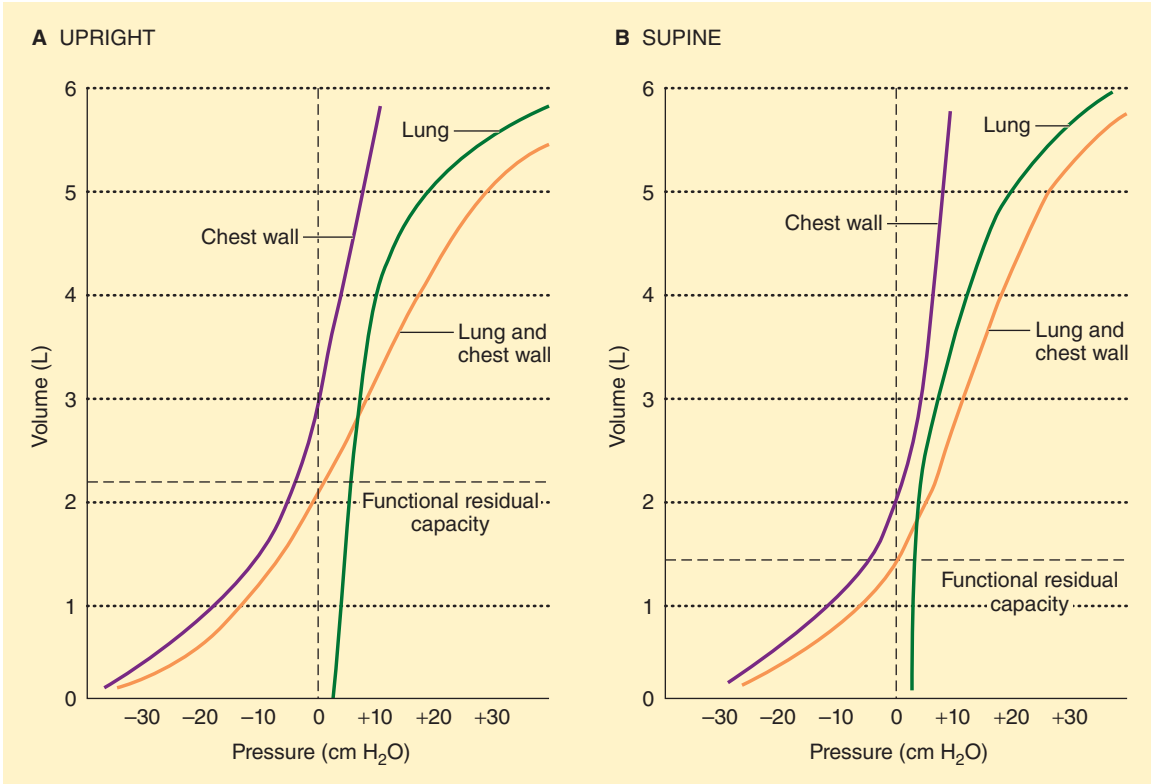

FIGURE 23–4 The pressure–volume relationship for the chest wall, lung, and both together in the upright (**A**) and supine (**B**) positions. (Modified and reproduced, with permission, from Scurr C, Feldman S: *Scientific Foundations of Anesthesia*. Heinemann, 1982.)

ability of the surfactant to lower surface tension is directly proportional to its concentration within the alveolus, resulting in lower intraalveolar pressure in smaller alveoli. As alveoli become smaller, the surfactant within becomes more concentrated, and surface tension is more effectively reduced. Conversely, when alveoli are overdistended, surfactant becomes less concentrated, and surface tension increases. The net effect is to stabilize alveoli; small alveoli are prevented from getting smaller, whereas large alveoli are prevented from getting larger.

Compliance

Elastic recoil is usually measured in terms of compliance (C), which is defined as the change in volume divided by the change in distending pressure. Compliance measurements can be obtained for either the chest, the lung, or both together (Figure 23–4). In the supine position, chest wall compliance (Cw) is reduced because of the weight of the abdominal contents against the diaphragm. Measurements are usually obtained under static conditions, (ie, at equilibrium). (Dynamic lung compliance [Cdyn,L], which is measured during rhythmic breathing, is also dependent on airway resistance.) **Lung compliance (CL)** is defined as

$$C_L = \frac{\text{Change in lung volume}}{\text{Change in transpulmonary pressure}}$$

CL is normally 150–200 mL/cm H_2O. A variety of factors, including lung volume, pulmonary blood volume, extravascular lung water, and pathological processes (eg, inflammation and fibrosis) affect CL

$$\text{Chest wall compliance (Cw)} = \frac{\text{Change in chest volume}}{\text{Change in transthoracic pressure}}$$

where transthoracic pressure equals atmospheric pressure minus intrapleural pressure.

Normal chest wall compliance is 200 mL/cm H_2O. Total compliance (lung and chest wall together) is 100 mL/cm H_2O and is expressed by the following equation:

$$\frac{1}{C_{total}} = \frac{1}{Cw} + \frac{1}{C_L}$$

2. Lung Volumes

Lung volumes are important parameters in respiratory physiology and clinical practice (Table 23–1 and Figure 23–5). The sum of all of the named lung volumes equals the maximum to which the lung can be inflated. Lung capacities are clinically useful measurements that represent a combination of two or more volumes.

TABLE 23–1 Lung volumes and capacities.

Measurement	Definition	Average Adult Values (mL)
Tidal volume (V_T)	Each normal breath	500
Inspiratory reserve volume (IRV)	Maximal additional volume that can be inspired above V_T	3000
Expiratory reserve volume (ERV)	Maximal volume that can be expired below V_T	1100
Residual volume (RV)	Volume remaining after maximal exhalation	1200
Total lung capacity (TLC)	RV + ERV + V_T + IRV	5800
Functional residual capacity (FRC)	RV + ERV	2300

Functional Residual Capacity

3 The lung volume at the end of a normal exhalation is called functional residual capacity (FRC). At this volume, the inward elastic recoil of the lung approximates the outward elastic recoil of the chest (including resting diaphragmatic tone). Thus, the elastic properties of both chest and lung define the point from which normal breathing takes place. Functional residual capacity can be measured by nitrogen washout or helium washin technique or

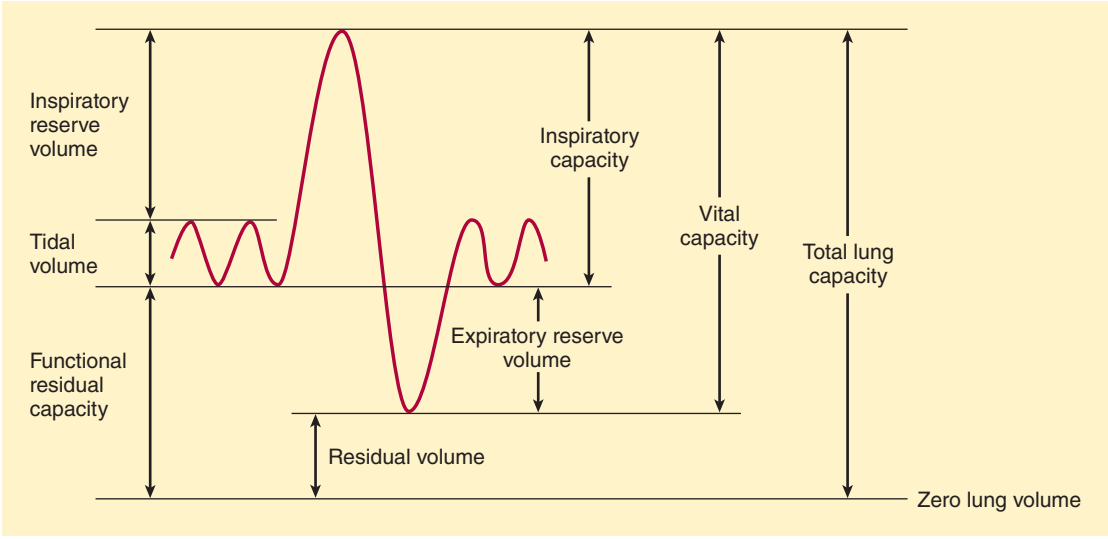

FIGURE 23–5 Spirogram showing static lung volumes. (Reproduced, with permission, from Nunn JF: *Nunn's Applied Physiology*, 4th ed. Butterworth, 2000.)

by body plethysmography. Factors known to alter the FRC include the following:

- **Body habitus:** FRC is directly proportional to height. Obesity, however, can markedly decrease FRC (primarily as a result of reduced chest compliance).
- **Sex:** FRC is reduced by about 10% in females compared with males.
- **Posture:** FRC decreases as a patient is moved from an upright to a supine or prone position. This is the result of reduced chest compliance as the abdominal contents push up against the diaphragm. The greatest change occurs between 0° and 60° of inclination. No further decrease is observed with a head-down position of up to 30°.
- **Lung disease:** Decreased compliance of the lung, chest, or both is characteristic of restrictive pulmonary disorders all of which are associated with a low FRC.
- **Diaphragmatic tone:** This normally contributes to FRC.

Closing Capacity

As described above (see the section on Functional Respiratory Anatomy), small airways lacking cartilaginous support depend on radial traction caused by the elastic recoil of surrounding tissue to keep them open; patency of these airways, particularly in basal areas of the lung, is highly dependent on lung volume. The volume at which these airways begin to close in dependent areas of the lung is called the **closing capacity**. At lower lung volumes, alveoli in dependent areas continue to be perfused but are no longer ventilated; **intrapulmonary shunting** of deoxygenated blood promotes hypoxemia (see below).

Closing capacity is usually measured using a tracer gas (xenon-133), which is inhaled near residual volume and then exhaled from total lung capacity.

4 Closing capacity is normally well below FRC (Figure 23–6), but rises steadily with age (Figure 23–7). This increase is probably responsible for the normal age-related decline in arterial O_2 tension. At an average age of 44 years, closing capacity

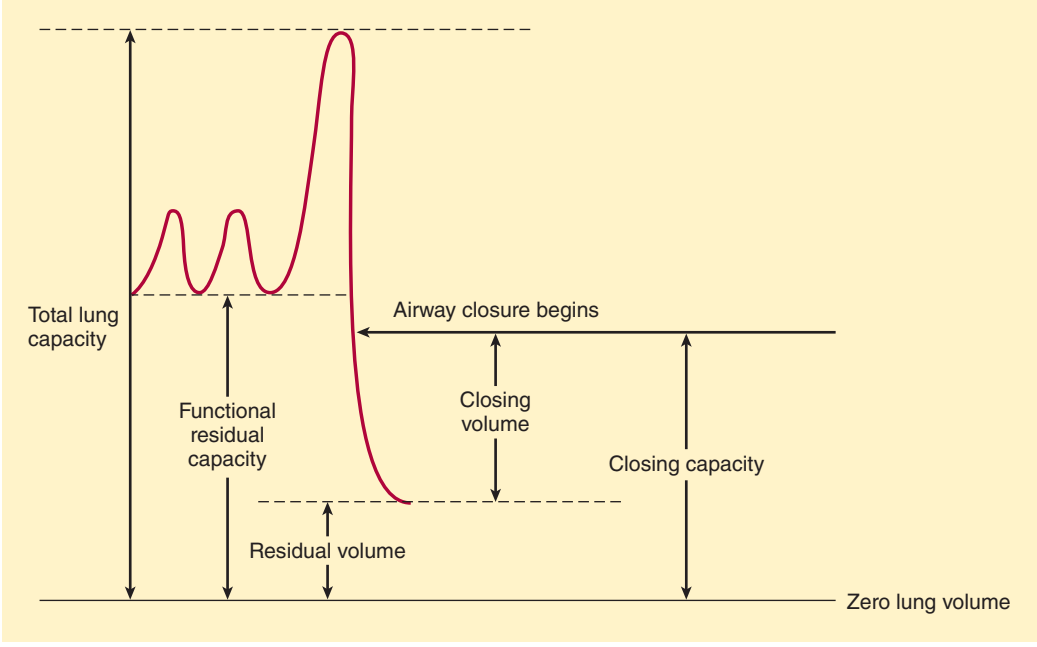

FIGURE 23–6 The relationship between functional residual capacity, closing volume, and closing capacity. (Reproduced, with permission, from Nunn JF: *Nunn's Applied Physiology*, 4th ed. Butterworth, 2000.)

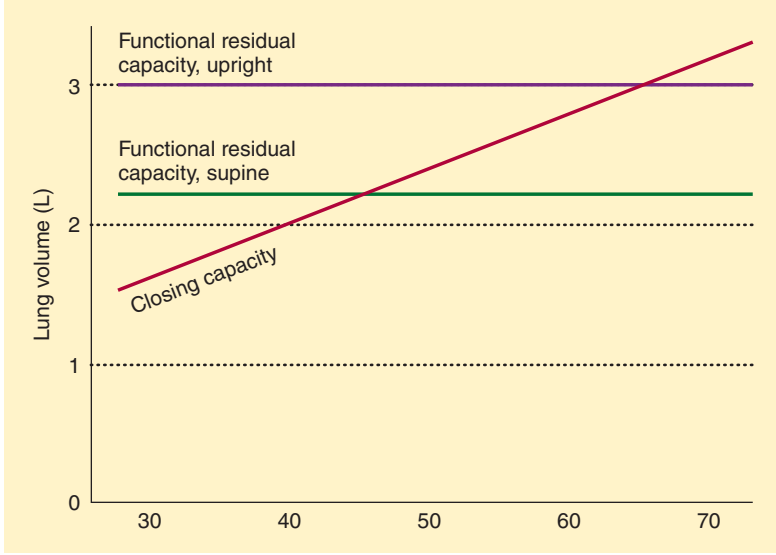

FIGURE 23–7 The effect of age on closing capacity and its relationship to functional residual capacity (FRC). Note that FRC does not change. (Reproduced, with permission, from Nunn JF: *Nunn's Applied Physiology*, 4th ed. Butterworth, 2000.)

equals FRC in the supine position; by age 66, closing capacity equals or exceeds FRC in the upright position in most individuals. Unlike FRC, closing capacity is unaffected by posture.

Vital Capacity

Vital capacity (VC) is the maximum volume of gas that can be exhaled following maximal inspiration. In addition to body habitus, VC is also dependent on respiratory muscle strength and chest–lung compliance. Normal VC is about 60–70 mL/kg.

3. Nonelastic Resistances

Airway Resistance to Gas Flow

Gas flow in the lung is a mixture of laminar and turbulent flow. Laminar flow can be thought of as consisting of concentric cylinders of gas flowing at different velocities; velocity is highest in the center and decreases toward the periphery. During laminar flow,

$$\text{Flow} = \frac{\text{Pressure gradient}}{R_{aw}}$$

where R_{aw} is airway resistance.

$$R_{aw} = \frac{8 \times \text{Length} \times \text{Gas viscosity}}{\pi \times (\text{Radius})^4}$$

Turbulent flow is characterized by random movement of the gas molecules down the air passages. Mathematical description of turbulent flow is considerably more complex:

$$\text{Pressure gradient} \approx \text{Flow}^2 \times \frac{\text{Gas density}}{\text{Radius}^5}$$

Resistance is not constant but increases in proportion to gas flow. Moreover, resistance is directly proportional to gas density and inversely proportional to the fifth power of the radius. As a result, turbulent gas flow is extremely sensitive to airway caliber.

Turbulence generally occurs at high gas flows, at sharp angles or branching points, and in response to abrupt changes in airway diameter. Whether turbulent or laminar flow occurs can be predicted by the Reynolds number, which results from the following equation:

$$\text{Reynolds number} = \frac{\text{Linear velocity} \times \text{Diameter} \times \text{Gas density}}{\text{Gas viscosity}}$$

A low Reynolds number (<1000) is associated with laminar flow, whereas a high value (>1500) produces turbulent flow. Laminar flow normally occurs only distal to small bronchioles (<1 mm). Flow in larger airways is probably turbulent. Of the

TABLE 23–2 Physical properties of several gas mixtures.[1]

Mixture	Viscosity[2]	Density[2]	Density/Viscosity[2]
Oxygen (100%)	1.11	1.11	1.00
N_2O/O_2	0.89	1.41	1.49
Helium/O_2 (80:20)	1.08	0.33	0.31

[1]Data from Nunn JF: *Nunn's Applied Physiology*, 4th ed. Butterworth, 2000.

[2]Viscosities and densities are expressed relative to air.

gases used clinically, only helium has a significantly lower density-to-viscosity ratio, making it useful clinically during severe turbulent flow (as caused by upper airway obstruction). A helium–O_2 mixture not only is less likely to cause turbulent flow but also reduces airway resistance when turbulent flow is present (Table 23–2).

Normal total airway resistance is about 0.5–2 cm H_2O/L/sec, with the largest contribution coming from medium-sized bronchi (before the seventh generation). Resistance in large bronchi is low because of their large diameters, whereas resistance in small bronchi is low because of their large total cross-sectional area. The most important causes of increased airway resistance include bronchospasm, secretions, and mucosal edema as well as volume-related and flow-related airway collapse.

A. Volume-Related Airway Collapse

At low lung volumes, loss of radial traction increases the contribution of small airways to total resistance; airway resistance becomes inversely proportional to lung volume (Figure 23–8). Increasing lung volume up to normal with positive end-expiratory pressure (PEEP) can reduce airway resistance.

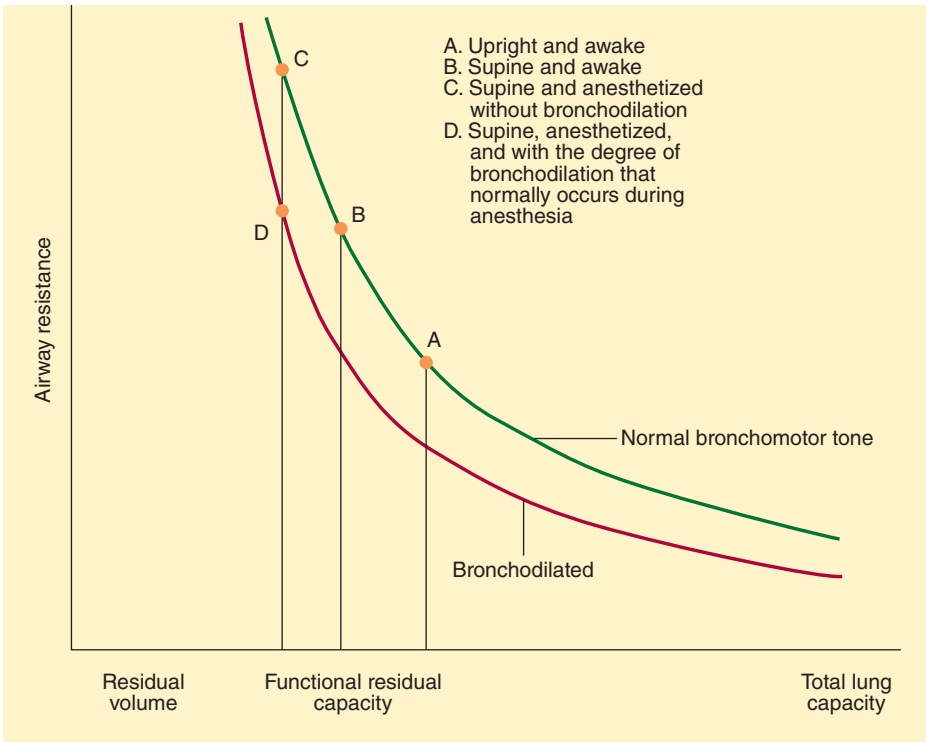

FIGURE 23–8 The relationship between airway resistance and lung volume. (Reproduced, with permission, from Nunn JF: *Nunn's Applied Physiology*, 4th ed. Butterworth, 2000.)

B. Flow-Related Airway Collapse

During forced exhalation, reversal of the normal transmural airway pressure can cause collapse of these airways (dynamic airway compression). Two contributing factors are responsible: generation of a positive pleural pressure and a large pressure drop across intrathoracic airways as a result of increased airway resistance. The latter is in turn due to high (turbulent) gas flow and the reduced lung volume. The terminal portion of the flow/volume curve is therefore considered to be effort independent (Figure 23–9).

The point along the airways where dynamic compression occurs is called the equal pressure point. It is normally beyond the eleventh to thirteenth generation of bronchioles where cartilaginous support is

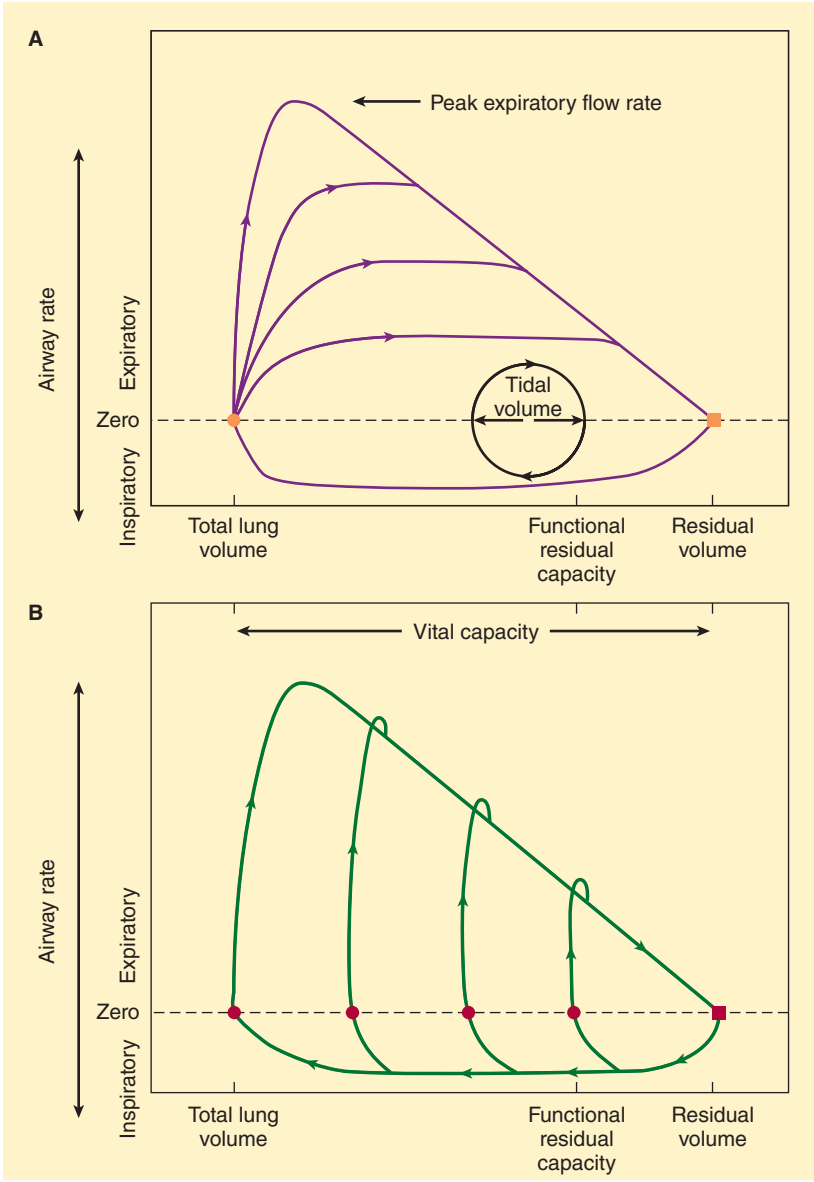

FIGURE 23–9 Gas flow (**A**) during forced exhalation from total lung capacity with varying effort and (**B**) with maximal effort from different lung volumes. Note that regardless of initial lung volume or effort, terminal expiratory flows are effort independent. (Reproduced, with permission, from Nunn JF: *Nunn's Applied Physiology*, 4th ed. Butterworth, 2000.)

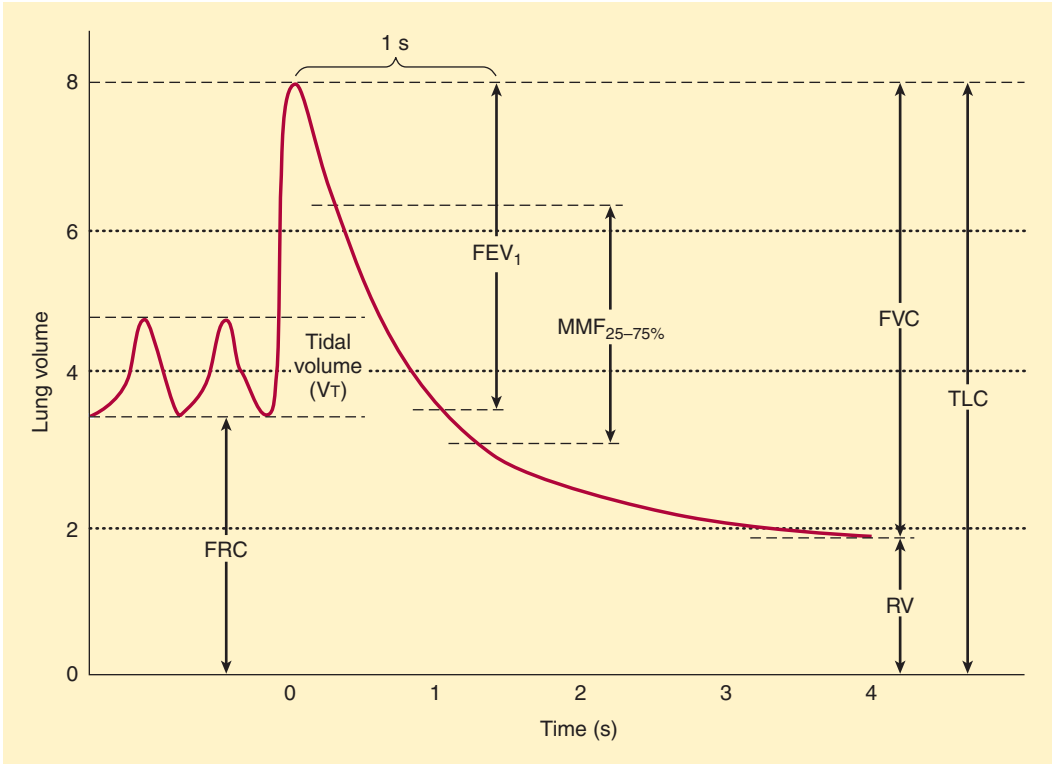

FIGURE 23–10 The normal forced exhalation curve. $FEF_{25–75\%}$ is also called the maximum midexpiratory flow rate ($MMF_{25–75\%}$). FRC, functional residual capacity; FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.

absent (see above). The equal pressure point moves toward smaller airways as lung volume decreases. Emphysema or asthma predisposes patients to dynamic airway compression. Emphysema destroys the elastic tissues that normally support smaller airways. In patients with asthma, bronchoconstriction and mucosal edema intensify airway collapse and promote reversal of transmural pressure gradients across airways. Patients may terminate exhalation prematurely or purse their lips to increase expiratory resistance at the mouth. Premature termination of exhalation may increase FRC above normal, resulting in air trapping and auto-PEEP.

C. Forced Vital Capacity

Measuring vital capacity as an exhalation that is as forceful and rapid as possible (Figure 23–10) provides important information about airway resistance. The ratio of the forced expiratory volume in the first second of exhalation (FEV_1) to the total forced vital capacity (FVC) is proportional to the degree of airway obstruction. Normally, FEV_1/FVC is ≥80%. Whereas both FEV_1 and FVC are effort dependent, forced midexpiratory flow ($FEF_{25–75\%}$) is more effort independent and may be a more reliable measurement of obstruction.

Tissue Resistance

This component of nonelastic resistance is generally underestimated and often overlooked, but may account for up to half of total airway resistance. It seems to be primarily due to viscoelastic (frictional) resistance of tissues to gas flow.

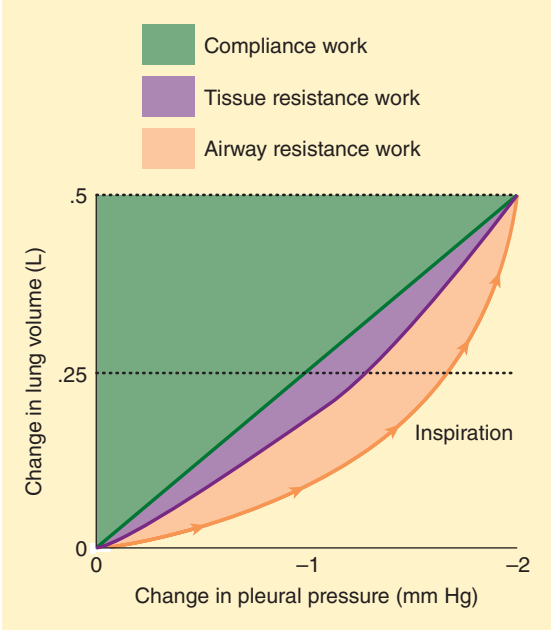

FIGURE 23–11 The work of breathing and its components during inspiration. (Reproduced, with permission, from Guyton AC: *Textbook of Medical Physiology*, 7th ed. W.B. Saunders, 1986.)

4. Work of Breathing

Because expiration is normally entirely passive, both the inspiratory and the expiratory work of breathing is performed by the inspiratory muscles (primarily the diaphragm). Three factors must be overcome during ventilation: the elastic recoil of the chest and lung, frictional resistance to gas flow in the airways, and tissue frictional resistance.

Respiratory work can be expressed as the product of volume and pressure (Figure 23–11). During inhalation, both inspiratory airway resistance and pulmonary elastic recoil must be overcome; nearly 50% of the energy expended is stored pulmonary elastic recoil. During exhalation, the stored potential energy is released and overcomes expiratory airway resistance. Increases in either inspiratory or expiratory resistance are compensated by increased inspiratory muscle effort. When expiratory resistance increases, the normal compensatory response is to increase lung volume such that VT breathing occurs at an abnormally high FRC. The greater elastic recoil energy stored at a higher lung volume overcomes the added expiratory resistance. Excessive amounts of expiratory resistance also activate expiratory muscles (see above).

Respiratory muscles normally account for only 2% to 3% of O_2 consumption but operate at about 10% efficiency. Ninety percent of the work is dissipated as heat (due to elastic and airflow resistance). In pathological conditions that increase the load on the diaphragm, muscle efficiency usually progressively decreases, and contraction may become uncoordinated with increasing ventilatory effort; moreover, a point may be reached whereby any increase in O_2 uptake (because of augmented ventilation) is consumed by the respiratory muscles themselves.

The work required to overcome elastic resistance increases as VT increases, whereas the work required to overcome airflow resistance increases as respiratory rate (and, necessarily, expiratory flow) increases. Faced with either condition, patients minimize the work of breathing by altering the respiratory rate and VT (Figure 23–12). **Patients with reduced compliance tend to have rapid, shallow breaths, whereas those with increased airflow resistance have a slow, deep breathing pattern**.

5. Effects of Anesthesia on Pulmonary Mechanics

The effects of anesthesia on breathing are complex and relate to changes both in position and anesthetic agent.

Effects on Lung Volumes & Compliance

6 Changes in lung mechanics due to general anesthesia occur shortly after induction. The supine position reduces the FRC by 0.8–1.0 L, and induction of general anesthesia further reduces the FRC by 0.4–0.5 L. FRC reduction is a consequence of alveolar collapse and compression atelectasis due to loss of inspiratory muscle tone, change in chest wall rigidity, and upward shift of the diaphragm. The mechanisms may be more complex; for example, only the dependent (dorsal) part of the diaphragm in the supine position moves cephalad. Other factors are likely due to a change in intrathoracic volume secondary to increased blood volume in the lung and changes in

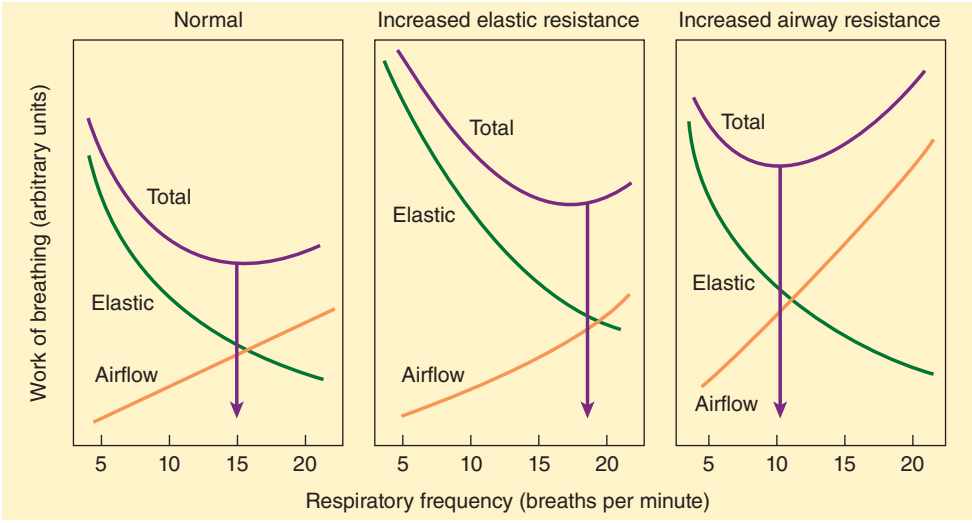

FIGURE 23–12 The work of breathing in relation to respiratory rate for normal individuals, patients with increased elastic resistance, and patients with increased airway resistance. (Reproduced, with permission, from Nunn JF: *Nunn's Applied Physiology*, 4th ed. Butterworth, 2000.)

chest wall shape (Figure 23–13). The higher position of the dorsal diaphragm and changes in the thoracic cavity itself decrease lung volumes. This decrease in FRC is not related to anesthetic depth and may persist for several hours or days after anesthesia. Steep head-down (Trendelenburg) position (>30°) may reduce FRC even further as intrathoracic blood volume increases. In contrast, induction of anesthesia in the sitting position seems to have little effect on FRC. Muscle paralysis does not seem to change FRC significantly when the patient is already anesthetized.

The effects of anesthesia on closing capacity are more variable. Both FRC and closing capacity, however, are generally reduced to the same extent under anesthesia. Thus, the risk of increased intrapulmonary shunting under anesthesia is similar to that in the conscious state; it is greatest in the elderly, in obese patients, and in those with underlying pulmonary disease.

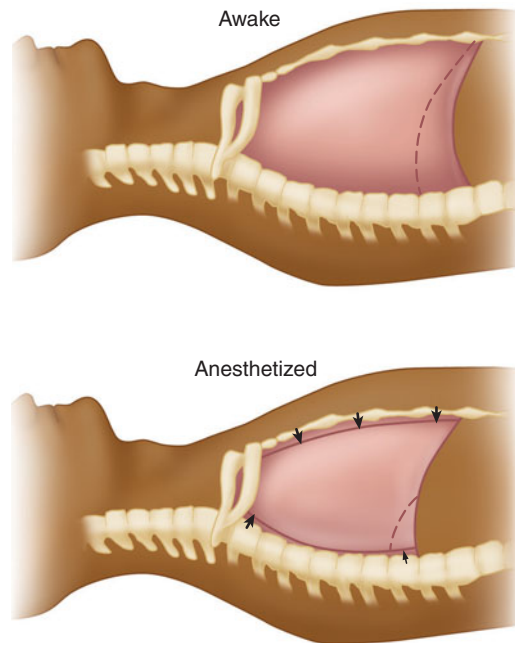

FIGURE 23–13 With induction of anesthesia in the supine position, the abdominal contents exert cephalad pressure on the diaphragm. At end-expiration, the dorsal portion of the diaphragm is more cephalad and the ventral portion is more caudal than when awake, the thoracic spine is more lordotic, and the rib cage moves inward, all secondary to loss of motor tone.

Effects on Airway Resistance

The reduction in FRC associated with general anesthesia would be expected to increase airway resistance. Increases in airway resistance are not usually observed, however, because of the bronchodilating properties of the volatile inhalation anesthetics.

Increased airway resistance is more commonly due to pathological factors (posterior displacement of the tongue; laryngospasm; bronchoconstriction; or secretions, blood, or tumor in the airway) or equipment problems (small tracheal tubes or connectors, malfunction of valves, or obstruction of the breathing circuit).

Effects on the Work of Breathing

Increases in the work of breathing under anesthesia are most often secondary to reduced lung and chest wall compliance, and, less commonly, increases in airway resistance (see above). The problems of increased work of breathing are usually circumvented by controlled mechanical ventilation.

Effects on the Respiratory Pattern

Regardless of the agent used, light anesthesia often results in irregular breathing patterns; breath holding is common. Breaths become regular with deeper levels of anesthesia. Inhalation agents generally produce rapid, shallow breaths, whereas nitrous–opioid techniques result in slow, deep breaths.

VENTILATION/PERFUSION RELATIONSHIPS

1. Ventilation

Ventilation is usually measured as the sum of all exhaled gas volumes in 1 min (minute ventilation, or $\dot{V}$).

$$\text{Minute ventilation} = \text{Respiratory rate} \times \text{Tidal volume}$$

For the average adult at rest, minute ventilation is about 5 L/min.

Not all of the inspired gas mixture reaches alveoli; some of it remains in the airways and is exhaled without being exchanged with alveolar gases. The part of the V_T not participating in alveolar gas exchange is known as dead space (V_D). Alveolar ventilation ($\dot{V}_A$) is the volume of inspired gases actually taking part in gas exchange in 1 min.

$$\dot{V}_A = \text{Respiratory rate} \times V_T - V_D$$

Dead space is actually composed of gases in nonrespiratory airways **(anatomic dead space)** and alveoli that are not perfused **(alveolar dead space)**. The sum of the two components is referred to as **physiological dead space**. In the upright position, dead space is normally about 150 mL for most adults (approximately 2 mL/kg) and is nearly all anatomic. The weight of an individual in pounds is roughly equivalent to dead space in milliliters. Dead space can be affected by a variety of factors (Table 23–3).

TABLE 23–3 Factors affecting dead space.

Factor	Effect
Posture	
Upright	↑
Supine	↓
Position of airway	
Neck extension	↑
Neck flexion	↓
Age	↑
Artificial airway	↓
Positive-pressure ventilation	↑
Drugs—anticholinergic	↑
Pulmonary perfusion	
Pulmonary emboli	↑
Hypotension	↑
Pulmonary vascular disease	
Emphysema	↑

Because V_T in the average adult is approximately 450 mL (6 mL/kg), V_D/V_T is normally 33%. This ratio can be derived by the Bohr equation:

$$\frac{V_D}{V_T} = \frac{P_{ACO_2} - P_{ECO_2}}{P_{ACO_2}}$$

where P_{ACO_2} is the alveolar CO_2 tension and P_{ECO_2} is the mixed expired CO_2 tension. This equation is useful clinically if arterial CO_2 tension (P_{aCO_2}) is used to approximate the alveolar concentration and the CO_2 tension in expired air gases is the average measured over several minutes.

Distribution of Ventilation

Regardless of body position, alveolar ventilation is unevenly distributed in the lungs. The right lung receives more ventilation than the left lung

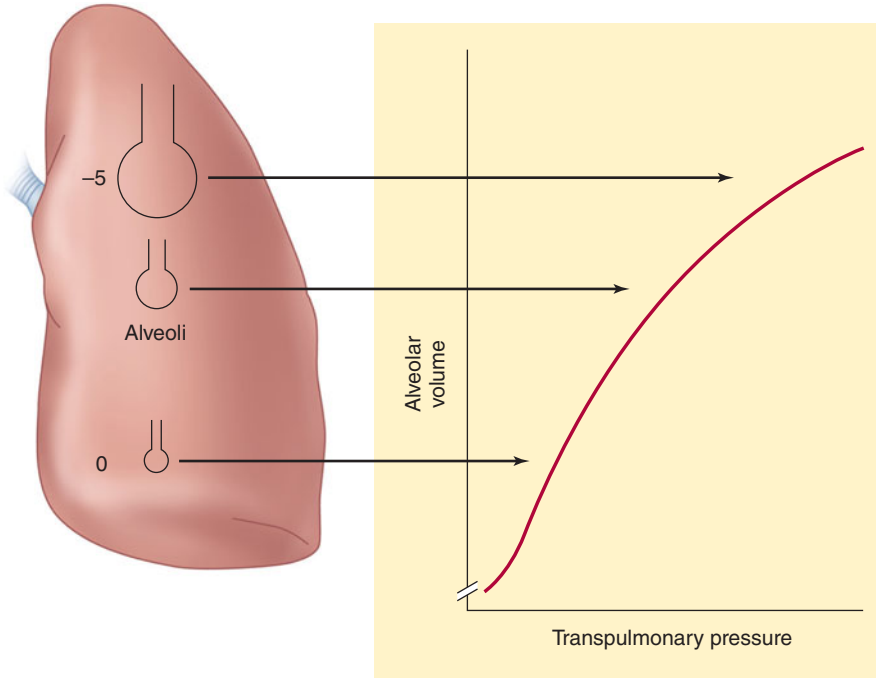

FIGURE 23–14 The effect of gravity on alveolar compliance in the upright position.

(53% vs 47%), and the lower (dependent) areas of both lungs tend to be better ventilated than do the upper areas because of a gravitationally induced gradient in intrapleural pressure (transpulmonary pressure). Pleural pressure decreases about 1 cm H_2O (becomes less negative) per 3-cm decrease in lung height. This difference places alveoli from different areas at different points on the pulmonary compliance curve (Figure 23–14). Because of a higher transpulmonary pressure, alveoli in upper lung areas are near-maximally inflated and relatively noncompliant, and they undergo little expansion during inspiration. In contrast, the smaller alveoli in dependent areas have a lower transpulmonary pressure, are more compliant, and undergo greater expansion during inspiration.

Airway resistance can also contribute to regional differences in pulmonary ventilation. Final alveolar inspiratory volume is solely dependent on compliance only if inspiratory time is unlimited. In reality, inspiratory time is necessarily limited by the respiratory rate and the time necessary for expiration; consequently, an excessively short inspiratory time will prevent alveoli from reaching the expected change in volume. Moreover, alveolar filling follows an exponential function that is dependent on both compliance and airway resistance. Therefore, even with a normal inspiratory time, abnormalities in either compliance or resistance can prevent complete alveolar filling.

Time Constants

Lung inflation can be described mathematically by the time constant, τ.

$$\tau = \text{Total compliance} \times \text{Airway resistance}$$

Regional variations in resistance or compliance not only interfere with alveolar filling but can cause asynchrony in alveolar filling during inspiration; some alveolar units may continue to fill as others empty.

Variations in time constants within the normal lung can be demonstrated in normal individuals breathing spontaneously during abnormally high respiratory rates. Rapid shallow breathing reverses

the normal distribution of ventilation, preferentially favoring upper (nondependent) areas of the lung over the lower areas.

2. Pulmonary Perfusion

Of the approximately 5 L/min of blood flowing through the lungs, only about 70–100 mL at any one time are within the pulmonary capillaries undergoing gas exchange. At the alveolar–capillary membrane, this small volume forms a 50–100 m^2-sheet of blood approximately one red cell thick. Moreover, to ensure optimal gas exchange, each capillary perfuses more than one alveolus.

Although capillary volume remains relatively constant, total pulmonary blood volume can vary between 500 mL and 1000 mL. Large increases in either cardiac output or blood volume are tolerated with little change in pressure as a result of passive dilation of open vessels and perhaps some recruitment of collapsed pulmonary vessels. Small increases in pulmonary blood volume normally occur during cardiac systole and with each normal (spontaneous) inspiration. A shift in posture from supine to erect decreases pulmonary blood volume (up to 27%); Trendelenburg positioning has the opposite effect. Changes in systemic capacitance also influence pulmonary blood volume: systemic venoconstriction shifts blood from the systemic to the pulmonary circulation, whereas vasodilation causes a pulmonary-to-systemic redistribution. In this way, the lung acts as a reservoir for the systemic circulation.

7 Local factors are more important than the autonomic system in influencing pulmonary vascular tone (above). Hypoxia is a powerful stimulus for pulmonary vasoconstriction (the opposite of its systemic effect). Both pulmonary arterial (mixed venous) and alveolar hypoxia induce vasoconstriction, but the latter is a more powerful stimulus. This response seems to be due to either the direct effect of hypoxia on the pulmonary vasculature or increased production of leukotrienes relative to vasodilatory prostaglandins. Inhibition of nitric oxide production may also play a role. Hypoxic pulmonary vasoconstriction is an important physiological mechanism in reducing intrapulmonary shunting and preventing hypoxemia (see below). Hyperoxia has little effect on the pulmonary circulation in normal individuals. Hypercapnia and acidosis have a constrictor effect, whereas hypocapnia causes pulmonary vasodilation, the opposite of what occurs in the systemic circulation.

Distribution of Pulmonary Perfusion

Pulmonary blood flow is also not uniform. Regardless of body position, lower (dependent) areas of the lung receive greater blood flow than upper (nondependent) areas. This pattern is the result of a gravitational gradient of 1 cm H_2O/cm lung height. The normally low pressures in the pulmonary circulation allow gravity to exert a significant influence on blood flow. Also, in vivo perfusion scanning in normal individuals has shown an "onion-like" layering distribution of perfusion, with reduced flow at the periphery of the lung and increased perfusion toward the hilum.

Although the pulmonary perfusion pressure is not uniform across the lung, the alveolar distending pressure is relatively constant. The interplay of these pressures results in the dividing of the lung into four distinct zones (ie, the West Zones) (**Figure 23–15**). In zone 1 (P_A > Pa > Pv), alveolar pressure (P_A) is greater than both the arterial pulmonary pressure (Pa) and venous pulmonary pressure (Pv), resulting in obstruction of blood flow and creation of alveolar dead space. Zone 1 is fairly small in a spontaneously breathing individual, but can enlarge during positive pressure ventilation. In lower areas of the lungs, Pa progressively increases due to lower elevation above the heart. In zone 2 (Pa > P_A > Pv), Pa is higher than P_A, but Pv remains lower than both, resulting in blood flow that is dependent on the differential between Pa and P_A. The bulk of the lung is described by zone 3 (Pa > Pv > P_A), where both Pa and Pv are higher than P_A, resulting in blood flow independent of the alveolar pressure. Zone 4, the most dependent part of the lung, is where atelectasis and/or interstitial pulmonary edema occur, resulting in blood flow that is dependent on the differential between Pa and pulmonary interstitial pressure.

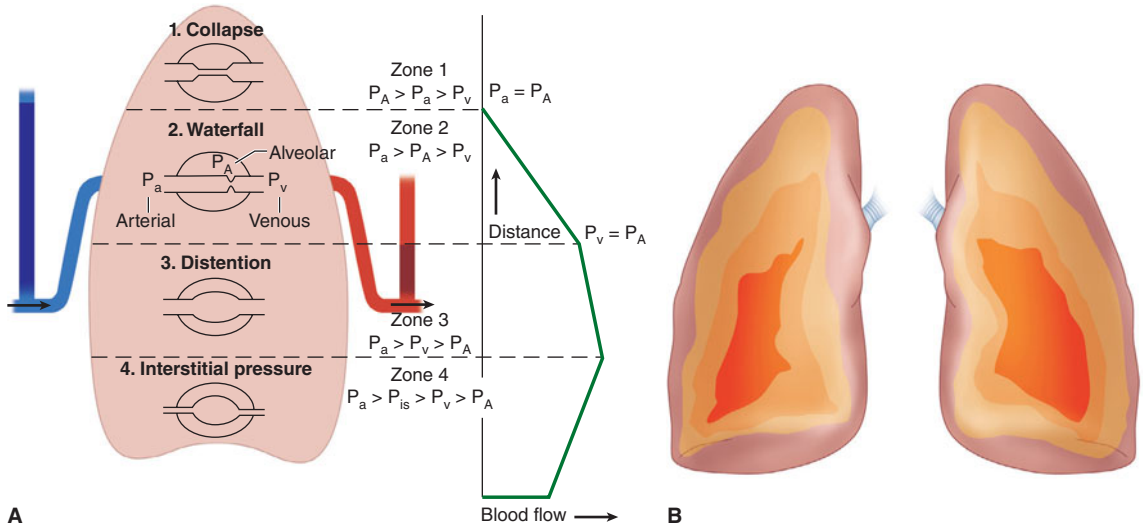

FIGURE 23–15 Pulmonary blood flow distribution relative to the alveolar pressure (P_A), the pulmonary arterial pressure (P_a), the pulmonary venous pressure (P_V), and the interstitial pressure (P_{IS}) at various gravitation levels. **A**: Classic West Zones of blood flow distribution in the upright position. (Modified and reproduced, with permission, from West JB: *Respiratory Physiology: The Essentials*, 6th edition. Williams and Wilkins, 2000. p. 37.). **B**: In vivo perfusion scanning illustrating central-to-peripheral, in addition to gravitational blood flow distribution, in the upright position. (Reproduced, with permission, from Lohser J: Evidence based management of one lung ventilation. Anesthesiol Clin 2008;26:241.)

Ventilation/Perfusion Ratios

8 Because alveolar ventilation ($\dot{V}_A$) is normally about 4 L/min, and pulmonary capillary perfusion ($\dot{Q}$) is 5 L/min, the overall $\dot{V}/\dot{Q}$ ratio is about 0.8. $\dot{V}/\dot{Q}$ for individual lung units (each alveolus and its capillary) can range from 0 (no ventilation) to infinity (no perfusion); the former is referred to as intrapulmonary shunt, whereas the latter constitutes alveolar dead space. $\dot{V}/\dot{Q}$ normally ranges between 0.3 and 3.0; the majority of lung areas, however, are close to 1.0 (Figure 23–16A). Because perfusion increases at a greater rate than ventilation, nondependent (apical) areas tend to have higher $\dot{V}/\dot{Q}$ ratios than do dependent (basal) areas (Figure 23–16B).

The importance of $\dot{V}/\dot{Q}$ ratios relates to the efficiency with which lung units resaturate venous blood with O_2 and eliminate CO_2. **Pulmonary venous blood (the effluent) from areas with low $\dot{V}/\dot{Q}$ ratios has a low O_2 tension and high CO_2 tension—similar to systemic mixed venous blood.** Blood from these units tends to depress arterial O_2 tension and elevate arterial CO_2 tension. Their effect on arterial O_2 tension is much more profound than that on CO_2 tension; in fact, arterial CO_2 tension often decreases from a hypoxemia-induced reflex increase in alveolar ventilation. An appreciable compensatory increase in O_2 uptake cannot take place in remaining areas where $\dot{V}/\dot{Q}$ is normal, because pulmonary end-capillary blood is usually already maximally saturated with O_2 (see below).

3. Shunts

9 Shunting denotes the process whereby desaturated, mixed venous blood from the right heart returns to the left heart without being resaturated with O_2 in the lungs (Figure 23–17). The overall effect of shunting is to decrease (dilute) arterial O_2 content; this type of shunt is referred to as right-to-left. Left-to-right shunts (in the absence of

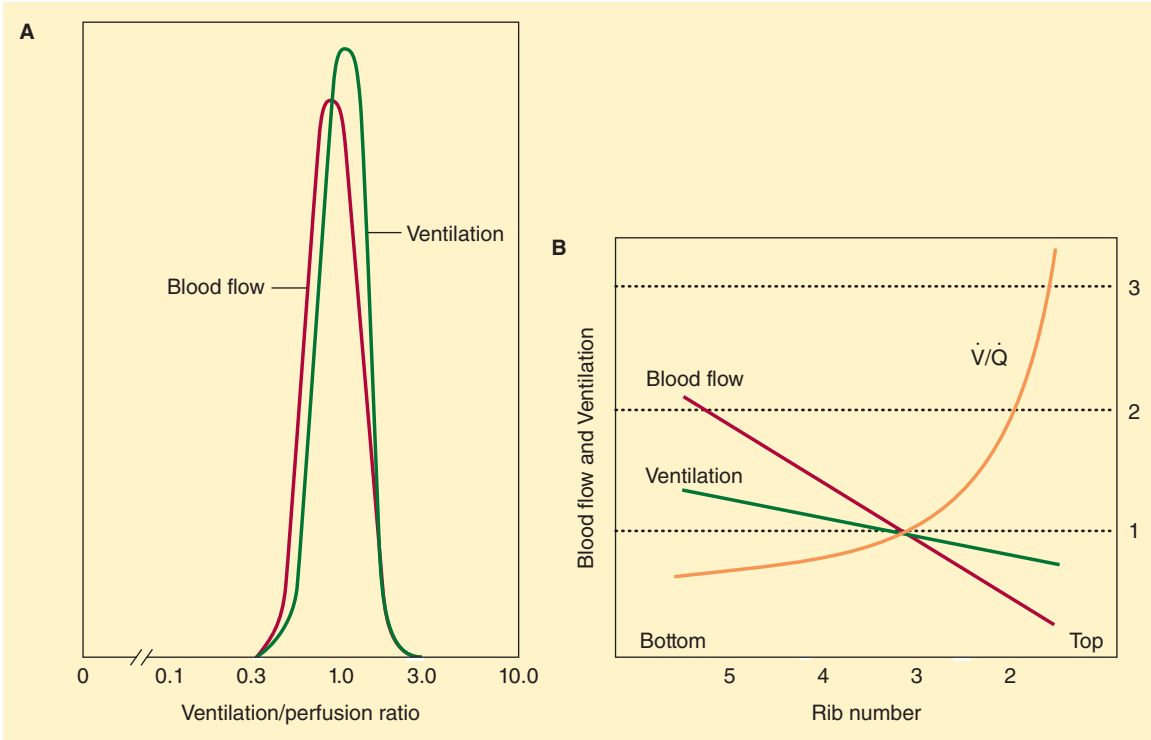

FIGURE 23–16 The distribution of $\dot{V}/\dot{Q}$ ratios for the whole lung (**A**) and according to height (**B**) in the upright position. Note that blood flow increases more rapidly than ventilation in dependent areas. (Reproduced, with permission, from West JB: *Ventilation/Blood Flow and Gas Exchange*, 3rd ed. Blackwell, 1977.)

pulmonary congestion), however, do not produce hypoxemia.

Intrapulmonary shunts are often classified as absolute or relative. Absolute shunt refers to anatomic shunts and lung units where $\dot{V}/\dot{Q}$ is zero. A relative shunt is an area of the lung with a low $\dot{V}/\dot{Q}$ ratio. Clinically, hypoxemia from a relative shunt can usually be partially corrected by increasing the inspired O_2 concentration; hypoxemia caused by an absolute shunt cannot.

Venous Admixture

Venous admixture refers to a concept rather than an actual physiological entity. **Venous admixture** is the amount of mixed venous blood that would have to be mixed with pulmonary end-capillary blood to account for the difference in O_2 tension between arterial and pulmonary end-capillary blood. Pulmonary end-capillary blood is considered to have the same concentrations as alveolar gas. Venous admixture is usually expressed as a fraction of total cardiac output ($\dot{Q}s/\dot{Q}T$). The equation for $\dot{Q}s/\dot{Q}T$ may be derived with the law for the conservation of mass for O_2 across the pulmonary bed:

$$\dot{Q}T \times Cao_2 = (\dot{Q}s \times C\bar{v}o_2) + (\dot{Q}c' \times Cc'o_2)$$

where

Qs = blood flow through the physiologic shunt compartment
QT = total cardiac output
$\dot{Q}c'$ = blood flow across normally ventilated pulmonary capillaries
$\dot{Q}T = \dot{Q}c' + \dot{Q}s$
$Cc'o_2$ = oxygen content of ideal pulmonary end-capillary blood
Cao_2 = arterial oxygen content
$C\bar{v}o_2$ = mixed venous content

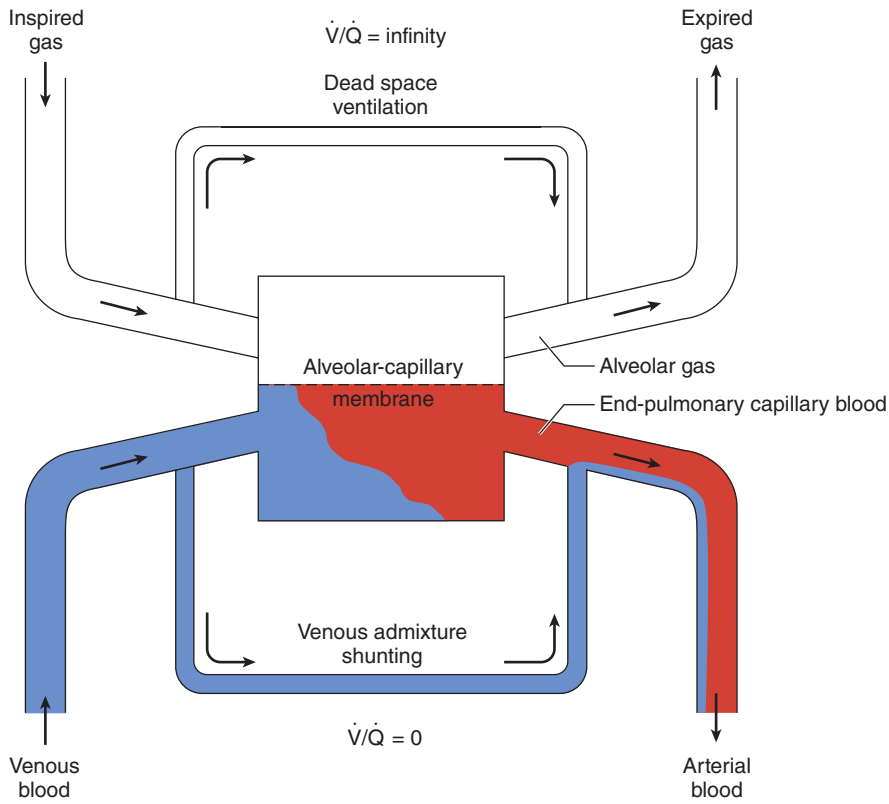

FIGURE 23–17 A three-compartment model of gas exchange in the lungs, showing dead space ventilation, normal alveolar–capillary exchange, and shunting (venous admixture). (Reproduced, with permission, from Nunn JF: *Nunn's Applied Physiology*, 4th ed. Butterworth, 2000.)

The simplified equation is

$$\dot{Q}s/\dot{Q}T = \frac{Cc'O_2 - CaO_2}{Cc'O_2 - C\bar{v}O_2}$$

The formula for calculating the O_2 content of blood is given below.

$\dot{Q}s/\dot{Q}T$ can be calculated clinically by obtaining mixed venous and arterial blood gas measurements; the former requires a pulmonary artery catheter. The alveolar gas equation is used to derive pulmonary end-capillary O_2 tension. Pulmonary capillary blood is usually assumed to be 100% saturated for an $FIO_2 \geq 0.21$.

The calculated venous admixture assumes that all shunting is intrapulmonary and due to absolute shunts ($\dot{V}/\dot{Q} = 0$). In reality, neither is ever the case; nonetheless, the concept is useful clinically. Normal $\dot{Q}s/\dot{Q}T$ is primarily due to communication between deep bronchial veins and pulmonary veins, the thebesian circulation in the heart, and areas of low $\dot{V}/\dot{Q}$ in the lungs (**Figure 23–18**). The venous admixture in normal individuals (physiological shunt) is typically less than 5%.

4. Effects of Anesthesia on Gas Exchange

Abnormalities in gas exchange during anesthesia are common. They include increased dead space, hypoventilation, and increased intrapulmonary shunting. There is increased scatter of $\dot{V}/\dot{Q}$ ratios. Increases in alveolar dead space are most commonly seen during controlled ventilation, but may also

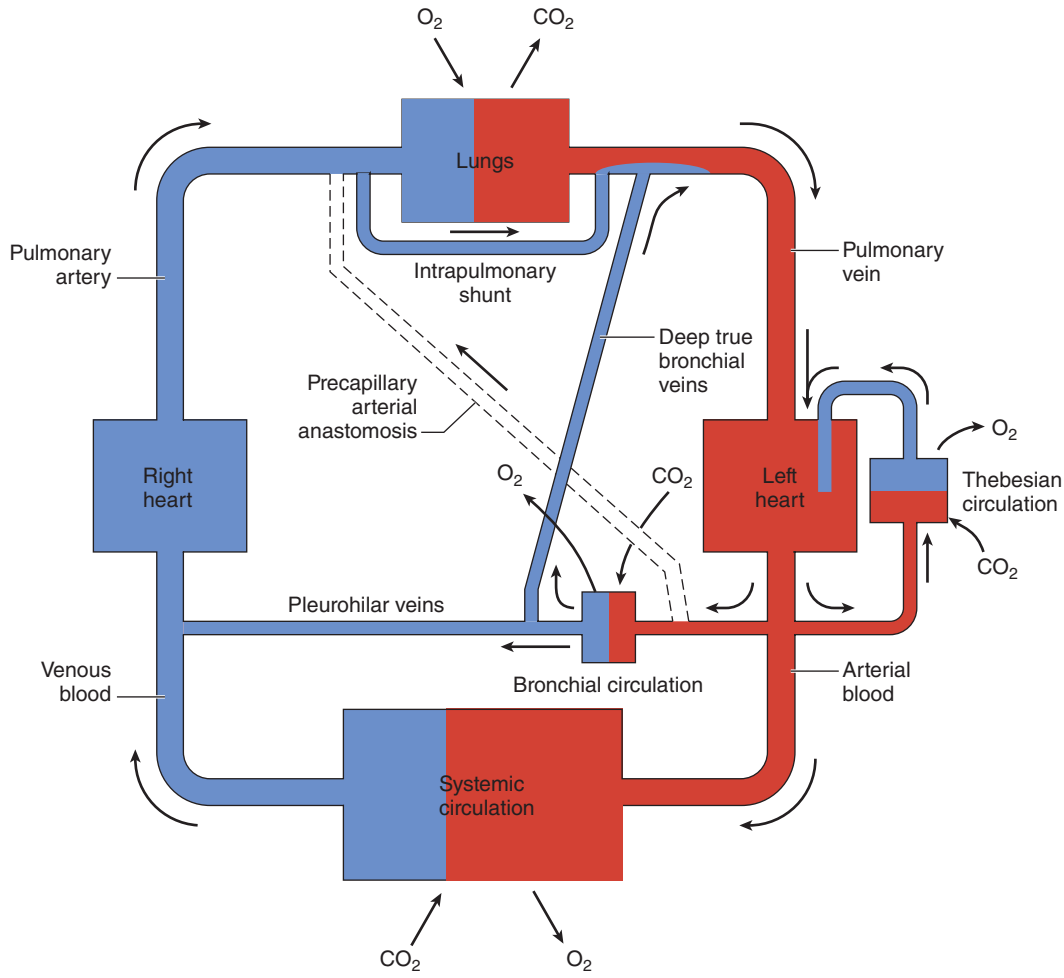

FIGURE 23–18 Components of the normal venous admixture. (Reproduced, with permission, from Nunn JF: *Nunn's Applied Physiology*, 4th ed. Butterworth, 2000.)

10 occur during spontaneous ventilation. General anesthesia commonly increases venous admixture to 5% to 10%, probably as a result of atelectasis and airway collapse in dependent areas of the lung. Inhalation agents, including nitrous oxide, also can inhibit **hypoxic pulmonary vasoconstriction** in high doses; for volatile agents, the ED_{50} is about 2 minimum alveolar concentration (MAC). Elderly patients seem to have the largest increases in $\dot{Q}s/\dot{Q}T$. Inspired O_2 tensions of 30% to 40% usually prevent hypoxemia, suggesting anesthesia increases relative shunt. PEEP is often effective in reducing venous admixture and preventing hypoxemia during general anesthesia, as long as cardiac output is maintained Prolonged administration of high inspired O_2 concentrations may be associated with atelectasis formation and increases in absolute shunt. Atelectasis in this situation is known as resorption atelectasis and appears in areas with a low $\dot{V}/\dot{Q}$ ratio ventilated at an O_2-inspired concentration close to 100%. Perfusion results in O_2 being transported out of the alveoli at a rate faster than it enters the alveoli, leading to an emptying of the alveoli and collapse.

ALVEOLAR, ARTERIAL, & VENOUS GAS TENSIONS

When dealing with gas mixtures, each gas is considered to contribute separately to total gas pressure, and its partial pressure is directly proportional to its concentration. Air has an O_2 concentration of approximately 21%; therefore, if the barometric pressure is 760 mm Hg (sea level), the partial pressure of O_2 (P_{O_2}) in air is normally 159.6 mm Hg:

$$760 \text{ mm Hg} \times 0.21 = 159.6 \text{ mm Hg}$$

In its general form, the equation may be written as follows:

$$P_{IO_2} = P_B \times F_{IO_2}$$

where P_B = barometric pressure and F_{IO_2} = the fraction of inspired O_2.

Two general rules can also be used:

- Partial pressure in millimeters of mercury approximates the percentage × 7
- Partial pressure in kilopascals is approximately the same as the percentage.

1. Oxygen

Alveolar Oxygen Tension

With every breath, the inspired gas mixture is humidified at 37°C in the upper airway. The inspired tension of O_2 (P_{IO_2}) is therefore reduced by the added water vapor. Water vapor pressure is dependent only upon temperature and is 47 mm Hg at 37°C. In humidified air, the normal partial pressure of O_2 at sea level is 149.7 mm Hg:

$$(760 - 47) \times 0.21 = 149.1 \text{ mm Hg}$$

The general equation is

$$P_{IO_2} = (P_B - P_{H_2O}) \times F_{IO_2}$$

where P_{H_2O} = the vapor pressure of water at body temperature.

In alveoli, the inspired gases are mixed with residual alveolar gas from previous breaths, O_2 is taken up, and CO_2 is added. The final alveolar O_2 tension (P_{AO_2}) is therefore dependent on all of these factors and can be estimated by the following equation:

$$P_{AO_2} = P_{IO_2} - \frac{P_{aCO_2}}{R_Q}$$

where P_{aCO_2} = arterial CO_2 tension and R_Q = respiratory quotient.

11 R_Q is usually not measured. Note that large increases in P_{aCO_2} (>75 mm Hg) readily produce hypoxia (P_{aO_2} < 60 mm Hg) at room air, but not at high inspired O_2 concentrations.

A yet simpler method of approximating P_{AO_2} in millimeters of mercury is to multiply the percentage of inspired O_2 concentration by 6. Thus, at 40%, P_{AO_2} is 6 × 40, or 240 mm Hg.

Pulmonary End-Capillary Oxygen Tension

For all practical purposes, pulmonary end-capillary O_2 tension ($P_{c'O_2}$) may be considered identical to P_{AO_2}; the P_{AO_2}–$P_{c'O_2}$ gradient is normally minute. $P_{c'O_2}$ is dependent on the rate of O_2 diffusion across the alveolar–capillary membrane, as well as on pulmonary capillary blood volume and transit time. The large capillary surface area in alveoli and the 0.4–0.5 µm thickness of the alveolar–capillary membrane greatly facilitate O_2 diffusion. Enhanced O_2 binding to hemoglobin at saturations above 80% also augments O_2 diffusion (see below). Capillary transit time can be estimated by dividing pulmonary capillary blood volume by cardiac output (pulmonary blood flow); thus, normal capillary transit time is 70 mL ÷ 5000 mL/min (0.8 s). Maximum $P_{c'O_2}$ is usually attained after only 0.3 sec, providing a large safety margin.

12 The binding of O_2 to hemoglobin seems to be the principal rate-limiting factor in the transfer of O_2 from alveolar gas to blood. Therefore, pulmonary diffusing capacity reflects not only the capacity and permeability of the alveolar–capillary membrane, but also pulmonary blood flow. Moreover, O_2 uptake is normally limited by pulmonary blood flow, not O_2 diffusion across the alveolar–capillary membrane; the latter may become significant during exercise in normal individuals at high altitudes and in patients with extensive destruction of the alveolar–capillary membrane.

O_2 transfer across the alveolar–capillary membrane is expressed as O_2 diffusing capacity (D_{LO_2}):

$$D_{LO_2} = \frac{\text{Oxygen uptake}}{P_{AO_2} - P_{c'O_2}}$$

Because $P_{c'O_2}$ cannot be measured accurately, measurement of carbon monoxide diffusion capacity (D_{LCO}) is used instead to assess gas transfer across the alveolar–capillary membrane. Because carbon monoxide has a very high affinity for hemoglobin, there is little or no CO in pulmonary capillary blood, so that even when it is administered at low concentration, $P_{c'CO}$ can be considered zero. Therefore,

$$D_{LCO} = \frac{\text{Carbon monoxide uptake}}{P_{ACO}}$$

Reductions in D_{LCO} imply an impediment in gas transfer across the alveolar–capillary membrane. Such impediments may be due to abnormal $\dot{V}/\dot{Q}$ ratios, extensive destruction of the gas alveolar–capillary membrane, or very short capillary transit times. Abnormalities are accentuated by increases in O_2 consumption and cardiac output, such as occurs during exercise.

Arterial Oxygen Tension

P_{aO_2} cannot be calculated like P_{AO_2} but must be measured at room air. The alveolar-to-arterial O_2 partial pressure gradient (A–a gradient) is normally less than 15 mm Hg, but progressively increases with age up to 20–30 mm Hg. Arterial O_2 tension can be approximated by the following formula (in mm Hg):

$$P_{aO_2} = 120 - \frac{\text{Age}}{3}$$

The range is 60–100 mm Hg (8–13 kPa). Decreases are probably the result of a progressive increase in closing capacity relative to FRC (see above). Table 23–4 lists the mechanisms of hypoxemia (P_{aO_2} <60 mm Hg).

The most common mechanism for hypoxemia is an increased alveolar–arterial gradient. The A–a gradient for O_2 depends on the amount of right-to-left shunting, the amount of $\dot{V}/\dot{Q}$ scatter, and the mixed venous O_2 tension (see below). The last

TABLE 23–4 Mechanisms of hypoxemia.

Low alveolar oxygen tension
Low inspired oxygen tension
Low fractional inspired concentration
High altitude
Alveolar hypoventilation
Diffusion hypoxia
Increased oxygen consumption
Increased alveolar–arterial gradient
Right-to-left shunting
Increased areas of low $\dot{V}/\dot{Q}$[1] ratios
Low mixed venous oxygen tension
Decreased cardiac output
Increased oxygen consumption
Decreased hemoglobin concentration

[1]$\dot{V}/\dot{Q}$, ventilation/perfusion.

depends on cardiac output, O_2 consumption, and hemoglobin concentration.

The A–a gradient for O_2 is directly proportional to shunt, but inversely proportional to mixed venous O_2 tension. The effect of each variable on P_{AO_2} (and consequently the A–a gradient) can be determined only when the other variables are held constant. Figure 23–19 shows the effect of different degrees of shunting on P_{aO_2}. It should also be noted that the greater the shunt, the less likely the possibility that an increase in F_{IO_2} will prevent hypoxemia. Moreover, isoshunt lines seem to be most useful for O_2 concentrations between 35% and 100%. Lower O_2 concentrations require modification of isoshunt lines to account for the effect of $\dot{V}/\dot{Q}$ scatter.

The effect of cardiac output on the A–a gradient (Figure 23–20) is due not only to its secondary effects on mixed venous O_2 tension but also to a direct relationship between cardiac output and intrapulmonary shunting. As can be seen, a low cardiac output tends to accentuate the effect of shunt on P_{aO_2}. A reduction in venous admixture may be observed with low-normal cardiac outputs secondary to accentuated pulmonary vasoconstriction from a lower mixed venous O_2 tension. On the other hand, high cardiac outputs can increase venous admixture by elevating mixed venous O_2 tension, which in turn inhibits hypoxic pulmonary vasoconstriction.

O_2 consumption and hemoglobin concentration can also affect P_{aO_2} through their secondary effects on mixed venous O_2 tension (below). High O_2

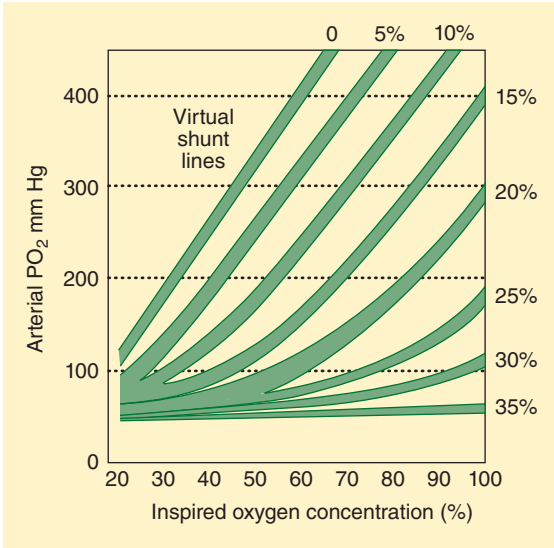

FIGURE 23–19 Isoshunt curves showing the effect of varying amounts of shunt on Pao_2. Note that there is little benefit in increasing inspired oxygen concentration in patients with very large shunts. (Modified and reproduced, with permission, from Benatar SR, Hewlett AM, Nunn JF: The use of isoshunt lines for control of oxygen therapy. Br J Anaesth 1973;45:711.)

consumption rates and low hemoglobin concentrations can increase the A–a gradient and depress Pao_2.

Mixed Venous Oxygen Tension

Normal mixed venous O_2 tension ($P\bar{v}O_2$) is about 40 mm Hg and represents the overall balance between O_2 consumption and O_2 delivery (Table 23–5). A true mixed venous blood sample contains venous drainage from the superior vena cava, the inferior vena cava, and the heart; it must therefore be obtained from a pulmonary artery catheter.

2. Carbon Dioxide

Carbon dioxide is a by-product of aerobic metabolism in mitochondria. There are therefore small continuous gradients for CO_2 tension from mitochondria to cell cytoplasm, extracellular fluid, venous blood, and alveoli, where the CO_2 is finally eliminated.

Mixed Venous Carbon Dioxide Tension

Normal mixed venous CO_2 tension ($P\bar{v}CO_2$) is about 46 mm Hg and is the end result of mixing of blood from tissues of varying metabolic activity. Venous CO_2 tension is lower in tissues with low metabolic activity (eg, skin), but higher in blood from those with relatively high activity (eg, heart).

Alveolar Carbon Dioxide Tension

Alveolar CO_2 tension ($PACO_2$) is generally considered to represent the balance between total CO_2 production ($\dot{V}CO_2$) and alveolar ventilation (elimination):

$$PACO_2 = \frac{\dot{V}CO_2}{\dot{V}A}$$

where $\dot{V}A$ is alveolar ventilation (Figure 23–21). In reality, $PACO_2$ is related to CO_2 elimination rather than production. Although the two are equal in a steady state, an imbalance occurs during periods

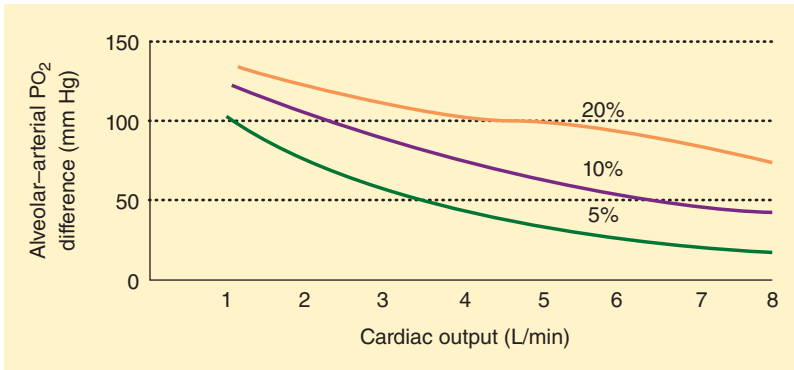

FIGURE 23–20 The effect of cardiac output on the alveolar–arterial Po_2 difference with varying degrees of shunting. $\dot{V}o_2$ = 200 mL/min and Pao_2 = 180 mm Hg.) (Reproduced, with permission, from Nunn JF: *Nunn's Applied Physiology*, 4th ed. Butterworth, 2000.)

TABLE 23–5 Alterations in mixed venous oxygen tension (and saturation).

Decreased $P\bar{v}_{O_2}$
Increased O_2 consumption
Fever
Shivering
Exercise
Malignant hyperthermia
Thyroid storm
Decreased O_2 delivery
Hypoxia
Decreased cardiac output
Decreased hemoglobin concentration
Abnormal hemoglobin
Increased $P\bar{v}_{O_2}$
Left-to-right shunting
High cardiac output
Impaired tissue uptake
Cyanide poisoning
Decreased oxygen consumption
Hypothermia
Combined mechanisms
Sepsis
Sampling error
Wedged pulmonary artery catheter

of acute hypoventilation or hypoperfusion, and the excess CO_2 increases total body CO_2 content. Clinically, P_{ACO_2} is more dependent on alveolar ventilation than is $\dot{V}_{CO_2}$, because CO_2 output does not vary appreciably under most circumstances. Moreover, the body's large capacity to store CO_2 (see below) buffers acute changes in $\dot{V}_{CO_2}$.

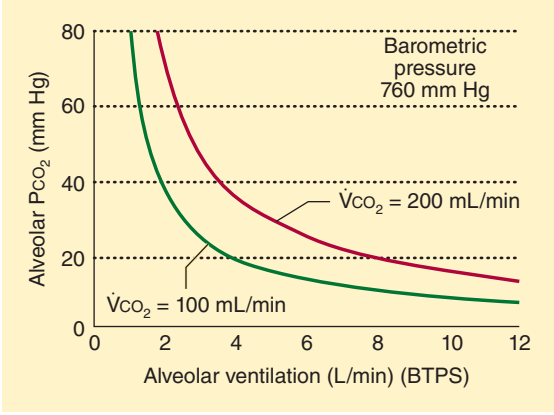

FIGURE 23–21 The effect of alveolar ventilation on alveolar P_{CO_2} at two rates of CO_2 production. (Reproduced, with permission, from Nunn JF: *Nunn's Applied Physiology*, 4th ed. Butterworth, 2000.)

Pulmonary End-Capillary Carbon Dioxide Tension

Pulmonary end-capillary CO_2 tension ($P_{c'CO_2}$) is virtually identical to P_{ACO_2} for the same reasons as those discussed in the section about O_2. In addition, the diffusion rate for CO_2 across the alveolar–capillary membrane is 20 times that of O_2.

Arterial Carbon Dioxide Tension

Arterial CO_2 tension (P_{aCO_2}), which is readily measurable, is identical to $P_{c'CO_2}$, and, necessarily, P_{ACO_2}. Normal P_{aCO_2} is 38 ± 4 mm Hg (5.1 ± 0.5 kPa); in practice, 40 mm Hg is usually considered normal.

Although low $\dot{V}/\dot{Q}$ ratios tend to increase P_{aCO_2}, whereas high $\dot{V}/\dot{Q}$ ratios tend to decrease it (in contrast to the case for O_2 [see above]), significant arterial-to-alveolar gradients for CO_2 develop only in the presence of marked $\dot{V}/\dot{Q}$ abnormalities (>30% venous admixture); even then the gradient is relatively small (2–3 mm Hg). Moreover, small increases in the gradient appreciably increase CO_2 output into alveoli with relatively normal $\dot{V}/\dot{Q}$. Even moderate to severe disturbances usually fail to appreciably alter arterial CO_2 because of a reflex increase in ventilation from concomitant hypoxemia.

End-Tidal Carbon Dioxide Tension

Because end-tidal gas is primarily alveolar gas and P_{ACO_2} is virtually identical to P_{aCO_2}, end-tidal CO_2 tension (P_{ETCO_2}) is used clinically as an estimate of P_{aCO_2}. The P_{ACO_2}–P_{ETCO_2} gradient is normally less than 5 mm Hg and represents dilution of alveolar gas with CO_2-free gas from nonperfused alveoli (alveolar dead space).

TRANSPORT OF RESPIRATORY GASES IN BLOOD

1. Oxygen

O_2 is carried in blood in two forms: dissolved in solution and in reversible association with hemoglobin.

Dissolved Oxygen

The amount of O_2 dissolved in blood can be derived from **Henry's law**, which states that the concentration of any gas in solution is proportional to its partial pressure. The mathematical expression is as follows:

$$\text{Gas concentration} = \alpha \times \text{Partial pressure}$$

where α = the gas solubility coefficient for a given solution at a given temperature.

The solubility coefficient for O_2 at normal body temperature is 0.003 mL/dL/mm Hg. Even with a Pao_2 of 100 mm Hg, the maximum amount of O_2 dissolved in blood is very small (0.3 mL/dL) compared with that bound to hemoglobin.

Hemoglobin

Hemoglobin is a complex molecule consisting of four heme and four protein subunits. Heme is an iron–porphyrin compound that is an essential part of the O_2-binding sites; only the divalent form (+2 charge) of iron can bind O_2. The normal hemoglobin molecule (hemoglobin A_1) consists of two α and two β chains (subunits); the four subunits are held together by weak bonds between the amino acid residues. Each gram of hemoglobin can theoretically carry up to 1.39 mL of O_2.

Hemoglobin Dissociation Curve

Each hemoglobin molecule binds up to four O_2 molecules. The complex interaction between the hemoglobin subunits results in nonlinear (an elongated S shape) binding with O_2 (**Figure 23–22**). Hemoglobin saturation is the amount of O_2 bound as a percentage of its total O_2-binding capacity. Four separate chemical reactions are involved in binding each of the four O_2 molecules. The change in molecular conformation induced by the binding of the first three molecules greatly accelerates binding of the fourth O_2 molecule. The last reaction is responsible for the accelerated binding between 25% and 100% saturation. At about 90% saturation, the decrease in available O_2 receptors flattens the curve until full saturation is reached.

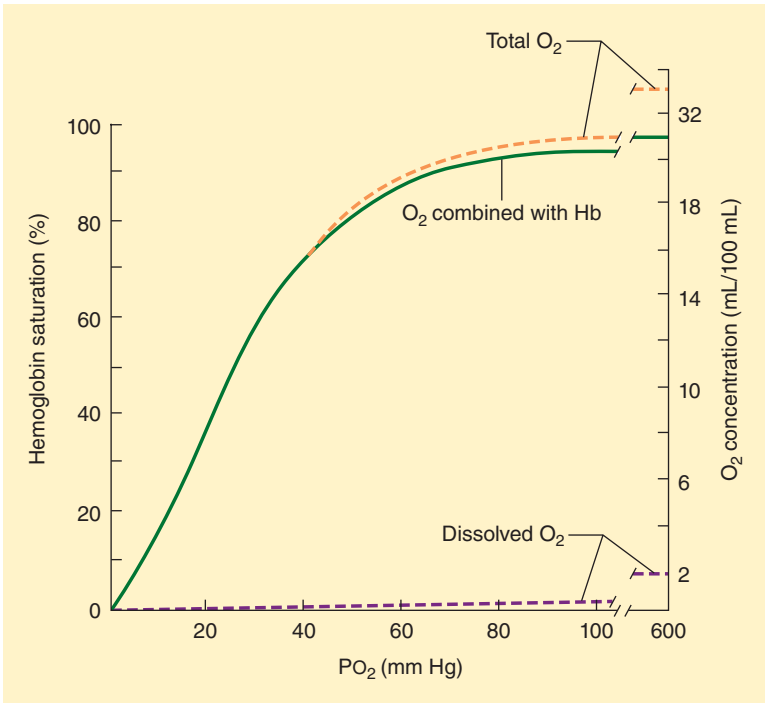

FIGURE 23–22 The normal adult hemoglobin–oxygen dissociation curve. (Modified and reproduced, with permission, from West JB: *Respiratory Physiology—The Essentials*, 6th ed. Williams & Wilkins, 2000.)

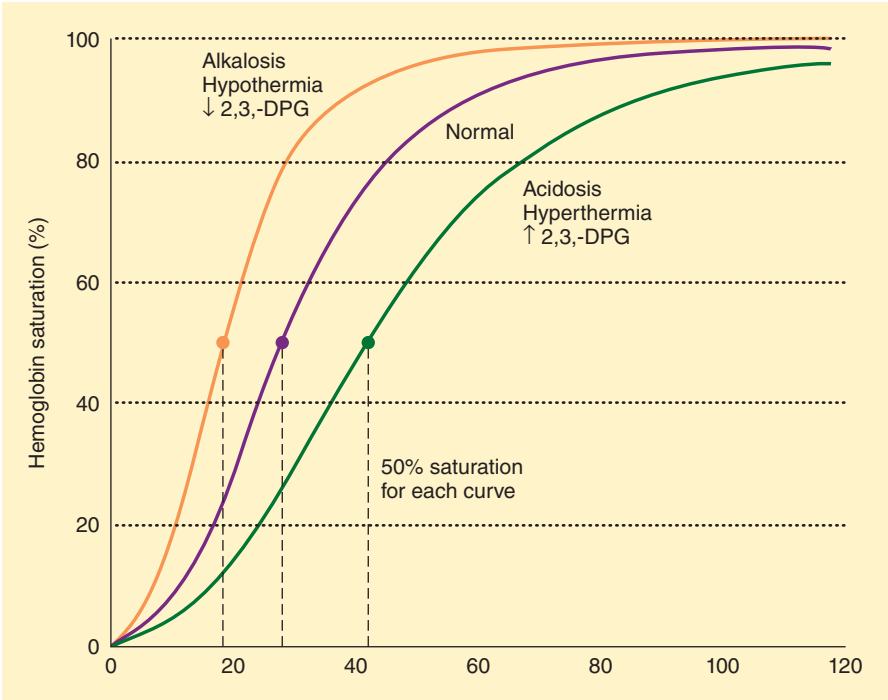

FIGURE 23–23 The effects of changes in acid–base status, body temperature, and 2,3-DPG concentration on the hemoglobin–oxygen dissociation curve.

Factors Influencing the Hemoglobin Dissociation Curve

Clinically important factors altering O_2 binding include hydrogen ion concentration, CO_2 tension, temperature, and 2,3-diphosphoglycerate (2,3-DPG) concentration. Their effect on hemoglobin–O_2 interaction can be expressed by P_{50}, the O_2 tension at which hemoglobin is 50% saturated (Figure 23–23). Each factor shifts the dissociation curve either to the right (increasing P_{50}) or to the left (decreasing P_{50}).

14 A rightward shift in the oxygen–hemoglobin dissociation curve lowers O_2 affinity, displaces O_2 from hemoglobin, and makes more O_2 available to tissues; a leftward shift increases hemoglobin's affinity for O_2, reducing its availability to tissues. The normal P_{50} in adults is 26.6 mm Hg (3.4 kPa).

An increase in blood hydrogen ion concentration reduces O_2 binding to hemoglobin (Bohr effect). Because of the shape of the **hemoglobin dissociation curve**, the effect is more important in venous blood than arterial blood (Figure 23–23); the net result is facilitation of O_2 release to tissue with little impairment in O_2 uptake (unless severe hypoxia is present).

The influence of CO_2 tension on hemoglobin's affinity for O_2 is important physiologically and is secondary to the associated rise in hydrogen ion concentration when CO_2 tension increases. The high CO_2 content of venous capillary blood, by decreasing hemoglobin's affinity for O_2, facilitates the release of O_2 to tissues; conversely, the lower CO_2 content in pulmonary capillaries increases hemoglobin's affinity for O_2 again, facilitating O_2 uptake from alveoli.

2,3-DPG is a by-product of glycolysis (the Rapoport–Luebering shunt) and accumulates during anaerobic metabolism. Although its effects on hemoglobin under these conditions are theoretically beneficial, its physiological importance normally seems minor. 2,3-DPG levels may, however, play an important compensatory role in patients

with chronic anemia and may significantly affect the O_2-carrying capacity of blood transfusions.

Abnormal Ligands & Abnormal Forms of Hemoglobins

Carbon monoxide, cyanide, nitric acid, and ammonia can combine with hemoglobin at O_2-binding sites. They can displace O_2 and shift the saturation curve to the left. Carbon monoxide is particularly potent, having 200–300 times the affinity of O_2 for hemoglobin, combining with it to form carboxyhemoglobin. Carbon monoxide decreases hemoglobin's O_2-carrying capacity and impairs the release of O_2 to tissues.

Methemoglobin results when the iron in heme is oxidized to its trivalent (+3) form. Nitrates, nitrites, sulfonamides, and other drugs can rarely result in significant methemoglobinemia. Methemoglobin cannot combine with O_2 unless reconverted by the enzyme methemoglobin reductase; methemoglobin also shifts the normal hemoglobin saturation curve to the left. Methemoglobinemia, like carbon monoxide poisoning, therefore decreases the O_2-carrying capacity and impairs the release of O_2. Reduction of methemoglobin to normal hemoglobin is facilitated by such agents as methylene blue or ascorbic acid.

Abnormal hemoglobins can also result from variations in the protein subunit composition. Each variant has its own O_2-saturation characteristics. These include fetal hemoglobin, hemoglobin A_2, and sickle hemoglobin.

Oxygen Content

The total O_2 content of blood is the sum of that in solution plus that carried by hemoglobin. In reality, O_2 binding to hemoglobin never achieves the theoretical maximum (see above), but is closer to 1.31 mL O_2/dL blood per mm Hg. Total O_2 content is expressed by the following equation:

$$\begin{aligned} O_2 \text{ content} = &([0.003 \text{ mL } O_2\text{/dL blood per mm Hg}] \\ &\times Po_2) + (So_2 \times Hb \times 1.31 \text{ mL/dL blood}) \end{aligned}$$

where Hb is hemoglobin concentration in g/dL blood, and So_2 is hemoglobin saturation at the given Po_2.

Using the above formula and a hemoglobin of 15 g/dL, the normal O_2 content for both arterial and mixed venous blood and the arteriovenous difference can be calculated as follows:

$$\begin{aligned} Cao_2 &= (0.003 \times 100) + (0.975 \times 15 \times 1.39) \\ &= 19.5 \text{ mL/dL blood} \\ C\bar{v}o_2 &= (0.003 \times 40) + (0.75 \times 15 \times 1.31) \\ &= 14.8 \text{ mL/dL blood} \\ Cao_2 - C\bar{v}o_2 &= 4.7 \text{ mL/dL blood} \end{aligned}$$

Oxygen Transport

O_2 transport is dependent on both respiratory and circulatory function. Total O_2 delivery ($\dot{D}o_2$) to tissues is the product of arterial O_2 content and cardiac output:

$$\dot{D}o_2 = Cao_2 \times \dot{Q}T$$

Note that arterial O_2 content is dependent on Pao_2 as well as hemoglobin concentration. **As a result, deficiencies in O_2 delivery may be due to a low Pao_2, a low hemoglobin concentration, or an inadequate cardiac output**. Normal O_2 delivery can be calculated as follows:

$$\begin{aligned} O_2 \text{ delivery} &= 20 \text{ mL } O_2\text{/dL blood} \\ &\quad \times 50 \text{ dL per blood/min} \\ &= 1000 \text{ mL } O_2\text{/min} \end{aligned}$$

The Fick equation expresses the relationship between O_2 consumption, O_2 content, and cardiac output:

$$O_2 \text{ consumption} = \dot{V}o_2 = \dot{Q}T \times (Cao_2 - C\bar{v}o_2)$$

Rearranging the equation:

$$Cao_2 = \frac{\dot{V}o_2}{\dot{Q}T} + C\bar{v}o_2$$

Consequently, the arteriovenous difference is a good measure of the overall adequacy of O_2 delivery.

As calculated above, the arteriovenous difference ($Cao_2 - C\bar{v}o_2$) is about 5 mL O_2/dL blood (20 mL O_2/dL – 15 mL O_2/dL). Note that the normal extraction fraction for O_2 [$(Cao_2 - C\bar{v}o_2)/Cao_2$] is 5 mL ÷ 20 mL, or 25%; thus, the body normally consumes only 25% of the O_2 carried on hemoglobin. When O_2 demand exceeds supply, the extraction fraction exceeds 25%. Conversely, if O_2 supply exceeds demand, the extraction fraction falls below 25%.

When $\dot{D}o_2$ is even moderately reduced, $\dot{V}o_2$ usually remains normal because of increased O_2 extraction (mixed venous O_2 saturation decreases); $\dot{V}o_2$ remains independent of delivery. With further reductions in $\dot{D}o_2$, however, a critical point is reached beyond which $\dot{V}o_2$ becomes directly proportional to $\dot{D}o_2$. **This state of supply-dependent O_2 is typically associated with progressive lactic acidosis caused by cellular hypoxia**.

Oxygen Stores

The concept of O_2 stores is important in anesthesia. When the normal flux of O_2 is interrupted by apnea, existing O_2 stores are consumed by cellular metabolism; if stores are depleted, hypoxia and eventual cell death follow. Theoretically, normal O_2 stores in adults are about 1500 mL. This amount includes the O_2 remaining in the lungs, that bound to hemoglobin (and myoglobin), and that dissolved in body fluids. Unfortunately, the high affinity of hemoglobin for O_2 (the affinity of myoglobin is even higher), and the very limited quantity of O_2 in solution, restrict the availability of these stores. The O_2 contained within the lungs at FRC (initial lung volume during apnea), therefore, becomes the most important source of O_2. Of that volume, however, probably only 80% is usable.

Apnea in a patient previously breathing room air leaves approximately 480 mL of O_2 in the lungs. (If F_{IO_2} = 0.21 and FRC = 2300 mL, O_2 content = $F_{IO_2} \times$ FRC.) The metabolic activity of tissues rapidly depletes this reservoir (presumably at a rate equivalent to $\dot{V}o_2$); severe hypoxemia usually occurs within 90 sec. The onset of hypoxemia can be delayed by increasing the F_{IO_2} prior to the apnea. Following ventilation with 100% O_2, FRC contains about 2300 mL of O_2; this delays hypoxemia following apnea for 4–5 min. This concept is the basis for preoxygenation prior to induction of anesthesia.

2. Carbon Dioxide

Carbon dioxide is transported in blood in three forms: dissolved in solution, as bicarbonate, and with proteins in the form of carbamino compounds (Table 23–6). The sum of all three forms is the total CO_2 content of blood (routinely reported with electrolyte measurements).

Dissolved Carbon Dioxide

Carbon dioxide is more soluble in blood than O_2, with a solubility coefficient of 0.031 mmol/L/mm Hg (0.067 mL/dL/mm Hg) at 37°C.

TABLE 23–6 Contributions to carbon dioxide transport in 1 L of whole blood.[1,2]

Form	Plasma	Erythrocytes	Combined	Contribution (%)
Mixed venous whole blood				
Dissolved CO_2	0.76	0.51	1.27	5.5
Bicarbonate	14.41	5.92	20.33	87.2
Carbamino CO_2	Negligible	1.70	1.70	7.3
Total CO_2	15.17	8.13	23.30	
Arterial whole blood				
Dissolved CO_2	0.66	0.44	1.10	5.1
Bicarbonate	13.42	5.88	19.30	89.9
Carbamino CO_2	Negligible	1.10	1.10	5.1
Total CO_2	14.08	7.42	21.50	

[1]Data from Nunn JF: *Nunn's Applied Physiology*, 4th ed. Butterworth, 2000.
[2]Values are expressed in millimoles, except where indicated otherwise.

Bicarbonate

In aqueous solutions, CO_2 slowly combines with water to form carbonic acid and bicarbonate, according to the following reaction:

$$H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

In plasma, although less than 1% of the dissolved CO_2 undergoes this reaction, the presence of the enzyme **carbonic anhydrase** within erythrocytes and endothelium greatly accelerates the reaction. As a result, bicarbonate represents the largest fraction of the CO_2 in blood (see Table 23–6). Administration of acetazolamide, a carbonic anhydrase inhibitor, can impair CO_2 transport between tissues and alveoli.

On the venous side of systemic capillaries, CO_2 enters red blood cells and is converted to bicarbonate, which diffuses out of red cells into plasma; chloride ions move from plasma into red cells to maintain electrical balance. In the pulmonary capillaries, the reverse occurs: chloride ions move out of red cells as bicarbonate ions reenter them for conversion back to CO_2, which diffuses out into alveoli. This sequence is referred to as the chloride or Hamburger shift.

Carbamino Compounds

Carbon dioxide can react with amino groups on proteins, as shown by the following equation:

$$R\text{-}NH_2 + CO_2 \rightarrow RNH - CO_2^- + H^+$$

At physiological pH, only a small amount of CO_2 is carried in this form, mainly as carbaminohemoglobin. Deoxygenated hemoglobin (deoxyhemoglobin) has a greater affinity (3.5 times) for CO_2 than does oxyhemoglobin. As a result, venous blood carries more CO_2 than does arterial blood (Haldane effect; see Table 23–6). P_{CO_2} normally has little effect on the fraction of CO_2 carried as carbaminohemoglobin.

Effects of Hemoglobin Buffering on Carbon Dioxide Transport

The buffering action of hemoglobin also accounts for part of the Haldane effect. Hemoglobin can act as a buffer at physiological pH because of its high content of histidine. Moreover, the acid–base behavior of hemoglobin is influenced by its oxygenation state:

$$H^+ + HbO_2 \rightarrow HbH^+ + O_2$$

Removal of O_2 from hemoglobin in tissue capillaries causes the hemoglobin molecule to behave more like a base; by taking up hydrogen ions, hemoglobin shifts the CO_2–bicarbonate equilibrium in favor of greater bicarbonate formation:

$$CO_2 + H_2O + HbO_2 \rightarrow HbH^+ + HCO_3^- + O_2$$

As a direct result, deoxyhemoglobin also increases the amount of CO_2 that is carried in venous blood as bicarbonate. As CO_2 is taken up from tissue and converted to bicarbonate, the total CO_2 content of blood increases (see Table 23–6).

In the lungs, the reverse is true. Oxygenation of hemoglobin favors its action as an acid, and the release of hydrogen ions shifts the equilibrium in favor of greater CO_2 formation:

$$O_2 + HCO_3^- + HbH^+ \rightarrow H_2O + CO_2 + HbO_2$$

Bicarbonate concentration decreases as CO_2 is formed and eliminated, so that the total CO_2 content of blood decreases in the lungs. Note that there is a difference between CO_2 content (concentration per liter) of whole blood (see Table 23–6) and plasma (Table 23–7).

Carbon Dioxide Dissociation Curve

A CO_2 dissociation curve can be constructed by plotting the total CO_2 content of blood against P_{CO_2}.

TABLE 23–7 Carbon dioxide content of plasma (mmol/L).[1,2]

	Arterial	Venous
Dissolved CO_2	1.2	1.4
Bicarbonate	24.4	26.2
Carbamino CO_2	Negligible	Negligible
Total CO_2	25.6	27.6

[1]Data from Nunn JF: *Nunn's Applied Physiology*, 4th ed. Butterworth, 2000.

[2]Values are expressed in millimoles, except where indicated otherwise.

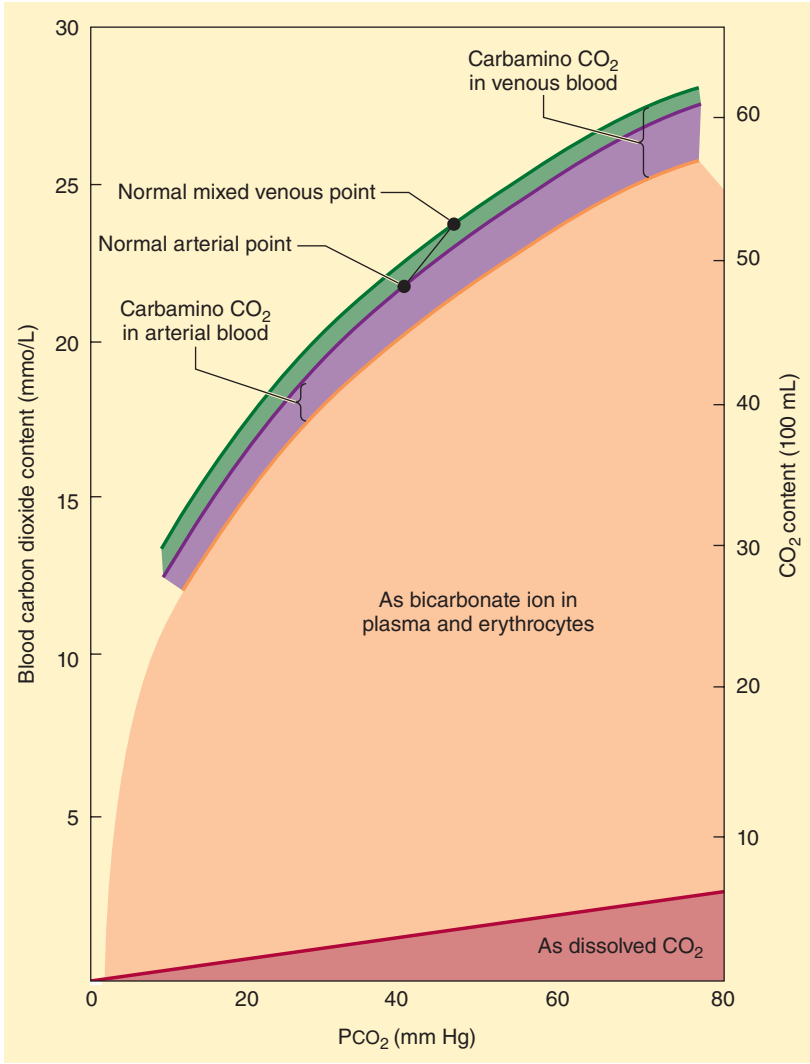

FIGURE 23–24 The CO_2 dissociation curve for whole blood. (Reproduced, with permission, from Nunn JF: *Nunn's Applied Physiology*, 4th ed. Butterworth, 2000.)

The contribution of each form of CO_2 can also be quantified in this manner (Figure 23–24).

Carbon Dioxide Stores

Carbon dioxide stores in the body are large (approximately 120 L in adults) and primarily in the form of dissolved CO_2 and bicarbonate. When an imbalance occurs between production and elimination, establishing a new CO_2 equilibrium requires 20–30 min (compared with less than 4–5 min for O_2; see above). Carbon dioxide is stored in the rapid-, intermediate-, and slow-equilibrating compartments. Because of the larger capacity of the intermediate and slow compartments, the rate of rise in arterial CO_2 tension is generally slower than its fall following acute changes in ventilation.

CONTROL OF BREATHING

Spontaneous ventilation is the result of rhythmic neural activity in respiratory centers within the brainstem. This activity regulates respiratory muscles to maintain normal tensions of O_2 and CO_2 in the body. The basic neuronal activity is modified by inputs from other areas in the brain, volitional and

autonomic, as well as various central and peripheral receptors (sensors).

1. Central Respiratory Centers

The basic breathing rhythm originates in the medulla. Two medullary groups of neurons are generally recognized: a dorsal respiratory group, which is primarily active during inspiration, and a ventral respiratory group, which is active during expiration. The close association of the dorsal respiratory group of neurons with the tractus solitarius may explain reflex changes in breathing from vagal or glossopharyngeal nerve stimulation.

Two pontine areas influence the dorsal (inspiratory) medullary center. A lower pontine (apneustic) center is excitatory, whereas an upper pontine (pneumotaxic) center is inhibitory. The pontine centers appear to fine-tune respiratory rate and rhythm.

2. Central Sensors

The most important of these sensors are chemoreceptors that respond to changes in hydrogen ion concentration. Central chemoreceptors are thought to lie on the anterolateral surface of the medulla and respond primarily to changes in cerebrospinal fluid (CSF) $[H^+]$. This mechanism is effective in regulating $Paco_2$, because the blood–brain barrier is permeable to dissolved CO_2, but not to bicarbonate ions. Acute changes in $Paco_2$, but not in arterial $[HCO_3^-]$, are reflected in CSF; thus, a change in CO_2 must result in a change in $[H^+]$:

$$CO_2 + H_2O \leftrightarrow H^+ + HCO_3^-$$

Over the course of a few days, CSF $[HCO_3^-]$ can compensate to match any change in arterial $[HCO_3^-]$.

Increases in $Paco_2$ elevate CSF hydrogen ion concentration and activate the chemoreceptors. Secondary stimulation of the adjacent respiratory medullary centers increases alveolar ventilation (**Figure 23–25**) and reduces $Paco_2$ back to normal. Conversely, decreases in CSF hydrogen ion concentration secondary to reductions in $Paco_2$ reduce alveolar ventilation and elevate $Paco_2$. Note that the relationship between $Paco_2$ and minute volume is nearly linear. Also note that very high arterial $Paco_2$ tensions depress the ventilatory response (CO_2 narcosis). The $Paco_2$ at which ventilation is zero (*x*-intercept) is known as the apneic threshold. Spontaneous

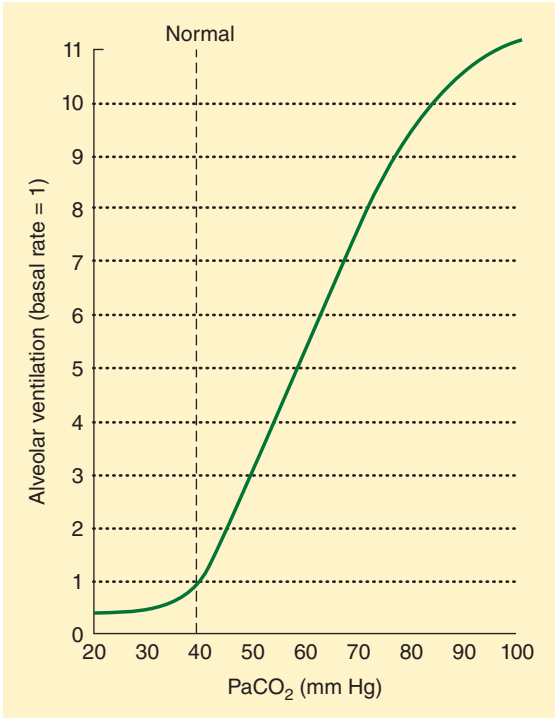

FIGURE 23–25 The normal relationship between $Paco_2$ and minute ventilation. (Reproduced, with permission, from Guyton AC: *Textbook of Medical Physiology*, 7th ed. W.B. Saunders, 1986.)

respirations are typically absent under anesthesia when $Paco_2$ falls below the apneic threshold. (In the awake state, cortical influences prevent apnea, so apneic thresholds are not ordinarily seen.) In contrast to peripheral chemoreceptors (see below), central chemoreceptor activity is depressed by hypoxia.

3. Peripheral Sensors

Peripheral Chemoreceptors

Peripheral chemoreceptors include the carotid bodies (at the bifurcation of the common carotid arteries) and the aortic bodies (surrounding the aortic arch). The carotid bodies are the principal peripheral chemoreceptors in humans and are sensitive to changes in Pao_2, $Paco_2$, pH, and arterial perfusion pressure. They interact with central respiratory centers via the glossopharyngeal nerves, producing reflex increases in alveolar ventilation in response to reductions in Pao_2, arterial perfusion, or elevations in $[H^+]$ and $Paco_2$. Peripheral chemoreceptors

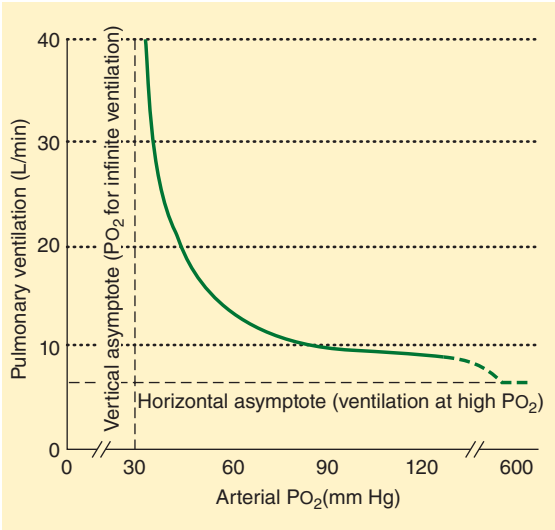

FIGURE 23–26 The relationship between Pa_{O_2} and minute ventilation at rest and with a normal Pa_{CO_2}. (Data from Weil JV, Byrne-Quinn E, Sodal IE, et al: Hypoxic ventilatory drive in normal man. J Clin Invest 1970;49:1061-1072; Dripps RD, Comroe JH: The effect of the inhalation of high and low oxygen concentration on respiration, pulse rate, ballistocardiogram and arterial oxygen saturation (oximeter) of normal individuals. Am J Physiol 1947;149: 277-291; Cormac RS, Cunningham DJC, Gee JBL: The effect of carbon dioxide on the respiratory response to want of oxygen in man. Q J Exp Physiol 1957;42:303-316.)

are also stimulated by cyanide, doxapram, and large doses of nicotine. In contrast to central chemoreceptors, which respond primarily to Pa_{CO_2} (really $[H^+]$), the carotid bodies are most sensitive to Pa_{O_2} (Figure 23–26). Note that receptor activity does not appreciably increase until Pa_{O_2} decreases below 50 mm Hg. Cells of the carotid body (glomus cells) are thought to be primarily dopaminergic neurons. Anti-dopaminergic drugs (such as phenothiazines), most commonly used anesthetics, and bilateral carotid surgery abolish the peripheral ventilatory response to hypoxemia.

Lung Receptors

Impulses from these receptors are carried centrally by the vagus nerve. Stretch receptors are distributed in the smooth muscle of airways; they are responsible for inhibition of inspiration when the lung is inflated to excessive volumes (Hering–Breuer inflation reflex) and shortening of exhalation when the lung is deflated (deflation reflex). Stretch receptors normally play a minor role in humans. In fact, bilateral vagal nerve blocks have a minimal effect on the normal respiratory pattern.

Irritant receptors in the tracheobronchial mucosa react to noxious gases, smoke, dust, and cold gases; activation produces reflex increases in respiratory rate, bronchoconstriction, and coughing. J (juxta-capillary) receptors are located in the interstitial space within alveolar walls; these receptors induce dyspnea in response to expansion of interstitial space volume and various chemical mediators following tissue damage.

Other Receptors

These include various muscle and joint receptors on pulmonary muscles and the chest wall. Input from these sources is probably important during exercise and in pathological conditions associated with decreased lung or chest compliance.

4. Effects of Anesthesia on the Control of Breathing

The most important effect of most general anesthetics on breathing is a tendency to promote hypoventilation. The mechanism is probably dual: central depression of the chemoreceptor and depression of external intercostal muscle activity. The magnitude of the hypoventilation is generally proportional to anesthetic depth. With increasing depth of anesthesia, the slope of the Pa_{CO_2}/minute ventilation curve decreases, and the apneic threshold increases (Figure 23–27). This effect is at least partially reversed by surgical stimulation.

The peripheral response to hypoxemia is even more sensitive to anesthetics than the central CO_2 response and is nearly abolished by even subanesthetic doses of most inhalation agents (including nitrous oxide) and many intravenous agents.

NONRESPIRATORY FUNCTIONS OF THE LUNG

Filtration & Reservoir Function

A. Filtration

The unique in-series position of the pulmonary capillaries within the circulation allows them to act

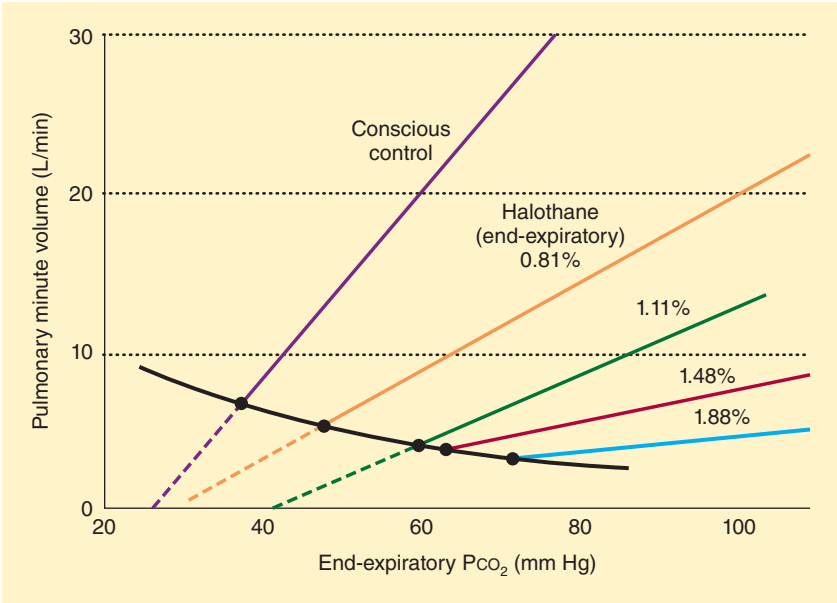

FIGURE 23–27 The effect of volatile agents (halothane) on the P_{ETCO_2}–ventilation response curve (see text). Data from Munson ES, Larson CP, Babad AA, et al: The effects of halothane, fluroxene and cyclopropane on ventilation: a comparative study in man. Anesthesiology 1966;27:716-728.

as a filter for debris in the bloodstream. The lungs' high content of heparin and plasminogen activator facilitates the breakdown of entrapped fibrin debris. Although pulmonary capillaries have an average diameter of 7 µm, larger particles have been shown to pass through to the left heart.

B. Reservoir Function

The role of the pulmonary circulation as a reservoir for the systemic circulation was discussed above.

Metabolism

The lungs are metabolically very active organs. In addition to surfactant synthesis, pneumocytes account for a major portion of extrahepatic mixed-function oxidation. Neutrophils and macrophages in the lung produce O_2-derived free radicals in response to infection. The pulmonary endothelium metabolizes a variety of vasoactive compounds, including norepinephrine, serotonin, bradykinin, and a variety of prostaglandins and leukotrienes. Histamine and epinephrine are generally not metabolized in the lungs; in fact the lungs can be a major site of histamine synthesis and release during allergic reactions.

The lungs are also responsible for converting angiotensin I to its physiologically active form, angiotensin II. The enzyme responsible, angiotensin-converting enzyme, is bound on the surface of the pulmonary endothelium.

CASE DISCUSSION

Unilaterally Diminished Breath Sounds During General Anesthesia

A 67-year-old man with carcinoma is undergoing colon resection under general anesthesia. His history includes an old anterior myocardial infarction and compensated congestive heart failure. Arterial and central venous catheters are placed preoperatively for monitoring during surgery. Following a smooth induction and an atraumatic intubation, anesthesia is maintained with 60% nitrous oxide in O_2, sevoflurane, and vecuronium. One-half hour into the operation, the surgeon asks for the Trendelenburg position to facilitate surgical exposure. The pulse

oximeter, which had been reading 99% saturation, suddenly drops and remains at 93%. The pulse oximeter's signal strength and waveform are unchanged. Auscultation of the lungs reveals diminished breath sounds over the left lung.

What is the most likely explanation?

Unilaterally diminished breath sounds under anesthesia are most commonly caused by accidental placement or migration of the tracheal tube into one of the two main bronchi. As a result, only one lung is ventilated. Other causes of unilaterally diminished breath sounds (such as pneumothorax, a large mucus plug, lobar atelectasis, or undiagnosed bullae) are less easily diagnosed, but are fortunately less common during anesthesia.

The Trendelenburg (head-down) position typically causes the tip of the tracheal tube to advance 1–2 cm relative to the carina. In this case, the tube was apparently placed just above the carina with the patient in the supine position, but migrated into the right bronchus when the Trendelenburg position was imposed. The diagnosis is confirmed by drawing the tube back 1–2 cm at a time as the chest is auscultated. Breath sounds will become equal again when the tip of the tube reenters the trachea. Following initial placement, tracheal tubes should be routinely checked for correct positioning by auscultating the chest, ascertaining depth of tube insertion by the markings on the tube (normally 20–24 cm at the teeth for an adult), and feeling for the cuff in the suprasternal notch. Tube position relative to the carina can also be quickly confirmed with a flexible fiberoptic bronchoscope.

Are tracheal tubes just as likely to enter either main bronchus?

In most cases of unintentional bronchial intubation, the tracheal tube enters the right bronchus because the latter diverges away from the trachea at a less acute angle than does the left bronchus.

Why did hemoglobin saturation decrease?

Failure to ventilate one lung as it continues to be perfused creates a large intrapulmonary shunt. Venous admixture increases and tends to depress Pa_{O_2} and hemoglobin saturation.

Does a saturation of 93% exclude bronchial intubation?

No; if both lungs continued to have equal blood flow, venous admixture should have theoretically increased to 50%, resulting in severe hypoxemia and very low hemoglobin saturation. Fortunately, hypoxic pulmonary vasoconstriction is a powerful compensatory response that tends to reduce flow to the hypoxic lung and reduces the expected venous admixture. In fact, if the patient has been receiving a higher inspired O_2 concentration (50% to 100%), the drop in arterial tension may not be detectable by the pulse oximeter due to the characteristics of the normal hemoglobin saturation curve. For example, bronchial intubation in a patient inspiring 50% O_2 might drop P_{AO_2} from 250 mm Hg to 95 mm Hg; the resulting change in pulse oximeter readings (100–99 to 98–97) would hardly be noticeable.

Arterial and mixed venous blood gas tensions are obtained with the following results:

$Pa_{O_2} = 69$ mm Hg; $Pa_{CO_2} = 42$ mm Hg; $Sa_{O_2} = 93\%$; $P\bar{v}_{O_2} = 40$ mm Hg; and $S\bar{v}_{O_2} = 75\%$. Hemoglobin concentration is 15 g/dL.

What is the calculated venous admixture?

In this case, $Pc'_{O_2} = P_{AO_2} = ([760 - 47] \times 0.4) - 42 = 243$ mm Hg. Therefore, $Cc'_{O_2} = (15 \times 1.31 \times 1.0) + (243 \times 0.003) = 20.4$ mL/dL.

$Ca_{O_2} = (15 \times 1.31 \times 0.93) + (69 \times 0.003) = 18.5$ mL/dL

$C\bar{v}_{O_2} = (15 \times 1.31 \times 0.75) + (40 \times 0.003) = 14.8$ mL/dL

$\dot{Q}_S/\dot{Q}_T = (20.4 - 18.5)/(20.4 - 14.8) = 34\%$

How does bronchial intubation affect arterial and end-tidal CO_2 tensions?

Pa_{CO_2} is typically not appreciably altered as long as the same minute ventilation is maintained (see One-Lung Anesthesia, Chapter 25). Clinically, the Pa_{CO_2}–P_{ETCO_2} gradient often widens, possibly because of increased alveolar dead space (overdistension of the ventilated lung). Thus, P_{ETCO_2} may decrease or remain unchanged.

SUGGESTED READING

Bruells C, Rossaint R: Physiology of gas exchange during anesthesia. Eur J Anaesthesiol 2011;29:570.

Campos J: Update on tracheobronchial anatomy and flexible fiberoptic bronchoscopy in thoracic anesthesia. Curr Opin Anaesthesiol 2009;22:4.

Lohser J: Evidence based management of one lung ventilation. Anesthesiol Clin 2008;26:241.

Minnich D, Mathisen D: Anatomy of the trachea, carina, and bronchi. Thorac Surg Clin 2007;17:571.

Warner DO: Diaphragm function during anesthesia: Still crazy after all these years. Anesthesiology 2002;97:295.