

Pulmonary Circulation and the Ventilation-Perfusion Ratio

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CHAPTER OUTLINE

- FUNCTIONAL ORGANIZATION OF THE PULMONARY CIRCULATION
- PULMONARY VASCULAR RESISTANCE
- FLUID EXCHANGE IN PULMONARY CAPILLARIES
- BLOOD FLOW DISTRIBUTION IN THE LUNGS
- SHUNTS AND VENOUS ADMIXTURE
- THE BRONCHIAL CIRCULATION

KEY CONCEPTS

1. The pulmonary circulation is a high-flow, low-resistance, and low-pressure system.
2. Capillary recruitment and capillary distension cause the pulmonary vascular resistance to fall with increased cardiac output.
3. Alveolar oxygen tension (PAO_2) regulates blood flow in the lungs.
4. High pulmonary capillary hydrostatic pressure leads to pulmonary edema.
5. Gravity causes lung perfusion to be better at the base than at the apex.
6. A mismatch of ventilation and blood flow occurs at both the base and the apex of the lungs.
7. Some of the blood that leaves the lungs is not fully oxygenated.
8. Poor regional ventilation is the major cause for a low ventilation-perfusion ratio in the lungs.
9. The bronchial circulation is part of the systemic circulation and does not participate in gas exchange.

FUNCTIONAL ORGANIZATION OF THE PULMONARY CIRCULATION

The heart drives two separate and distinct circulatory systems in the body: the pulmonary circulation and the systemic circulation. The pulmonary circulation is analogous to the entire systemic circulation. Similar to the systemic circulation, the pulmonary circulation receives all of the cardiac output. Therefore, the pulmonary circulation is not a regional circulation like the renal, hepatic, or coronary circulations. A change in pulmonary vascular resistance has the same implications for the right ventricle as a change in systemic vascular resistance has for the left ventricle.

The pulmonary arteries branch in the same tree-like manner as do the airways. Each time an airway branches, the arterial tree branches so that the two parallel each other (Fig. 20.1). More than 40% of lung weight is comprised of blood in the pulmonary blood vessels. The total blood volume of the pulmonary circulation (main pulmonary artery to left atrium) is approximately 500 mL or 10% of the total circulating blood volume (5,000 mL). The pulmonary veins contain more blood (270 mL) than the arteries (150 mL). The blood volume in the pulmonary capillaries is approxi-

mately equal to the stroke volume of the right ventricle (about 80 mL) under most physiological conditions.

The Pulmonary Circulation Functions in Gas Exchange and as a Filter, Metabolic Organ, and Blood Reservoir

The primary function of the pulmonary circulation is to bring venous blood from the superior and inferior vena cavae (i.e., mixed venous blood) into contact with alveoli for gas exchange. In addition to gas exchange, the pulmonary circulation has three secondary functions: it serves as a filter, a metabolic organ, and as a blood reservoir.

Pulmonary vessels protect the body against **thrombi** (blood clots) and **emboli** (fat globules or air bubbles) from entering important vessels in other organs. Thrombi and emboli often occur after surgery or injury and enter the systemic venous blood. Small pulmonary arterial vessels and capillaries trap the thrombi and emboli and prevent them from obstructing the vital coronary, cerebral, and renal vessels. Endothelial cells lining the pulmonary vessels release fibrinolytic substances that help dissolve thrombi. Emboli,

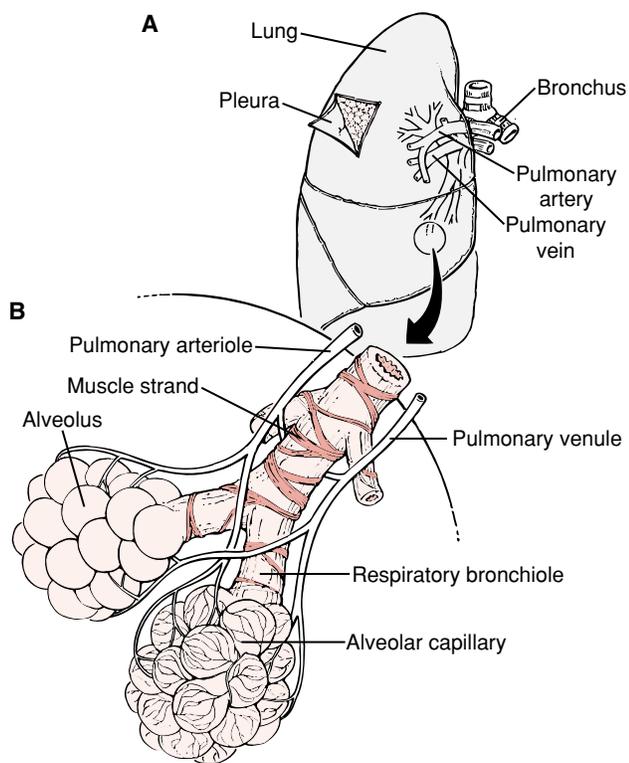


FIGURE 20.1 Parallel structure of the vascular and airway trees. **A**, Systemic venous blood flows through the pulmonary arteries into the alveolar capillaries and back to the heart via the pulmonary veins, to be pumped into the systemic circulation. **B**, A mesh of capillaries surrounds each alveolus. As the blood passes through the capillaries, it gives up carbon dioxide and takes up oxygen.

especially air emboli, are absorbed through the pulmonary capillary walls. If a large thrombus occludes a large pulmonary vessel, gas exchange can be severely impaired and can cause death. A similar situation occurs if emboli are extremely numerous and lodge all over the pulmonary arterial tree (see Clinical Focus Box 20.1).

Vasoactive hormones are metabolized in the pulmonary circulation. One such hormone is angiotensin I, which is activated and converted to angiotensin II in the lungs by **angiotensin-converting enzyme (ACE)** located on the surface of the pulmonary capillary endothelial cells. Activation is extremely rapid; 80% of angiotensin I (AI) can be converted to angiotensin II (AII) during a single passage through the pulmonary circulation. In addition to being a potent vasoconstrictor, AII has other important actions in the body (see Chapter 24). Metabolism of vasoactive hormones by the pulmonary circulation appears to be rather selective. Pulmonary endothelial cells inactivate bradykinin, serotonin, and the prostaglandins E_1 , E_2 and $F_{2\alpha}$. Other prostaglandins, such as PGA_1 and PGA_2 , pass through the lungs unaltered. Norepinephrine is inactivated, but epinephrine, histamine, and arginine vasopressin (AVP) pass through the pulmonary circulation unchanged. With acute lung injury (e.g., oxygen toxicity, fat emboli), the lungs can release histamine, prostaglandins, and leukotrienes, which can cause vasoconstriction of pulmonary arteries and pulmonary endothelial damage.

The lungs serve as a blood reservoir. Approximately 500 mL or 10% of the total circulating blood volume is in the pulmonary circulation. During hemorrhagic shock, some of this blood can be mobilized to improve the cardiac output.

The Pulmonary Circulation Has Unique Hemodynamic Features

In contrast to the systemic circulation, the pulmonary circulation is a high-flow, low-pressure, low-resistance system. The pulmonary artery and its branches have much thinner walls than the aorta and are more compliant. The pulmonary artery is much shorter and contains less elastin and smooth muscle in its walls. The pulmonary arterioles are thin-walled and contain little smooth muscle and, consequently, have less ability to constrict than the thick-walled, highly muscular systemic arterioles. The pulmonary veins are also thin-walled, highly compliant, and contain little smooth muscle compared with their counterparts in the systemic circulation.

The pulmonary capillary bed is also different. Unlike the systemic capillaries, which are often arranged as a network of tubular vessels with some interconnections, the pulmonary capillaries mesh together in the alveolar wall so that blood flows as a thin sheet. It is, therefore, misleading to refer to pulmonary capillaries as a capillary network; they comprise a dense **capillary bed**. The walls of the capillary bed are exceedingly thin, and a whole capillary bed can collapse if local alveolar pressure exceeds capillary pressure.

The systemic and pulmonary circulations differ strikingly in their pressure profiles (Fig. 20.2). Mean pulmonary arterial pressure is 15 mm Hg, compared with 93 mm Hg in the aorta. The driving pressure (10 mm Hg) for pulmonary flow is the difference between the mean pressure in the pulmonary artery (15 mm Hg) and the pressure in the left atrium (5 mm Hg). These pulmonary pressures are measured using a Swan-Ganz catheter, a thin, flexible tube with an inflatable rubber balloon surrounding the distal end. The balloon is inflated by injecting a small amount of air through the proximal end. Although the Swan-Ganz catheter is used for several pressure measurements, most useful is the **pulmonary wedge pressure** (Fig. 20.3). To measure wedge pressure, the catheter tip with balloon inflated is “wedged” into a small branch of the pulmonary artery. When the inflated balloon interrupts blood flow, the tip of the catheter measures downstream pressure. The downstream pressure in the occluded arterial branch represents pulmonary venous pressure, which, in turn, reflects left atrial pressure. Changes in pulmonary venous and left atrial pressures have a profound effect on gas exchange, and pulmonary wedge pressure provides an indirect measure of these important pressures.

PULMONARY VASCULAR RESISTANCE

The right ventricle pumps mixed venous blood through the pulmonary arterial tree, the alveolar capillaries (where oxygen is taken up and carbon dioxide is removed), the pulmonary veins, and then on to the left atrium. All of the cardiac output is pumped through the pulmonary circulation

CLINICAL FOCUS BOX 20.1

Pulmonary Embolism

Pulmonary embolism is clearly one of the more important disorders affecting the pulmonary circulation. The incidence of pulmonary embolism exceeds 500,000 per year with a mortality rate of approximately 10%. Pulmonary embolism is often misdiagnosed and, if improperly diagnosed, the mortality rate can exceed 30%.

The term **pulmonary embolism** refers to the movement of a blood clot or other plug from the systemic veins through the right heart and into the pulmonary circulation, where it lodges in one or more branches of the pulmonary artery. Although most pulmonary emboli originate from thrombosis in the leg veins, they can originate from the upper extremities as well. A thrombus is the major source of pulmonary emboli; however, air bubbles introduced during intravenous injections, hemodialysis, or the placement of central catheters can also cause emboli. Other sources of pulmonary emboli include fat emboli (a result of multiple long-bone fractures), tumor cells, amniotic fluid (secondary to strong uterine contractions), parasites, and various foreign materials in intravenous drug abusers.

The etiology of pulmonary emboli focuses on three factors that potentially contribute to the genesis of venous thrombosis: (1) hypercoagulability (e.g., a deficiency of antithrombin III, malignancies, the use of oral contraceptives, the presence of lupus anticoagulant); (2) endothelial damage (e.g., caused by atherosclerosis); and (3) stagnant blood flow (e.g., varicose veins). Several risk factors for thrombi include immobilization (e.g., prolonged bed rest, prolonged sitting during travel, or immobilization of an extremity after a fracture), congestive heart failure, obesity, underlying carcinoma, and chronic venous insufficiency.

When a thrombus migrates into the pulmonary circulation and lodges in pulmonary vessels, several pathophysi-

ological consequences ensue. When a vessel is occluded, blood flow stops and perfusion to pulmonary capillaries ceases, and the ventilation-perfusion ratio in that lung unit becomes very high because ventilation is wasted. As a result, there is a significant increase in physiological dead space. Besides the direct mechanical effects of vessel occlusion, thrombi release vasoactive mediators that cause bronchoconstriction of small airways, which leads to hypoxemia. These vasoactive mediators also cause endothelial damage that leads to edema and atelectasis. If the pulmonary embolus is large and occludes a major pulmonary vessel, an additional complication occurs in the lung parenchyma distal to the site of the occlusion. The distal lung tissue becomes anoxic because it does not receive oxygen (either from airways or from the bronchial circulation). Oxygen deprivation leads to necrosis of lung parenchyma (pulmonary infarction). The parenchyma will subsequently contract and form a permanent scar.

Pulmonary emboli are difficult to diagnose because they do not manifest any specific symptoms. The most common clinical features include dyspnea and sometimes pleuritic chest pains. If the embolism is severe enough, a decreased arterial PO_2 , decreased PCO_2 , and increased pH result. The major screening test for pulmonary embolism is the perfusion scan, which involves the injection of aggregates of human serum albumin labeled with a radionuclide into a peripheral vein. These albumin aggregates (approximately 10 to 50 μm wide) travel through the right side of the heart, enter the pulmonary vasculature, and lodge in small pulmonary vessels. Only lung areas receiving blood flow will manifest an uptake of the tracer; the nonperfused region will not show any uptake of the tagged albumin. The aggregates fragment and are removed from the lungs in about a day.

at a much lower pressure than through the systemic circulation. As shown in Figure 20.2, the 10 mm Hg pressure gradient across the pulmonary circulation drives the same blood flow (5 L/min) as in the systemic circulation, where the pressure gradient is almost 100 mm Hg. Remember that vascular resistance (R) is equal to the pressure gradient (ΔP) divided by blood flow (\dot{Q}) (see Chapter 12):

$$R = \Delta P / \dot{Q} \quad (1)$$

Pulmonary vascular resistance is extremely low, about one-tenth that of systemic vascular resistance. The difference in resistances is a result, in part, of the enormous number of small pulmonary resistance vessels that are dilated. By contrast, systemic arterioles and precapillary sphincters are partially constricted.

Pulmonary Vascular Resistance Falls With Increased Cardiac Output

Another unique feature of the pulmonary circulation is the ability to decrease resistance when pulmonary arterial pressure rises, as seen with an increase in cardiac output. When pressure rises, there is a marked decrease in pulmonary vas-

cular resistance (Fig. 20.4). Similarly, increasing pulmonary venous pressure causes pulmonary vascular resistance to fall. These responses are very different from those of the systemic circulation, where an increase in perfusion pressure increases vascular resistance. Two local mechanisms in the pulmonary circulation are responsible (Fig. 20.5). The first mechanism is known as **capillary recruitment**. Under normal conditions, some capillaries are partially or completely closed in the top part of the lungs because of the low perfusion pressure. As blood flow increases, the pressure rises and these collapsed vessels are opened, lowering overall resistance. This process of opening capillaries is the primary mechanism for the fall in pulmonary vascular resistance when cardiac output increases. The second mechanism is **capillary distension** or widening of capillary segments, which occurs because the pulmonary capillaries are exceedingly thin and highly compliant.

The fall in pulmonary vascular resistance with increased cardiac output has two beneficial effects. It opposes the tendency of blood velocity to speed up with increased flow rate, maintaining adequate time for pulmonary capillary blood to take up oxygen and dispose of carbon dioxide. It also results in an increase in capillary surface area, which

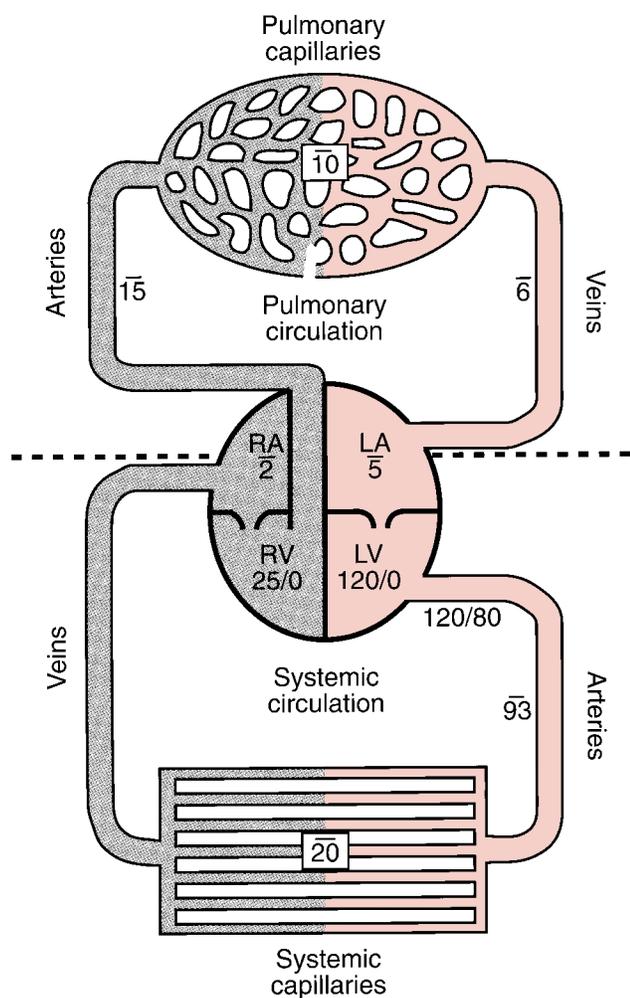


FIGURE 20.2 Pressure profiles of the pulmonary and systemic circulations. Unlike the systemic circulation, the pulmonary circulation is a low-pressure and low-resistance system. Pulmonary circulation is characterized as normally dilated, while the systemic circulation is characterized as normally constricted. Pressures are given in mm Hg; a bar over the number indicates mean pressure.

enhances the diffusion of oxygen into and carbon dioxide out of the pulmonary capillary blood.

Capillary recruitment and distension also have a protective function. High capillary pressure is a major threat to the lungs and can cause **pulmonary edema**, an abnormal accumulation of fluid, which can flood the alveoli and impair gas exchange. When cardiac output increases from a resting level of 5 L/min to 25 L/min with vigorous exercise, the decrease in pulmonary vascular resistance not only minimizes the load on the right heart but also keeps the capillary pressure low and prevents excess fluid from leaking out of the pulmonary capillaries.

Lung Volumes Affect Pulmonary Vascular Resistance

Pulmonary vascular resistance is also significantly affected by lung volume. Because pulmonary capillaries have little

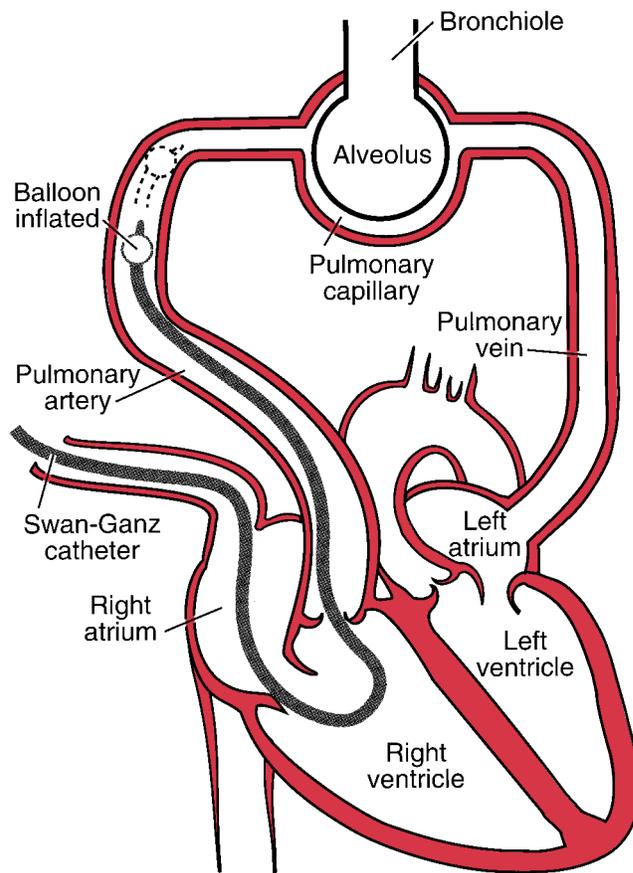


FIGURE 20.3 Measuring pulmonary wedge pressure. A catheter is threaded through a peripheral vein in the systemic circulation, through the right heart, and into the pulmonary artery. The wedged catheter temporarily occludes blood flow in a part of the vascular bed. The wedge pressure is a measure of downstream pressure, which is pulmonary venous pressure. Pulmonary venous pressure reflects left atrial pressure.

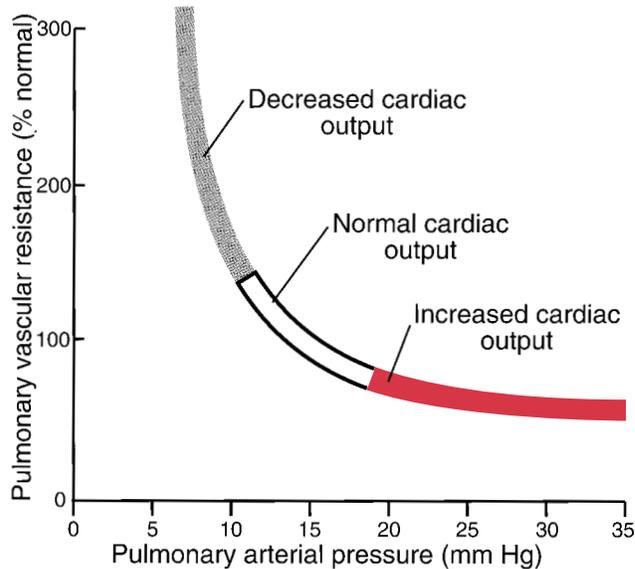


FIGURE 20.4 Effect of cardiac output on pulmonary vascular resistance. Pulmonary vascular resistance falls as cardiac output increases. Note that if pulmonary arterial pressure rises, pulmonary vascular resistance decreases.

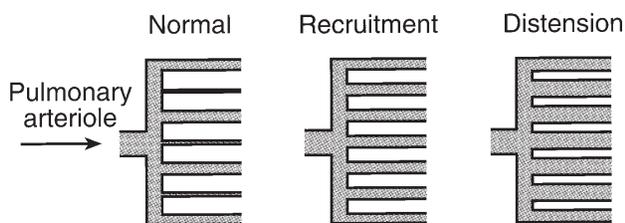


FIGURE 20.5 **Capillary recruitment and capillary distension.** These two mechanisms are responsible for decreasing pulmonary vascular resistance when arterial pressure increases. In the normal condition, not all capillaries are perfused. Capillary recruitment (the opening up of previously closed vessels) results in the perfusion of an increased number of vessels and a drop in resistance. Capillary distension (an increase in the caliber of vessels) also results in a lower resistance and higher blood flow.

structural support, they can be easily distended or collapsed, depending on the pressure surrounding them. It is the change in transmural pressure (pressure inside the capillary minus pressure outside the capillary) that influences vessel diameter. From a functional point of view, pulmonary vessels can be classified into two types: **extra-alveolar vessels** (pulmonary arteries and veins) and **alveolar vessels** (arterioles, capillaries, and venules). The extra-alveolar vessels are subjected to pleural pressure—any change in pleural pressure affects pulmonary vascular resistance in these vessels by changing transmural pressure. Alveolar vessels, however, are subjected primarily to alveolar pressure.

At high lung volumes, the pleural pressure is more negative. Transmural pressure in the extra-alveolar vessels increases, and they become distended (Fig. 20.6A). However, alveolar diameter increases at high lung volumes, causing transmural pressure in alveolar vessels to decrease. As the alveolar vessels become compressed, pulmonary vascular resistance increases. At low lung volumes, pulmonary vascular resistance also increases, as a result of more positive pleural pressure, which compresses the extra-alveolar vessels. Since alveolar and extra-alveolar vessels can be viewed as two groups of resistance vessels connected in series, their resistances are additive at any lung volume. Pulmonary vascular resistance is lowest at functional residual capacity (FRC) and increases at both higher and lower lung volumes (Fig. 20.6B).

Since smooth muscle plays a key role in determining the caliber of extra-alveolar vessels, drugs can also cause a change in resistance. Serotonin, norepinephrine, histamine, thromboxane A_2 , and leukotrienes are potent vasoconstrictors, particularly at low lung volumes when the vessel walls are already compressed. Drugs that relax smooth muscle in the pulmonary circulation include adenosine, acetylcholine, prostacyclin (prostaglandin I_2), and isoproterenol. The pulmonary circulation is richly innervated with sympathetic nerves but, surprisingly, pulmonary vascular resistance is virtually unaffected by autonomic nerves under normal conditions.

Low Oxygen Tension Increases Pulmonary Vascular Resistance

Although changes in pulmonary vascular resistance are accomplished mainly by passive mechanisms, resistance can be increased by low oxygen in the alveoli, **alveolar hy-**

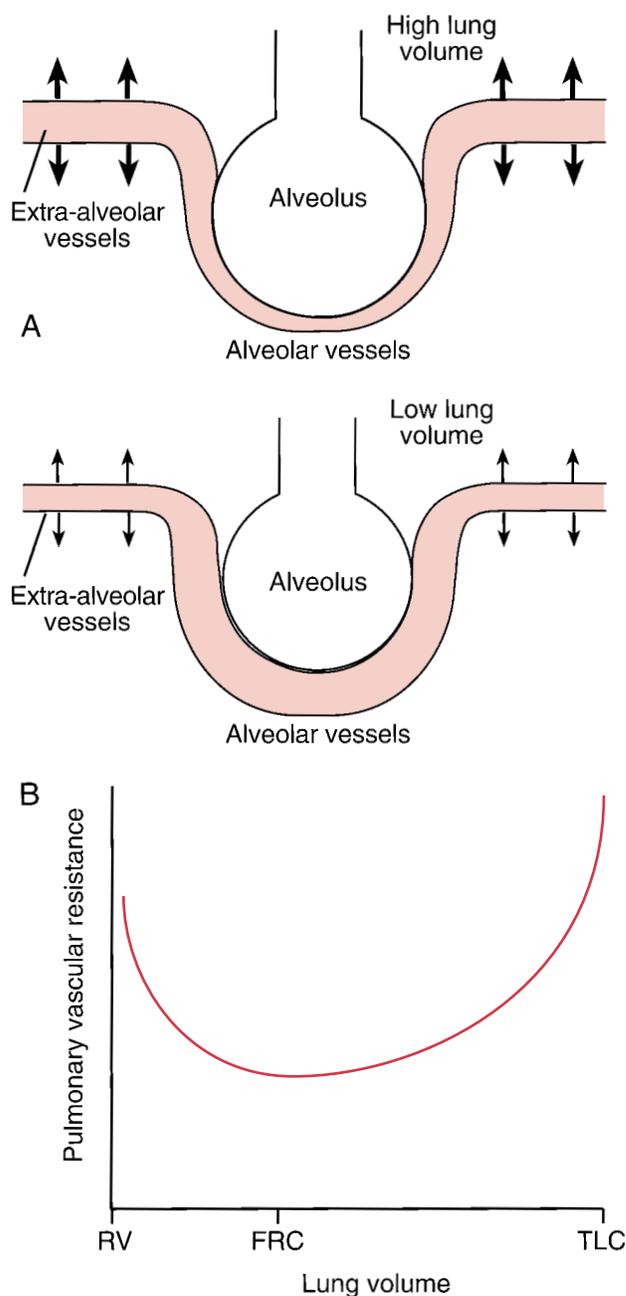


FIGURE 20.6 **Effect of lung volume on pulmonary vascular resistance.** A, At high lung volumes, alveolar vessels are compressed but extra-alveolar vessels are actually *distended* because of the lower pleural pressure. However, at low lung volumes, the extra-alveolar vessels are compressed from the pleural pressure and alveolar vessels are *distended*. B, Total pulmonary vascular resistance as a function of lung volumes follows a U-shaped curve, with resistance lowest at functional residual capacity (FRC).

poxia, and low oxygen in the blood, **hypoxemia**. Hypoxemia causes vasodilation in systemic vessels but, in pulmonary vessels, hypoxemia or alveolar hypoxia causes vasoconstriction of small pulmonary arteries. This unique phenomenon of **hypoxia-induced pulmonary vasoconstriction** is accentuated by high carbon dioxide and low blood pH. The exact mechanism is not known, but hypoxia

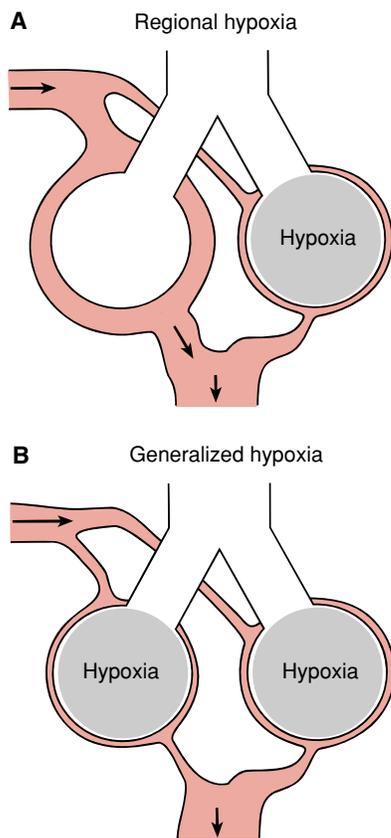


FIGURE 20.7 Effect of alveolar hypoxia on pulmonary arteries. Hypoxia-induced vasoconstriction is unique to vessels of the lungs and is the major mechanism regulating blood flow within normal lungs. **A**, With regional hypoxia, precapillary constriction diverts blood flow away from poorly ventilated regions; there is little change in pulmonary arterial pressure. **B**, In generalized hypoxia, which can occur with high altitude or with certain lung diseases, precapillary constriction occurs throughout the lungs and there is a marked increase in pulmonary arterial pressure.

can directly act on pulmonary vascular smooth muscle cells, independent of any agonist or neurotransmitter released by hypoxia.

Two types of alveolar hypoxia are encountered in the lungs, with different implications for pulmonary vascular resistance. In **regional hypoxia**, pulmonary vasoconstriction is localized to a specific region of the lungs and diverts blood away from a poorly ventilated region (e.g., caused by bronchial obstruction), minimizing effects on gas exchange (Fig. 20.7A). Regional hypoxia has little effect on pulmonary arterial pressure, and when alveolar hypoxia no longer exists, the vessels dilate and blood flow is restored. **Generalized hypoxia** causes vasoconstriction throughout both lungs, leading to a significant rise in resistance and pulmonary artery pressure (Fig. 20.7B). Generalized hypoxia occurs when the partial pressure of alveolar oxygen (PAO_2) is decreased with high altitude or with the chronic hypoxia seen in certain types of respiratory diseases (e.g., asthma, emphysema, and cystic fibrosis). Generalized hypoxia can lead to pulmonary hypertension (high pulmonary arterial pressure), which leads to pathophysiological

changes (hypertrophy and proliferation of smooth muscle cells, narrowing of arterial lumens, and a change in contractile function). Pulmonary hypertension causes a substantial increase in workload on the right heart, often leading to right heart hypertrophy (see Clinical Focus Box 20.2). Generalized hypoxia plays an important nonpathophysiological role before birth. In the fetus, pulmonary vascular resistance is extremely high as a result of generalized hypoxia—less than 15% of the cardiac output goes to the lungs, and the remainder is diverted to the left side of the heart via the **foramen ovale** and to the aorta via the **ductus arteriosus**. When alveoli are oxygenated on the newborn's first breath, pulmonary vascular smooth muscle relaxes, the vessels dilate, and vascular resistance falls dramatically. The foramen ovale and ductus arteriosus close and pulmonary blood flow increases enormously.

FLUID EXCHANGE IN PULMONARY CAPILLARIES

Starling forces, which govern the exchange of fluid across capillary walls in the systemic circulation (see Chapter 16), also operate in the pulmonary capillaries. Net fluid transfer across the pulmonary capillaries depends on the *difference* between hydrostatic and colloid osmotic pressures inside and outside the capillaries. In the pulmonary circulation, two additional forces play a role in fluid transfer—surface tension and alveolar pressure. The force of alveolar surface tension (see Chapter 19) pulls inward, which tends to lower interstitial pressure and draw fluid into the interstitial space. By contrast, alveolar pressure tends to compress the interstitial space and interstitial pressure is increased (Fig. 20.8).

Low Capillary Pressure Enhances Fluid Removal

Mean pulmonary capillary hydrostatic pressure is normally 8 to 10 mm Hg, which is lower than the plasma colloid osmotic pressure (25 mm Hg). This is functionally important because the low hydrostatic pressure in the pulmonary capillaries favors the net absorption of fluid. Alveolar surface tension tends to offset this advantage and results in a net force that still favors a small continuous flux of fluid out of the capillaries and into the interstitial space. This excess fluid travels through the interstitium to the perivascular and peribronchial spaces in the lungs, where it then passes into the lymphatic channels (see Fig. 20.8). The lungs have a more extensive lymphatic system than most organs. The lymphatics are not found in the alveolar-capillary area but are strategically located near the terminal bronchioles to drain off excess fluid. Lymphatic channels, like small pulmonary blood vessels, are held open by tethers from surrounding connective tissue. Total lung lymph flow is about 0.5 mL/min, and the lymph is propelled by smooth muscle in the lymphatic walls and by ventilatory movements of the lungs.

Fluid Imbalance Leads to Pulmonary Edema

Pulmonary edema occurs when excess fluid accumulates in the lung interstitial spaces and alveoli, and usually results when capillary filtration exceeds fluid removal. Pulmonary edema can be caused by an increase in capillary hydrostatic

CLINICAL FOCUS BOX 20.2**Hypoxia-Induced Pulmonary Hypertension**

Hypoxia has opposite effects on the pulmonary and systemic circulations. Hypoxia relaxes vascular smooth muscle in systemic vessels and elicits vasoconstriction in the pulmonary vasculature. Hypoxic pulmonary vasoconstriction is the major mechanism regulating the matching of regional blood flow to regional ventilation in the lungs. With regional hypoxia, the matching mechanism automatically adjusts regional pulmonary capillary blood flow in response to alveolar hypoxia and prevents blood from perfusing poorly ventilated regions in the lungs. Regional hypoxic vasoconstriction occurs without any change in pulmonary arterial pressure. However, when hypoxia affects all parts of the lung (generalized hypoxia), it causes pulmonary hypertension because all of the pulmonary vessels constrict. Hypoxia-induced pulmonary hypertension affects individuals who live at a high altitude (8,000 to 12,000 feet) and those with chronic obstructive pulmonary disease (COPD), especially patients with emphysema.

With chronic hypoxia-induced pulmonary hypertension, the pulmonary artery undergoes major remodeling during several days. An increase in wall thickness results from hypertrophy and hyperplasia of vascular smooth

muscle and an increase in connective tissue. These structural changes occur in both large and small arteries. Also, there is abnormal extension of smooth muscle into peripheral pulmonary vessels where muscularization is not normally present; this is especially pronounced in precapillary segments. These changes lead to a marked increase in pulmonary vascular resistance. With severe, chronic hypoxia-induced pulmonary hypertension, the obliteration of small pulmonary arteries and arterioles, as well as pulmonary edema, eventually occur. The latter is caused, in part, by the hypoxia-induced vasoconstriction of pulmonary veins, which results in a significant increase in pulmonary capillary hydrostatic pressure.

A striking feature of the vascular remodeling is that both the pulmonary artery and the pulmonary vein constrict with hypoxia; however, only the arterial side undergoes major remodeling. The postcapillary segments and veins are spared the structural changes seen with hypoxia. Because of the hypoxia-induced vasoconstriction and vascular remodeling, pulmonary arterial pressure increases. Pulmonary hypertension eventually causes right heart hypertrophy and failure, the major cause of death in COPD patients.

pressure, capillary permeability, or alveolar surface tension or by a decrease in plasma colloid osmotic pressure. Increased capillary hydrostatic pressure is the most frequent cause of pulmonary edema and is often the result of an abnormally high pulmonary venous pressure (e.g., with mitral stenosis or left heart failure).

The second major cause of pulmonary edema is increased capillary permeability, which results in excess fluid and

plasma proteins flooding the interstitial spaces and alveoli. Protein leakage makes pulmonary edema more severe because additional water is pulled from the capillaries to the alveoli when plasma proteins enter the interstitial spaces and alveoli. Increased capillary permeability occurs with pulmonary vascular injury, usually from oxidant damage (e.g., oxygen therapy, ozone toxicity), an inflammatory reaction (endotoxins), or neurogenic shock (e.g., head injury). High surface tension is the third major cause of pulmonary edema. Loss of surfactant causes high surface tension, lowering interstitial hydrostatic pressure and resulting in an increase of capillary fluid entering the interstitial space. A decrease in plasma colloid osmotic pressure occurs when plasma protein concentration is reduced (e.g., starvation).

Pulmonary edema is a hallmark of adult respiratory distress syndrome (ARDS), and it is often associated with abnormally high surface tension. Pulmonary edema is a serious problem because it hinders gas exchange and, eventually, causes arterial PO_2 to fall below normal (i.e., $PaO_2 < 85$ mm Hg) and arterial PCO_2 to rise above normal ($PaCO_2 > 45$ mm Hg). As mentioned earlier, abnormally low arterial PO_2 produces hypoxemia and the abnormally high arterial PCO_2 produces hypercapnia. Pulmonary edema also obstructs small airways, thereby, increasing airway resistance. Lung compliance is decreased with pulmonary edema because of interstitial swelling and the increase in alveolar surface tension. Decreased lung compliance, together with airway obstruction, greatly increases the work of breathing. The treatment of pulmonary edema is directed toward reducing pulmonary capillary hydrostatic pressure. This is accomplished by decreasing blood volume with a diuretic drug, increasing left ventricular function with digitalis, and administering a drug that causes vasodilation in systemic blood vessels.

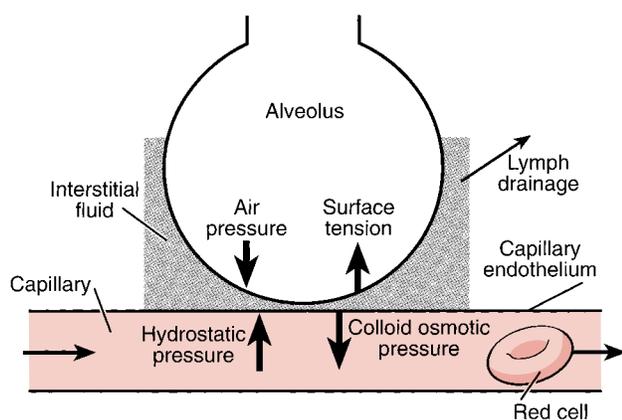


FIGURE 20.8 Fluid exchange in pulmonary capillaries.

Fluid movement in and out of capillaries depends on the net difference between hydrostatic and colloid osmotic pressures. Two additional factors involved in pulmonary fluid exchange are alveolar surface tension, which enhances filtration, and alveolar pressure, which opposes filtration. The relatively low pulmonary capillary hydrostatic pressure helps keep the alveoli "dry" and prevents pulmonary edema.

Although **fresh-water drowning** is often associated with aspiration of water into the lungs, the cause of death is not pulmonary edema but ventricular fibrillation. The low capillary pressure that normally keeps the alveolar-capillary membrane free of excess fluid becomes a severe disadvantage when fresh water accidentally enters the lungs. The aspirated water is rapidly pulled into the pulmonary capillary circulation via the alveoli because of the low capillary hydrostatic pressure and high colloid osmotic pressure. Consequently, the plasma is diluted and the hypotonic environment causes red cells to burst (hemolysis). The resulting elevation of plasma K^+ level and depression of Na^+ level alter the electrical activity of the heart. Ventricular fibrillation often occurs as a result of the combined effects of these electrolyte changes and hypoxemia. In **salt-water drowning**, the aspirated seawater is hypertonic, which leads to increased plasma Na^+ and pulmonary edema. The cause of death in this case is asphyxia.

BLOOD FLOW DISTRIBUTION IN THE LUNGS

As previously mentioned, blood accounts for approximately half the weight of the lungs. The effects of gravity on blood flow are dramatic and result in an uneven distribution of blood in the lungs. In an upright individual, the gravitational pull on the blood is downward. Since the vessels are highly compliant, gravity causes the blood volume and flow to be greater at the bottom of the lung (the base) than at the top (the apex). The pulmonary vessels can be compared with a continuous column of fluid. The difference in arterial pressure between the apex and base of the lungs is about 30 cm H_2O . Because the heart is situated midway between the top and bottom of the lungs, the arterial pressure is about 11 mm Hg less (15 cm $H_2O \div 1.36$ cm H_2O per mm Hg = 11 mm Hg) at the lungs' apex (15 cm above the heart) and about 11 mm Hg more than the mean pressure in the middle of the lungs at the lungs' base (15 cm below the heart). The low arterial pressure results in reduced blood flow in the capillaries at the lung's apex, while capillaries at the base are distended and blood flow is augmented.

Gravity Alters Capillary Perfusion

In an upright person, pulmonary blood flow increases almost linearly from apex to base (Fig. 20.9). Blood flow distribution is affected by gravity, and it can be altered by changes in body positions. For example, when an individual is lying down, blood flow is distributed relatively evenly from apex to base. The measurement of blood flow in a subject suspended upside-down would reveal an apical blood flow exceeding basal flow in the lungs. Exercise tends to offset the gravitational effects in an upright individual. As cardiac output increases with exercise, the increased pulmonary arterial pressure leads to capillary recruitment and distension in the lung's apex, resulting in increased blood flow and minimizing regional differences in blood flow in the lungs.

Since gravity causes capillary beds to be underperfused in the apex and overperfused in the base, the lungs are often divided into zones to describe the effect of gravity on

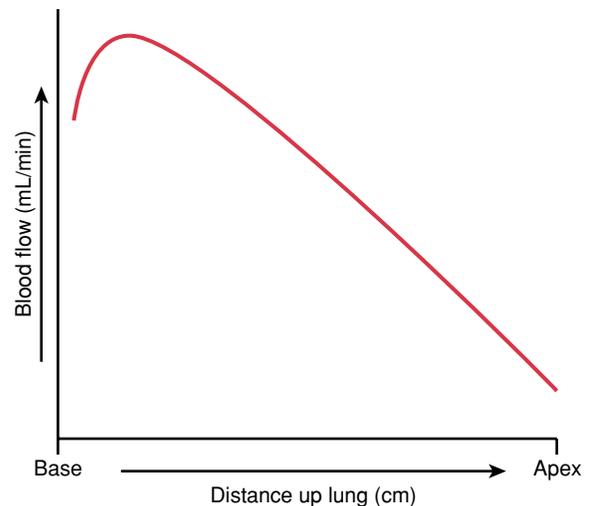


FIGURE 20.9 Effect of gravity on pulmonary blood flow. Gravity causes uneven pulmonary blood flow in the upright individual. The downward pull of gravity causes a lower blood pressure at the apex of the lungs. Consequently, pulmonary blood flow is very low at the apex and increases toward the base of the lungs.

pulmonary capillary blood flow (Fig. 20.10). **Zone 1** occurs when alveolar pressure is greater than pulmonary arterial pressure; pulmonary capillaries collapse and there is little or no blood flow. Pulmonary arterial pressure (P_a) is still greater than pulmonary venous pressure (P_v), hence, $P_a > P_a > P_v$. Because zone 1 is ventilated but not perfused (no blood flows through the pulmonary capillaries), alveolar dead space is increased (see Chapter 19). Zone 1 is usually very small or nonexistent in healthy individuals because the pulsatile pulmonary arterial pressure is sufficient to keep the capillaries partially open at the apex. Zone 1 may easily be created by conditions that elevate alveolar pressure or decrease pulmonary arterial pressure. For example, a zone 1 condition can be created when a patient is placed on a mechanical ventilator, which results in an increase in alveolar pressure with positive ventilation pressures. Hemorrhage or low blood pressure can create a zone 1 condition by lowering pulmonary arterial pressure. A zone 1 condition can also be created in the lungs of astronauts during a spacecraft launching. The rocket acceleration makes the gravitational pull even greater, causing arterial pressure in the top part of the lung to fall. To prevent or minimize a zone 1 from occurring, astronauts are placed in a supine position during blast-off.

A **zone 2** condition occurs in the middle of the lungs, where pulmonary arterial pressure, caused by the increased hydrostatic effect, is greater than alveolar pressure (see Fig 20.10). Venous pressure is less than alveolar pressure. As a result, blood flow in a zone 2 condition is determined not by the arterial-venous pressure difference, but by the difference between arterial pressure and alveolar pressure. The pressure gradient in zone 2 is represented as $P_a > P_a > P_v$. The functional importance of this is that venous pressure in zone 2 has no effect on flow. In **zone 3**, venous pressure exceeds alveolar pressure and blood flow is determined by the usual arterial-venous pressure difference.

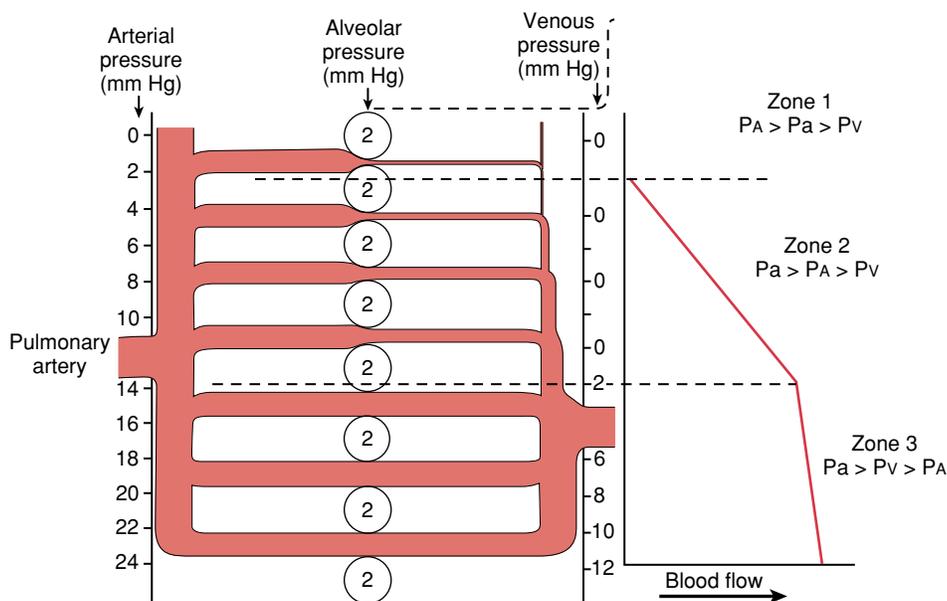


FIGURE 20.10 Zones of the lungs and the uneven distribution of pulmonary blood flow. The three zones depend on the relationship between pulmonary arterial pressure (P_a), pulmonary venous pressure (P_v), and alveolar pressure (P_A). In zone 1, alveolar pressure exceeds arterial pressure and there is no blood flow. Zone 1 occurs only in abnormal conditions in which alveolar pressure is increased (e.g., positive pressure ventilation) or when arterial pressure is decreased below normal (e.g., the gravitational pull during the launching of a

spacecraft). In zone 2, arterial pressure exceeds alveolar pressure, and blood flow depends on the difference between arterial and alveolar pressures. Blood flow is greater at the bottom than at the top of this zone. In zone 3, both arterial and venous pressures exceed alveolar pressure, and blood flow depends on the normal arterial-venous pressure difference. Note that arterial pressure increases down each zone, and transmural pressure also becomes greater, capillaries become more distended, and pulmonary vascular resistance falls.

The increase in blood flow down this region is primarily a result of capillary distension.

Regional Ventilation and Blood Flow Are Not Always Matched in the Lungs

Thus far, we have assumed that if ventilation and cardiac output are normal, gas exchange will also be normal. Unfortunately, this is not the case. Even though total ventilation and total blood flow (i.e., cardiac output) may be normal, there are regions in the lung where ventilation and blood flow are not matched, so that a certain fraction of the cardiac output is not fully oxygenated.

The matching of airflow and blood flow is best examined by considering the **ventilation-perfusion ratio**, which compares alveolar ventilation to blood flow in lung regions. Since resting healthy individuals have an alveolar ventilation (\dot{V}_A) of 4 L/min and a cardiac output (pulmonary blood flow or perfusion) of 5 L/min, the ideal alveolar ventilation-perfusion ratio (\dot{V}_A/\dot{Q} ratio) should be 0.8 (there are no units, as this is a ratio). We have already seen that gravity can cause regional differences in blood flow and alveolar ventilation (see Chapter 19). In an upright person, the base of the lungs is better ventilated and better perfused than the apex.

Regional alveolar ventilation and blood flow are illustrated in Figure 20.11. Three points are apparent from this figure:

- Ventilation and blood flow are both gravity-dependent; airflow and blood flow increase down the lung.

- Blood flow shows about a 5-fold difference between the top and bottom of the lung, while ventilation shows about a 2-fold difference. This causes gravity-dependent regional variations in the \dot{V}_A/\dot{Q} ratio that range from 0.7 at the base to 3 or higher at the apex. Blood flow is proportionately greater than ventilation at the base, and ventilation is proportionately greater than blood flow at the apex.

The functional importance of lung ventilation-perfusion ratios is that the crucial factor in gas exchange is the matching of *regional ventilation and blood flow*, as opposed to total alveolar ventilation and total pulmonary blood flow. The distribution of \dot{V}_A/\dot{Q} in a healthy adult is shown in Figure 20.12. Even in healthy lungs, most of the ventilation and perfusion go to lung units with a \dot{V}_A/\dot{Q} ratio of about 1 instead of the ideal ratio of 0.8. At the apical region, where the \dot{V}_A/\dot{Q} ratio is high, there is overventilation relative to blood flow. At the base, where the ratio is low, the opposite occurs (i.e., overperfusion relative to ventilation). In the latter case, a fraction of the blood passes through the pulmonary capillaries at the base of the lungs without becoming fully oxygenated.

The effect of regional \dot{V}_A/\dot{Q} ratio on blood gases is shown in Figure 20.13. Because overventilation relative to blood flow (high \dot{V}_A/\dot{Q}) occurs in the apex, the P_{AO_2} is high and the P_{ACO_2} is low at the apex of the lungs. Oxygen tension (P_{O_2}) in the blood leaving pulmonary capillaries at the base of the lungs is low because the blood is not fully oxygenated as a result of underventilation relative to blood

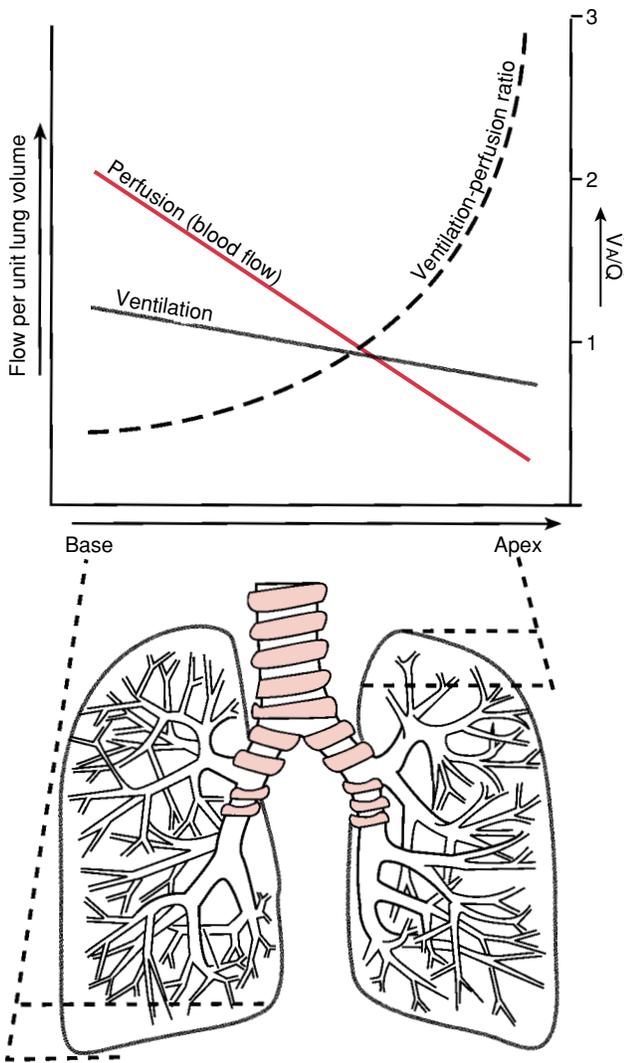


FIGURE 20.11 Regional alveolar ventilation and blood flow. Gravity causes a mismatch of blood flow and alveolar ventilation in the base and apex of the lungs. Both ventilation and perfusion are gravity-dependent. At the base of the lungs, blood flow exceeds alveolar ventilation, resulting in a low ventilation-perfusion ratio. At the apex, the opposite occurs; alveolar ventilation is greater than blood flow, resulting in a high ventilation-perfusion ratio.

flow. Regional differences in \dot{V}_A/\dot{Q} ratios tend to localize some diseases to the top or bottom parts of the lungs. For example, tuberculosis tends to be localized in the apex because of a more favorable environment (i.e., higher oxygen levels for *Mycobacterium tuberculosis*).

SHUNTS AND VENOUS ADMIXTURE

Matching of the lung's airflow and blood flow is not perfect. On one side of the

alveolar-capillary membrane there is "wasted air" (i.e., physiological dead space), and on the other side there is "wasted blood" (Fig. 20.14). Wasted blood refers to any frac-

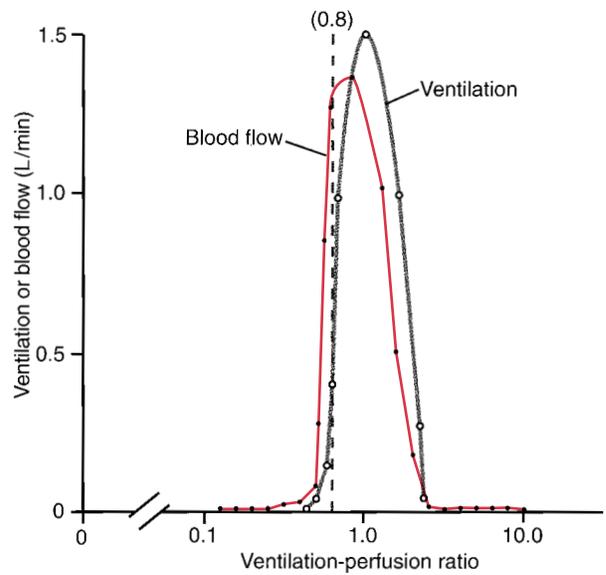


FIGURE 20.12 Profiles for alveolar ventilation and blood flow in healthy adults. The y-axis represents flow (either blood flow or airflow) in L/min. The ventilation-perfusion ratio is shown on the x-axis, plotted on a logarithmic scale. The optimal \dot{V}_A/\dot{Q} ratio is 0.8 in healthy lungs. (Adapted from Lumb AB. Nunn's Applied Respiratory Physiology. 5th Ed. Oxford: Butterworth-Heinemann, 2000.)

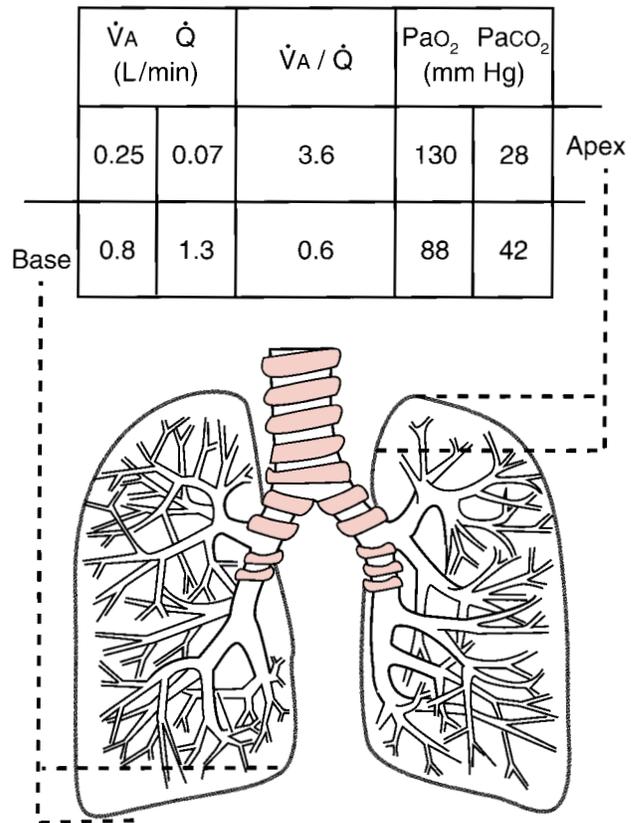


FIGURE 20.13 Effect of regional differences of ventilation-perfusion ratios on blood gases in the apex and base of the lungs.

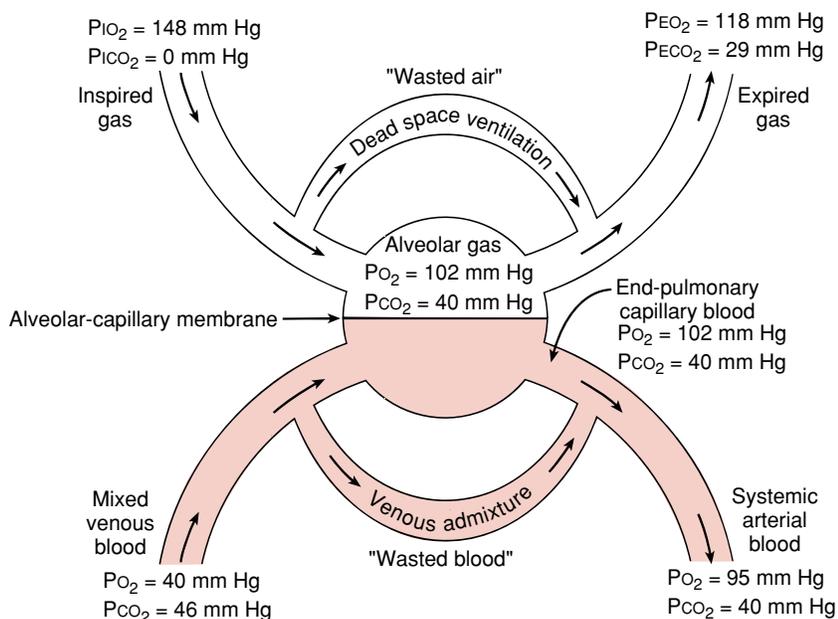


FIGURE 20.14 "Wasted air" and "wasted blood." The plumbing on both sides of the alveolar-capillary membrane is imperfect. On one side there is "wasted air" and on the other side there is "wasted blood." The total amount of wasted air constitutes physiological dead space and the total amount of wasted blood (venous admixture) constitutes physiological shunt.

tion of the venous blood that does not get fully oxygenated. The mixing of unoxygenated blood with oxygenated blood is known as **venous admixture**. There are two causes for venous admixture: a **shunt**, and a low \dot{V}_A/\dot{Q} ratio.

An **anatomic shunt** has a structural basis and occurs when blood bypasses alveoli through a channel, such as from the right to left heart through an atrial or ventricular septal defect or from a branch of the pulmonary artery connecting directly to the pulmonary vein. An anatomic shunt is often called a **right-to-left shunt**. The bronchial circulation also constitutes shunted blood because bronchial venous blood (deoxygenated blood) drains directly into the pulmonary veins that are carrying oxygenated blood.

The second cause for venous admixture is a low regional \dot{V}_A/\dot{Q} ratio. This occurs when a portion of the cardiac output goes through the regular pulmonary capillaries but there is insufficient alveolar ventilation to fully oxygenate all of the blood. With a low regional \dot{V}_A/\dot{Q} ratio, there is

no abnormal anatomic connection and the blood does not bypass the alveoli. Rather, blood that passes through the alveolar capillaries is not completely oxygenated. In a healthy individual, a low \dot{V}_A/\dot{Q} ratio occurs at the base of the lung (i.e., gravity dependent). A low regional \dot{V}_A/\dot{Q} ratio can also occur with a partially obstructed airway (Fig. 20.15), in which underventilation with respect to blood flow results in **regional hypoventilation**. A fraction of the blood passing through a hypoventilated region is not fully oxygenated, resulting in an increase in venous admixture.

The total amount of venous admixture as a result of anatomic shunt and a low \dot{V}_A/\dot{Q} ratio equals **physiological shunt** and represents the total amount of wasted blood that does not get fully oxygenated. Physiological shunt is analogous to physiological dead space; the two are compared in Table 20.1, in which one represents wasted blood flow and the other represents wasted air. It is important to remember that, in healthy individuals, there is some de-

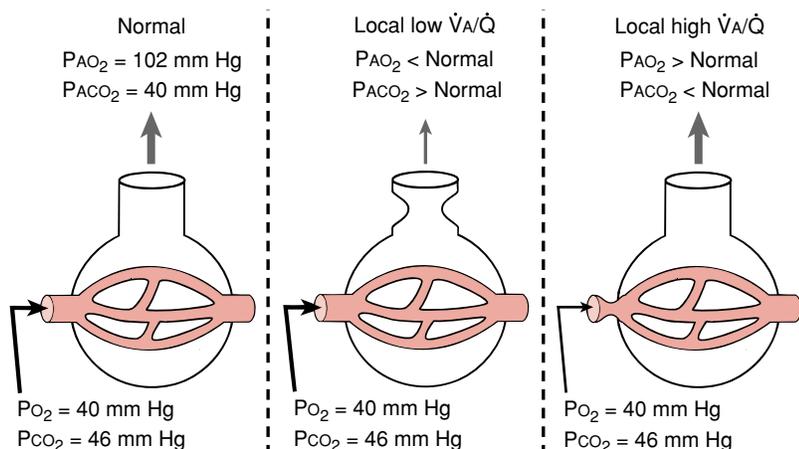


FIGURE 20.15 Abnormal ventilation-perfusion ratios. Airway obstruction (middle panel) causes a low regional ventilation-perfusion (\dot{V}_A/\dot{Q}) ratio. A partially blocked airway causes this region to be underventilated relative to blood flow. Note the alveolar gas composition. A low regional \dot{V}_A/\dot{Q} ratio causes venous admixture and will increase the physiological shunt. A partially obstructed pulmonary arteriole (right panel) will cause an abnormally high \dot{V}_A/\dot{Q} ratio in a lung region. Restricted blood flow causes this region to be overventilated relative to blood flow, which leads to an increase in physiological dead space.

TABLE 20.1 Shunts and Dead Spaces Compared

Shunt	Dead Space
Anatomic	Anatomic
+	+
Low \dot{V}_A/\dot{Q} ratio	Alveolar
=	=
Physiological shunt (calculated total "wasted blood")	Physiological dead space (calculated total "wasted air")

gree of physiological dead space as well as physiological shunt in the lungs.

In summary, venous admixture results from anatomic shunt and a low regional \dot{V}_A/\dot{Q} ratio. In healthy individuals, approximately 50% of the venous admixture comes from an anatomic shunt (e.g., bronchial circulation) and 50% from a low \dot{V}_A/\dot{Q} ratio at the base of the lungs as a result of gravity. Physiological shunt (i.e., total venous admixture) represents about 1 to 2% of cardiac output in healthy people. This amount can increase up to 15% of cardiac output with some bronchial diseases, and in certain congenital disorders, a right-to-left anatomic shunt can account for up to 50% of cardiac output. It is important to remember that any deviation of \dot{V}_A/\dot{Q} ratio from the ideal condition (0.8) impairs gas exchange and lowers oxygen tension in the arterial blood. A good way to remember the importance of a shunt is that it always leads to venous admixture and reduces the amount of oxygen carried in the systemic blood.

THE BRONCHIAL CIRCULATION

The conducting airways have a separate circulation known as the **bronchial circulation**, which is distinct from the pulmonary circulation. The primary function of the bronchial circulation is to nourish the walls of the conducting airways and surrounding tissues by distributing blood to the supporting structures of the lungs. Under normal conditions, the bronchial circulation does not supply blood to the terminal respiratory units (respiratory bronchioles, alveolar ducts, and alveoli); they receive their blood from the pulmonary circulation. Venous return from the bronchial circulation is by two routes: bronchial veins and pulmonary veins. About half of the bronchial blood flow returns to the right atrium by way of the bronchial veins, which empty into the azygos vein. The remainder returns through small bronchopulmonary anastomoses into the pulmonary veins.

Bronchial arterial pressure is approximately the same as aortic pressure, and bronchial vascular resistance is much higher than resistance in the pulmonary circulation. Bronchial blood flow is approximately 1 to 2% of cardiac output but, in certain inflammatory disorders of the airways (e.g., chronic bronchitis), it can be as high as 10% of cardiac output.

The bronchial circulation is the only portion of the circulation in the adult lung that is capable of undergoing **angiogenesis**, the formation of new vessels. This is extremely important in providing collateral circulation to the lung parenchyma, especially when the pulmonary circulation is compromised. When a clot or embolus obstructs pulmonary blood flow, the adjacent parenchyma is kept alive by the development of new blood vessels.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by an answer or by completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

- Which of the following best characterizes the pulmonary circulation?

Flow	Pressure	Resistance	Compliance
(A) Low	High	Low	High
(B) High	Low	High	Low
(C) Low	Low	Low	High
(D) High	Low	High	High
(E) High	Low	Low	High
- Pulmonary vascular resistance is decreased
 (A) At low lung volumes
 (B) By breathing low oxygen
 (C) At high lung volumes
 (D) With increased pulmonary arterial pressure
- In healthy individuals, the pulmonary and systemic circulations have the same
 (A) Mean pressure
 (B) Vascular resistance
 (C) Compliance
 (D) Flow per minute
 (E) Capillary blood volume
- The effect of gravity on the pulmonary circulation in an upright individual will cause
 (A) Blood flow to be the greatest in the middle of the lung
 (B) Capillary pressure to be greater at the base of the lung compared with the apex
 (C) Alveolar pressure to be greater than capillary pressure at the base of the lung
 (D) Lower vascular resistance at the apex of the lung compared with the base
 (E) Venous pressure to be greater than alveolar pressure at the apex
- A patient lying on his back and breathing normally has a mean left atrial pressure of 7 cm H₂O; a mean pulmonary arterial pressure of 15 cm H₂O; a cardiac output of 4 L/min; and an anteroposterior chest depth of 15 cm, measured at the xiphoid process. Most of his lung is perfused under which of the following conditions?
 (A) Zone 1
 (B) Zone 2
 (C) Zone 3
 (D) Zone 4
- Lowering pulmonary venous pressure will have the greatest effect on regional blood flow in
 (A) Zone 1
 (B) Zone 2
 (C) Zone 3
 (D) Zones 1 and 2
 (E) Zones 2 and 3
- Which of the following best characterizes alveolar ventilation and blood flow at the base, compared with the apex, of the lungs of a healthy standing person?

Ventilation	Blood flow	Ventilation-perfusion ratio
(A) Higher	Higher	Lower
(B) Lower	Higher	Higher
(C) Lower	Lower	Lower
(D) Higher	Lower	Higher
(E) Lower	Lower	Higher
- The regional changes seen in ventilation and perfusion in lungs of a

(continued)

- healthy standing individual are largely brought about by
- Differences in alveolar surface tension
 - The pyramidal shape of the lung
 - The effects of gravity
 - Differences in lung compliance
 - Differences in lung elastic recoil
9. Regional differences in ventilation-perfusion ratios affect gas tensions in the pulmonary blood. Which of the following best describes the gas tensions in the blood leaving the alveolar capillaries of a healthy standing individual?
- | | |
|--------------------------|----------------------------|
| O_2 tension (PO_2) | CO_2 tension (PCO_2) |
| (A) Lowest at base | Highest at apex |
| (B) Highest at base | Lowest at base |
| (C) Highest at apex | Lowest at apex |
| (D) Highest at apex | Lowest at base |
| (E) Lowest at base | Lowest at base |
10. A 26-year-old patient has a cardiac output of 5 L/min and mean

- pulmonary arterial and left atrial pressures of 20 and 5 mm Hg, respectively. What is her pulmonary vascular resistance?
- 4 mm Hg/L per minute
 - 3 mm Hg/L per minute
 - 0.33 mm Hg/L per minute
 - 0.25 mm Hg/L per minute
11. The apex of the lungs of a 21-year-old subject is 20 cm above the heart. What pressure (in mm Hg) must his right ventricle produce to pump blood to the top of the lungs?
- 25 mm Hg
 - 20 mm Hg
 - 15 mm Hg
 - 10 mm Hg
 - 5 mm Hg
12. A 32-year-old patient has a pulmonary vascular resistance of 4 mm Hg/L per minute and a cardiac output of 5 L/min. What is her driving pressure for moving

- blood through the pulmonary circulation?
- 10 mm Hg
 - 15 mm Hg
 - 20 mm Hg
 - 30 mm Hg
 - 40 mm Hg

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