NINTH EDITION

Respiratory Physiology

THE ESSENTIALS

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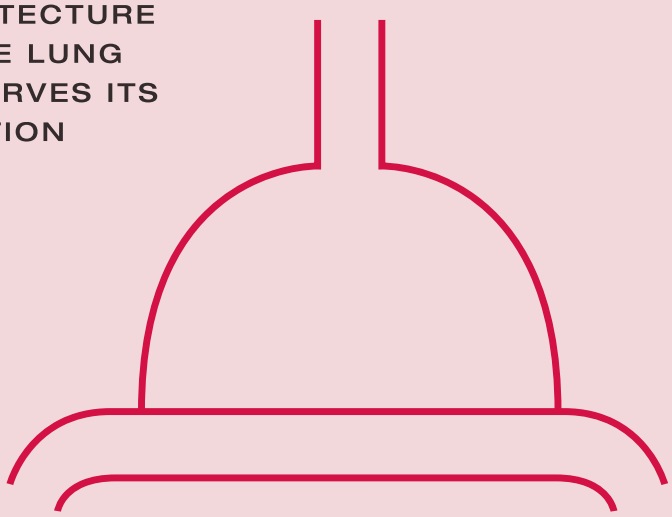
Wolters Kluwer Health | Lippincott Williams & Wilkins

Contents

Structure and Function 1

HOW THE ARCHITECTURE OF THE LUNG SUBSERVES ITS FUNCTION



We begin with a short review of the relationships between structure and function in the lung. First, we look at the blood-gas interface, where the exchange of the respiratory gases occurs. Next we look at how oxygen is brought to the interface through the airways and then how the blood removes the oxygen from the lung. Finally, two potential problems of the lung are briefly addressed: how the alveoli maintain their stability and how the lung is kept clean in a polluted environment.

The lung is for gas exchange. Its prime function is to allow oxygen to move from the air into the venous blood and carbon dioxide to move out. The lung does other jobs too. It metabolizes some compounds, filters unwanted materials from the circulation, and acts as a reservoir for blood. But its cardinal function is to exchange gas, and we shall therefore begin at the blood-gas interface where the gas exchange occurs.

Blood-Gas Interface

Oxygen and carbon dioxide move between air and blood by simple diffusion, that is, from an area of high to low partial pressure,* much as water runs downhill. Fick's law of diffusion states that the amount of gas that moves across a sheet of tissue is proportional to the area of the sheet but inversely proportional to its thickness. The blood-gas barrier is exceedingly thin (Figure 1-1) and has an area of between 50 and 100 square meters. It is therefore well suited to its function of gas exchange.

How is it possible to obtain such a prodigious surface area for diffusion inside the limited thoracic cavity? This is done by wrapping the small blood vessels (capillaries) around an enormous number of small air sacs called *alveoli* (Figure 1-2). There are about 500 million alveoli in the human lung, each about 1/3 mm in diameter. If they were spheres,† their total surface area would be 85 square meters, but their volume only 4 liters. By contrast, a single sphere of this volume would have an internal surface area of only 1/100 square meter. Thus, the lung generates this large diffusion area by being divided into a myriad of units.

Gas is brought to one side of the blood-gas interface by *airways*, and blood to the other side by *blood vessels*.

Airways and Airflow

The airways consist of a series of branching tubes, which become narrower, shorter, and more numerous as they penetrate deeper into the lung (Figure 1-3). The *trachea* divides into right and left main bronchi, which in turn divide into lobar, then segmental bronchi. This process continues down to the *terminal bronchioles*, which are the smallest airways without alveoli. All

*The partial pressure of a gas is found by multiplying its concentration by the total pressure. For example, dry air has 20.93% O_2. Its partial pressure (Po_2) at sea level (barometric pressure 760 mm Hg) is 20.93/100 × 760 = 159 mm Hg. When air is inhaled into the upper airways, it is warmed and moistened, and the water vapor pressure is then 47 mm Hg, so that the total dry gas pressure is only 760 – 47 = 713 mm Hg. The Po_2 of inspired air is therefore 20.93/100 × 713 = 149 mm Hg. A liquid exposed to a gas until equilibration takes place has the same partial pressure as the gas. For a more complete description of the gas laws, see Appendix A.

†The alveoli are not spherical but polyhedral. Nor is the whole of their surface available for diffusion (see Figure 1-1). These numbers are therefore only approximate.

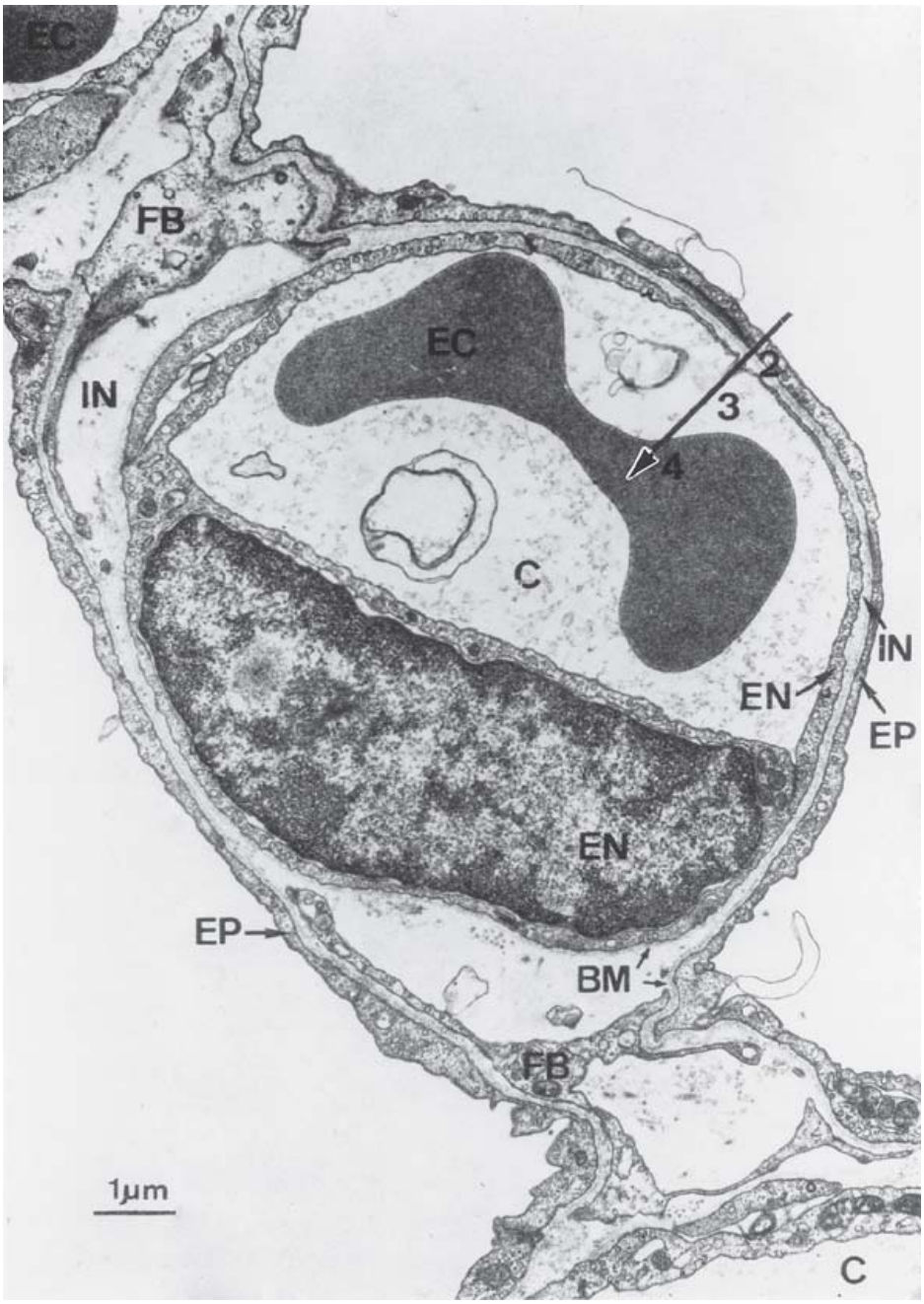


Figure 1-1. Electron micrograph showing a pulmonary capillary (C) in the alveolar wall. Note the extremely thin blood-gas barrier of about 0.3 μm in some places. The *large arrow* indicates the diffusion path from alveolar gas to the interior of the erythrocyte (EC) and includes the layer of surfactant (not shown in the preparation), alveolar epithelium (EP), interstitium (IN), capillary endothelium (EN), and plasma. Parts of structural cells called fibroblasts (FB), basement membrane (BM), and a nucleus of an endothelial cell are also seen.

of these bronchi make up the *conducting airways*. Their function is to lead inspired air to the gas-exchanging regions of the lung (Figure 1-4). Because the conducting airways contain no alveoli and therefore take no part in gas exchange, they constitute the *anatomic dead space*. Its volume is about 150 ml.

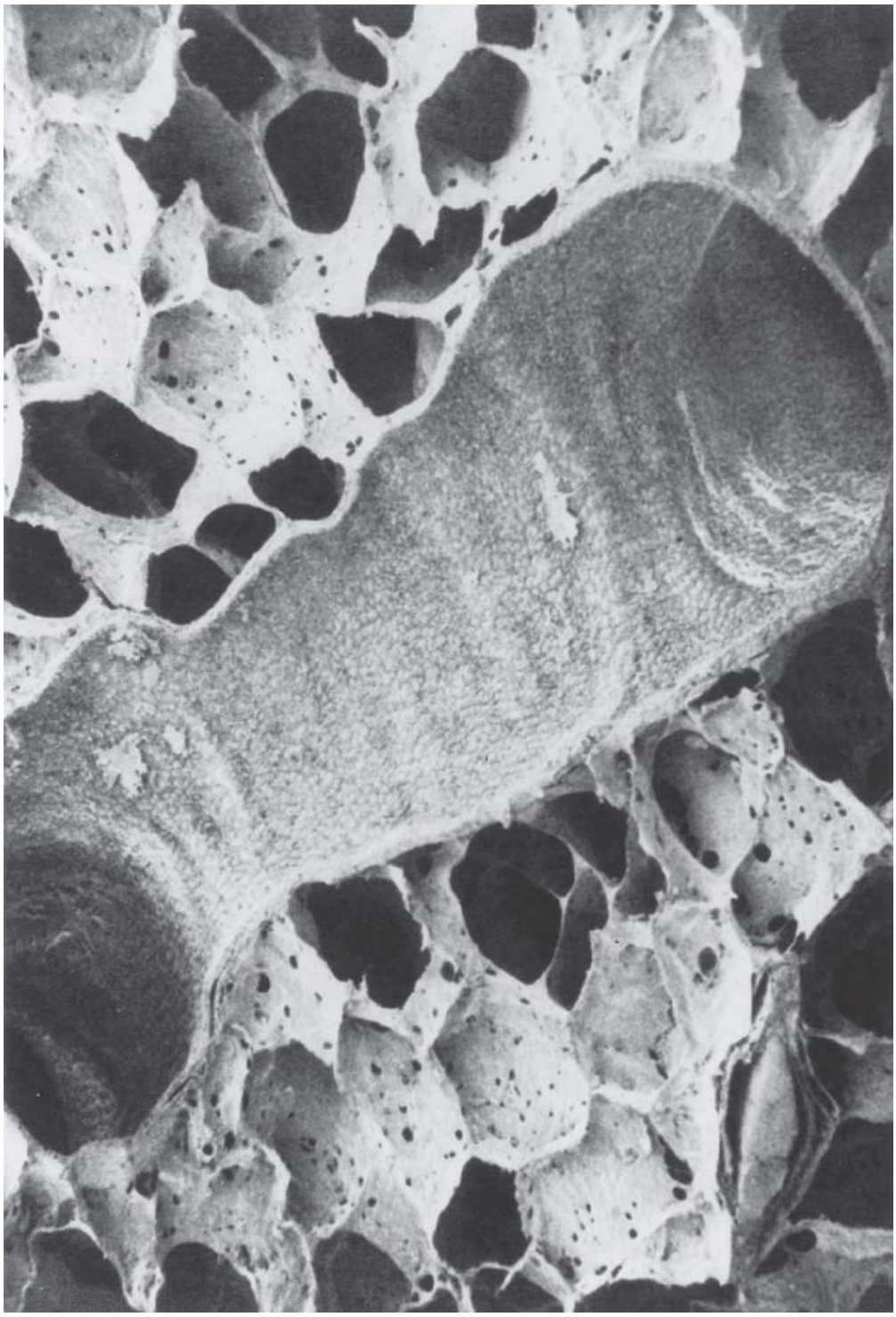


Figure 1-2. Section of lung showing many alveoli and a small bronchiole. The pulmonary capillaries run in the walls of the alveoli (Figure 1-1). The holes in the alveolar walls are the pores of Kohn.

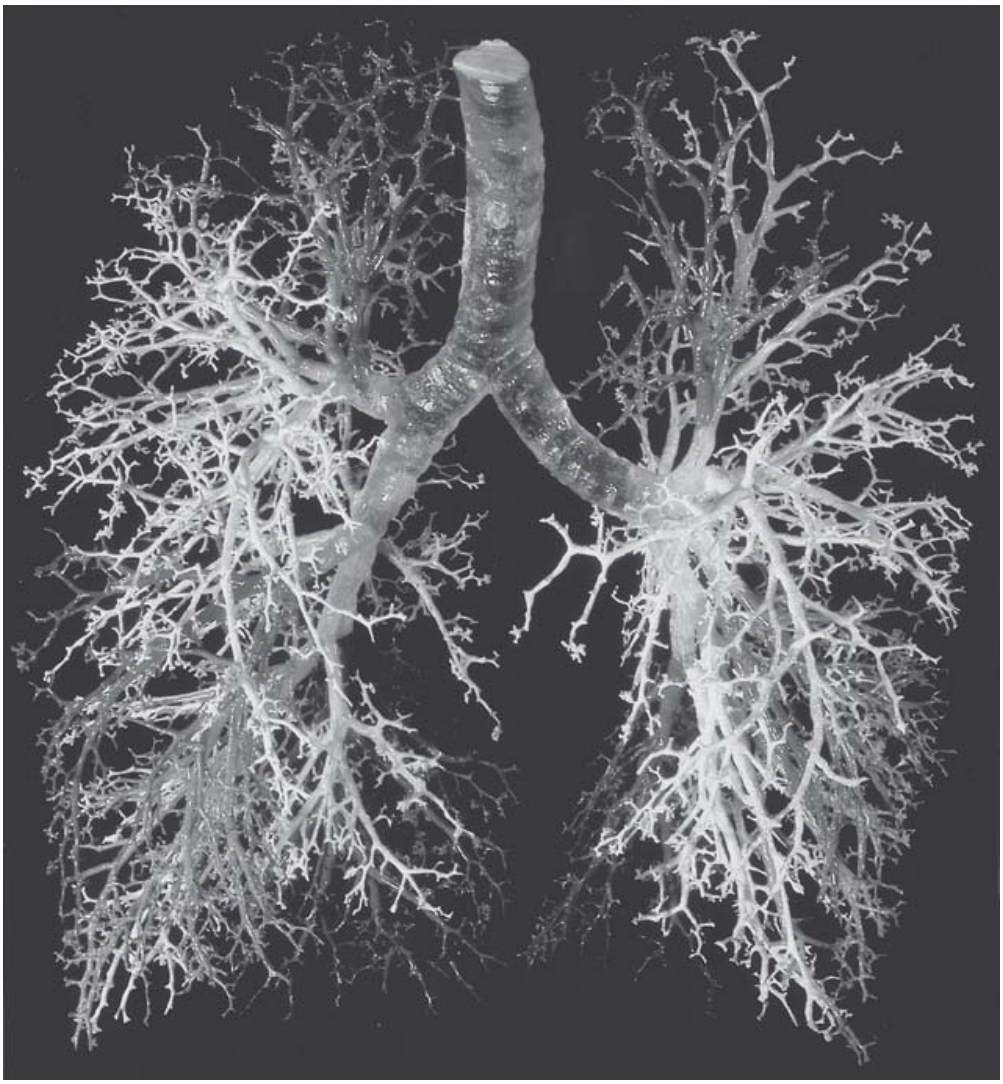


Figure 1-3. Cast of the airways of a human lung. The alveoli have been pruned away, allowing the conducting airways from the trachea to the terminal bronchioles to be seen.

The terminal bronchioles divide into *respiratory bronchioles*, which have occasional alveoli budding from their walls. Finally, we come to the *alveolar ducts*, which are completely lined with alveoli. This alveolated region of the lung where the gas exchange occurs is known as the *respiratory zone*. The portion of lung distal to a terminal bronchiole forms an anatomical unit called the *acinus*. The distance from the terminal bronchiole to the most distal alveolus is only a few millimeters, but the respiratory zone makes up most of the lung, its volume being about 2.5 to 3 liters during rest.

During inspiration, the volume of the thoracic cavity increases and air is drawn into the lung. The increase in volume is brought about partly by contraction of the diaphragm, which causes it to descend, and partly by the action of the intercostal muscles, which raise the ribs, thus increasing the cross-sectional area of the thorax. Inspired air flows down to about the terminal

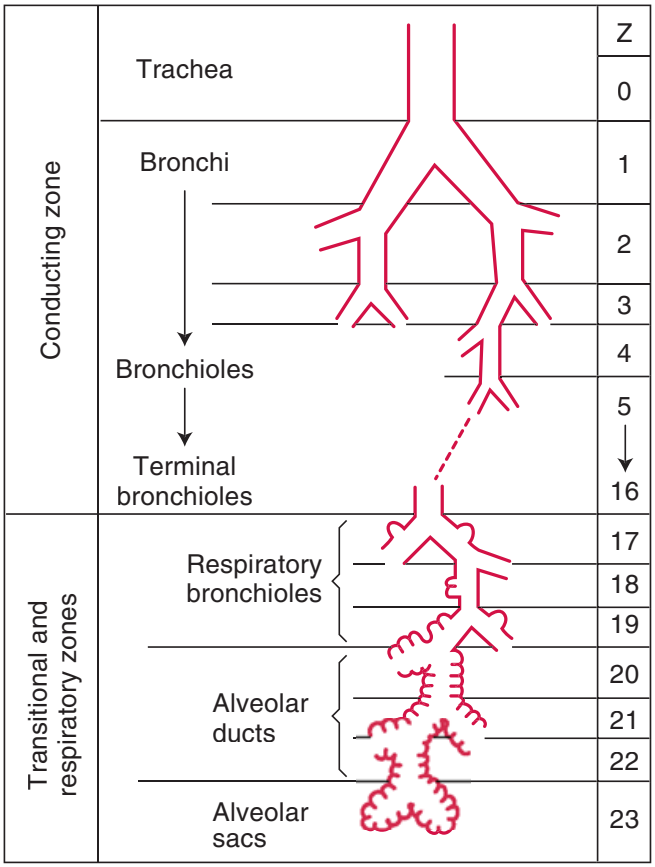


Figure 1-4. Idealization of the human airways according to Weibel. Note that the first 16 generations (Z) make up the conducting airways, and the last 7, the respiratory zone (or the transitional and respiratory zones).

bronchioles by bulk flow, like water through a hose. Beyond that point, the combined cross-sectional area of the airways is so enormous because of the large number of branches (Figure 1-5) that the forward velocity of the gas becomes small. Diffusion of gas within the airways then takes over as the dominant mechanism of ventilation in the respiratory zone. The rate of diffusion of gas molecules within the airways is so rapid and the distances to be covered so short that differences in concentration within the acinus are virtually abolished within a second. However, because the velocity of gas falls rapidly in the region of the terminal bronchioles, inhaled dust frequently settles out there.

The lung is elastic and returns passively to its preinspiratory volume during resting breathing. It is remarkably easy to distend. A normal breath of about 500 ml, for example, requires a distending pressure of less than 3 cm water. By contrast, a child's balloon may need a pressure of 30 cm water for the same change in volume.

The pressure required to move gas through the airways is also very small. During normal inspiration, an air flow rate of 1 liter. s^{-1} requires a pressure drop along the airways of less than 2 cm water. Compare a smoker's pipe, which needs a pressure of about 500 cm water for the same flow rate.

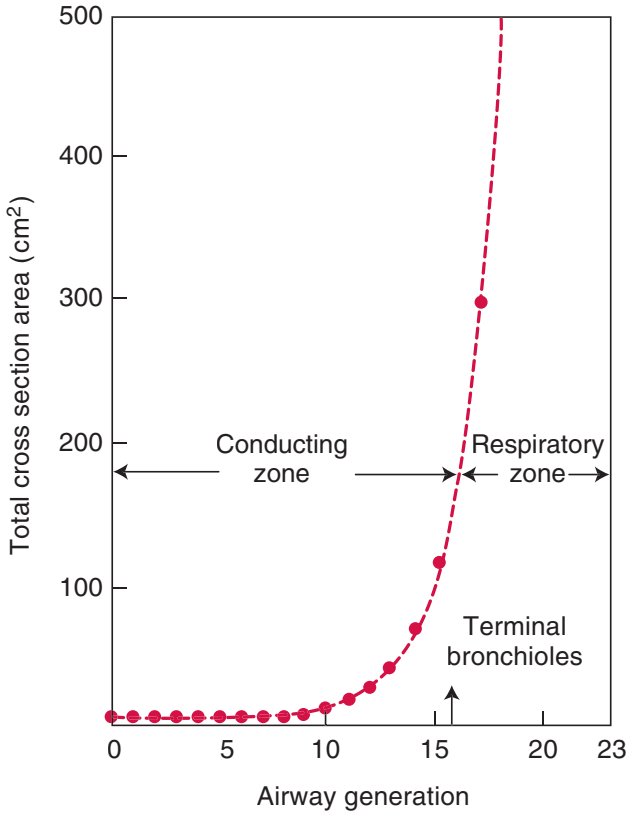


Figure 1-5. Diagram to show the extremely rapid increase in total cross-sectional area of the airways in the respiratory zone (compare Figure 1-4). As a result, the forward velocity of the gas during inspiration becomes very small in the region of the respiratory bronchioles, and gaseous diffusion becomes the chief mode of ventilation.

Airways

- Divided into a conducting zone and a respiratory zone
- Volume of the anatomic dead space is about 150 ml
- Volume of the alveolar region is about 2.5 to 3.0 liters
- Gas movement in the alveolar region is chiefly by diffusion

Blood Vessels and Flow

The pulmonary blood vessels also form a series of branching tubes from the *pulmonary artery* to the *capillaries* and back to the *pulmonary veins*. Initially, the arteries, veins, and bronchi run close together, but toward the periphery of the lung, the veins move away to pass between the lobules, whereas the arteries and bronchi travel together down the centers of the lobules. The capillaries form a dense network in the walls of the alveoli

(Figure 1-6). The diameter of a capillary segment is about 7 to 10 μm, just large enough for a red blood cell. The lengths of the segments are so short that the dense network forms an almost continuous sheet of blood in the alveolar wall, a very efficient arrangement for gas exchange. Alveolar walls are not often seen face on, as in Figure 1-6. The usual, thin microscopic cross section (Figure 1-7) shows the red blood cells in the capillaries and emphasizes the enormous exposure of blood to alveolar gas, with only the thin blood-gas barrier intervening (compare Figure 1-1).

The extreme thinness of the blood-gas barrier means that the capillaries are easily damaged. Increasing the pressure in the capillaries to high levels or inflating the lung to high volumes, for example, can raise the wall stresses of the capillaries to the point at which ultrastructural changes can occur. The capillaries then leak plasma and even red blood cells into the alveolar spaces.

The pulmonary artery receives the whole output of the right heart, but the resistance of the pulmonary circuit is astonishingly small. A mean pulmonary arterial pressure of only about 20 cm water (about 15 mm Hg) is required for a flow of 6 liter·min^{-1} (the same flow through a soda straw needs 120 cm water).

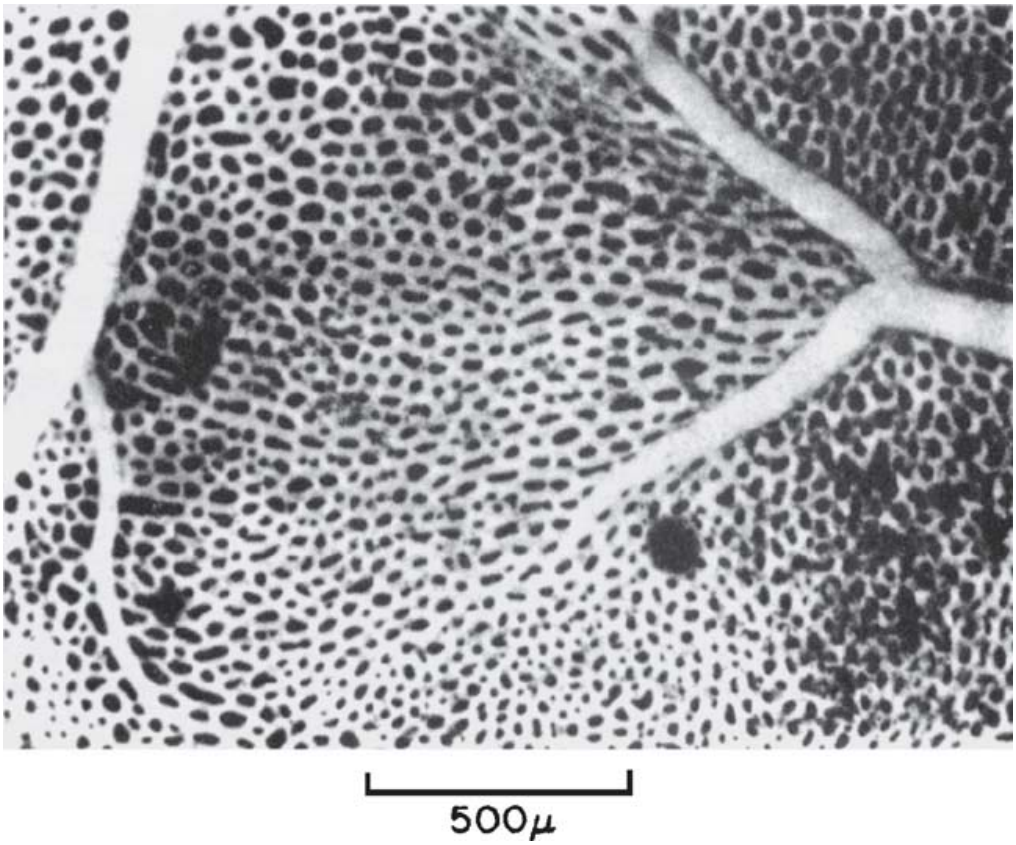


Figure 1-6. View of an alveolar wall (in the frog) showing the dense network of capillaries. A small artery (*left*) and vein (*right*) can also be seen. The individual capillary segments are so short that the blood forms an almost continuous sheet.

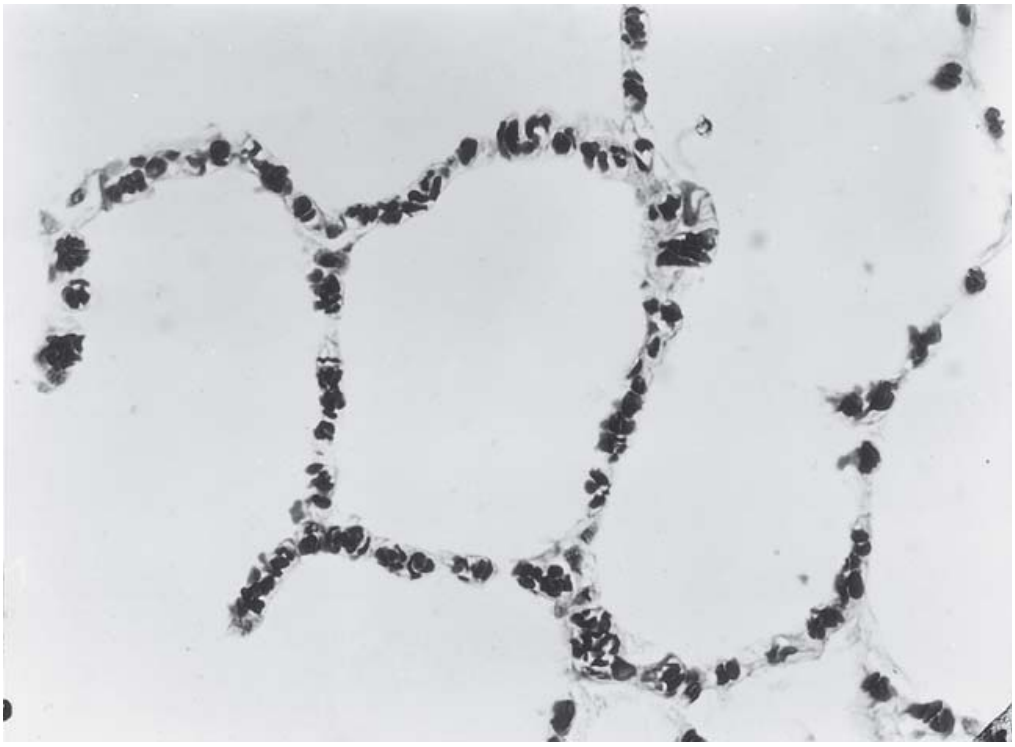


Figure 1-7. Microscopic section of dog lung showing capillaries in the alveolar walls. The blood-gas barrier is so thin that it cannot be identified here (compare Figure 1-1). This section was prepared from lung that was rapidly frozen while being perfused.

Each red blood cell spends about 0.75 second in the capillary network and during this time probably traverses two or three alveoli. So efficient is the anatomy for gas exchange that this brief time is sufficient for virtually complete equilibration of oxygen and carbon dioxide between alveolar gas and capillary blood.

The lung has an additional blood system, the bronchial circulation that supplies the conducting airways down to about the terminal bronchioles. Some of this blood is carried away from the lung via the pulmonary veins, and some enters the systemic circulation. The flow through the bronchial circulation is a mere fraction of that through the pulmonary circulation, and the lung can function fairly well without it, for example, following lung transplantation.

Blood-Gas Interface

- Extremely thin (0.2–0.3 μm) over much of its area
- Enormous surface area of 50 to 100 m^2
- Large area obtained by having about 500 million alveoli
- So thin that large increases in capillary pressure can damage the barrier

To conclude this brief account of the functional anatomy of the lung, let us glance at two special problems that the lung has overcome.

Stability of Alveoli

The lung can be regarded as a collection of 500 million bubbles, each 0.3 mm in diameter. Such a structure is inherently unstable. Because of the surface tension of the liquid lining the alveoli, relatively large forces develop that tend to collapse alveoli. Fortunately, some of the cells lining the alveoli secrete a material called *surfactant* that dramatically lowers the surface tension of the alveolar lining layer (see Chapter 7). As a consequence, the stability of the alveoli is enormously increased, although collapse of small air spaces is always a potential problem and frequently occurs in disease.

Blood Vessels

- The whole of the output of the right heart goes to the lung
- The diameter of the capillaries is about 7 to 10 μm
- The thickness of much of the capillary walls is less than 0.3 μm
- Blood spends about 0.75 second in the capillaries

Removal of Inhaled Particles

With its surface area of 50 to 100 square meters, the lung presents the largest surface of the body to an increasingly hostile environment. Various mechanisms for dealing with inhaled particles have been developed (see Chapter 9). Large particles are filtered out in the nose. Smaller particles that deposit in the conducting airways are removed by a moving staircase of mucus that continually sweeps debris up to the epiglottis, where it is swallowed. The mucus, secreted by mucous glands and also by goblet cells in the bronchial walls, is propelled by millions of tiny cilia, which move rhythmically under normal conditions but are paralyzed by some inhaled toxins.

The alveoli have no cilia, and particles that deposit there are engulfed by large wandering cells called macrophages. The foreign material is then removed from the lung via the lymphatics or the blood flow. Blood cells such as leukocytes also participate in the defense reaction to foreign material.

KEY CONCEPTS

1. The blood-gas barrier is extremely thin with a very large area, making it ideal for gas exchange by passive diffusion.
2. The conducting airways extend to the terminal bronchioles, with a total volume of about 150 ml. All the gas exchange occurs in the respiratory zone, which has a volume of about 2.5 to 3 liters.

3. Convective flow takes inspired gas to about the terminal bronchioles; beyond this, gas movement is increasingly by diffusion in the alveolar region.
4. The pulmonary capillaries occupy a huge area of the alveolar wall, and a red cell spends about 0.75 second in them.

QUESTIONS

For each question, choose the one best answer.

1. Concerning the blood-gas barrier of the human lung,

   A. The thinnest part of the blood-gas barrier has a thickness of about 3 μm.
   B. The total area of the blood-gas barrier is about 1 square meter.
   C. About 10% of the area of the alveolar wall is occupied by capillaries.
   D. If the pressure in the capillaries rises to unphysiologically high levels, the blood-gas barrier can be damaged.
   E. Oxygen crosses the blood-gas barrier by active transport.

2. When oxygen moves through the thin side of the blood-gas barrier from the alveolar gas to the hemoglobin of the red blood cell, it traverses the following layers in order:

   A. Epithelial cell, surfactant, interstitium, endothelial cell, plasma, red cell membrane.
   B. Surfactant, epithelial cell, interstitium, endothelial cell, plasma, red cell membrane.
   C. Surfactant, endothelial cell, interstitium, epithelial cell, plasma, red cell membrane.
   D. Epithelium cell, interstitium, endothelial cell, plasma, red cell membrane.
   E. Surfactant, epithelial cell, interstitium, endothelial cell, red cell membrane.

3. What is the P_{O_2} (in mm Hg) of moist inspired gas of a climber on the summit of Mt. Everest (assume barometric pressure is 247 mm Hg)?

   A. 32
   B. 42
   C. 52
   D. 62
   E. 72

4. Concerning the airways of the human lung,

   A. The volume of the conducting zone is about 50 ml.
   B. The volume of the rest of the lung during resting conditions is about 5 liters.
   C. A respiratory bronchiole can be distinguished from a terminal bronchiole because the latter has alveoli in its walls.
   D. On the average, there are about three branchings of the conducting airways before the first alveoli appear in their walls.
   E. In the alveolar ducts, the predominant mode of gas flow is diffusion rather than convection.

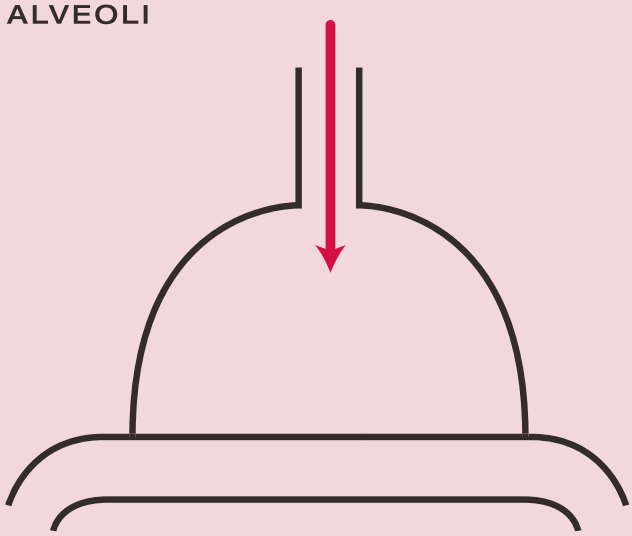
5. Concerning the blood vessels of the human lung,

   A. The pulmonary veins form a branching pattern that matches that of the airways.
   B. The average diameter of the capillaries is about 50 μm.
   C. The bronchial circulation has about the same blood flow as the pulmonary circulation.
   D. On the average, blood spends about 0.75 second in the capillaries under resting conditions.
   E. The mean pressure in the pulmonary artery is about 100 mm Hg.

Ventilation

2

HOW GAS GETS TO THE ALVEOLI



We now look in more detail at how oxygen is brought to the blood-gas barrier by the process of ventilation. First, lung volumes are briefly reviewed. Then total ventilation and alveolar ventilation, which is the amount of fresh gas getting to the alveoli, are discussed. The lung that does not participate in gas exchange is dealt with under the headings of anatomic and physiologic dead space. Finally, the uneven distribution of ventilation caused by gravity is introduced.

The next three chapters concern how inspired air gets to the alveoli, how gases cross the blood-gas interface, and how they are removed from the lung by the blood. These functions are carried out by ventilation, diffusion, and blood flow, respectively.

Figure 2-1 is a highly simplified diagram of a lung. The various bronchi that make up the conducting airways (Figures 1-3 and 1-4) are now represented by a single tube labeled "anatomic dead space." This leads into the gas-exchanging region of the lung, which is bounded by the blood-gas interface and the pulmonary capillary blood. With each inspiration, about 500 ml of air enters the lung (*tidal volume*). Note how small a proportion of the total lung volume is represented by the anatomic dead space. Also note the very small volume of capillary blood compared with that of alveolar gas (compare Figure 1-7).

Lung Volumes

Before looking at the movement of gas into the lung, a brief glance at the static volumes of the lung is helpful. Some of these can be measured with a spirometer (Figure 2-2). During exhalation, the bell goes up and the pen down, marking a moving chart. First, normal breathing can be seen (*tidal volume*). Next, the subject took a maximal inspiration and followed this by a maximal expiration. The exhaled volume is called the *vital capacity*. However, some gas remained in the lung after a maximal expiration; this is the *residual volume*. The volume of gas in the lung after a normal expiration is the *functional residual capacity (FRC)*.

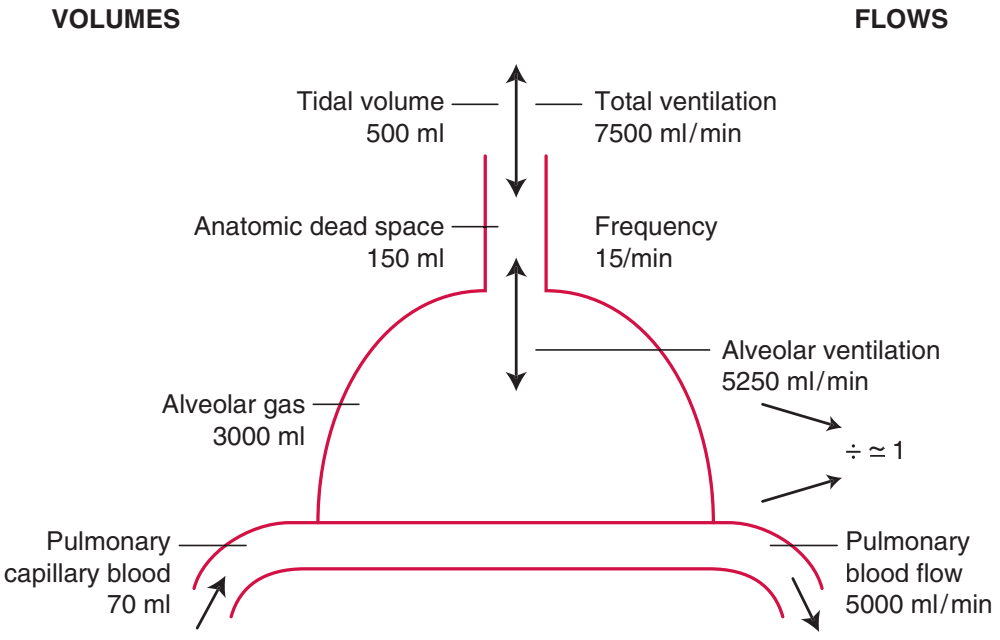


Figure 2-1. Diagram of a lung showing typical volumes and flows. There is considerable variation around these values.

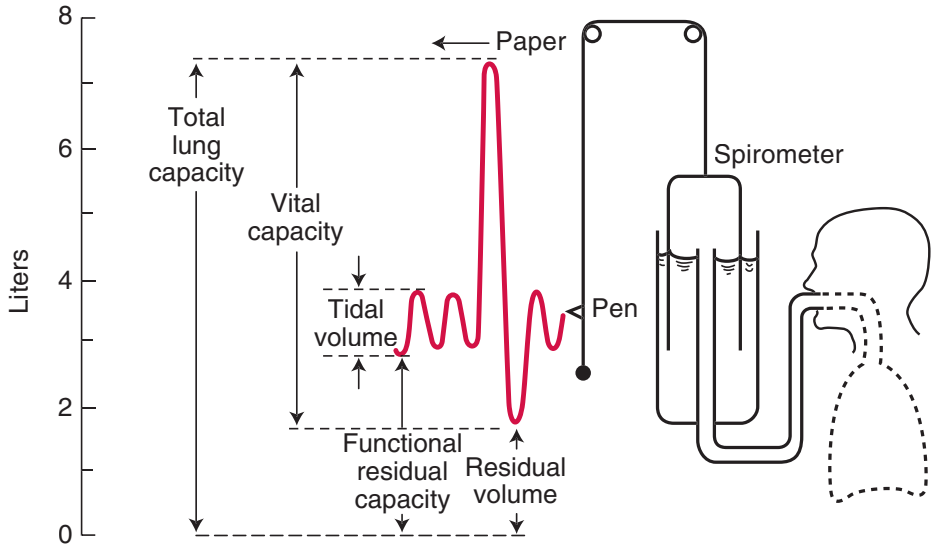
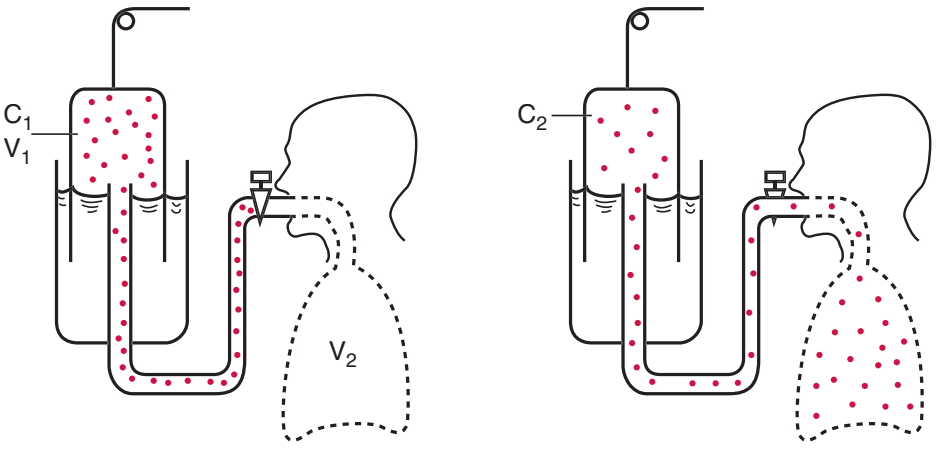


Figure 2-2. Lung volumes. Note that the total lung capacity, functional residual capacity, and residual volume cannot be measured with the spirometer.

Neither the FRC nor the residual volume can be measured with a simple spirometer. However, a gas dilution technique can be used, as shown in Figure 2-3. The subject is connected to a spirometer containing a known concentration of helium, which is virtually insoluble in blood. After some breaths, the helium concentrations in the spirometer and lung become the same.

Because no helium has been lost, the amount of helium present before equilibration (concentration times volume) is

$$C_1 \times V_1$$



$$C_1 \times V_1 = C_2 \times (V_1 + V_2)$$

Figure 2-3. Measurement of the functional residual capacity by helium dilution.

and equals the amount after equilibration:

$$C_2 \times (V_1 + V_2)$$

From this,

$$V_2 = V_1 \times \frac{C_1 - C_2}{C_2}$$

In practice, oxygen is added to the spirometer during equilibration to make up for that consumed by the subject, and also carbon dioxide is absorbed.

Another way of measuring the FRC is with a body plethysmograph (Figure 2-4). This is a large airtight box, like an old telephone booth, in which the subject sits. At the end of a normal expiration, a shutter closes the mouthpiece and the subject is asked to make respiratory efforts. As the subject tries to inhale, he (or she) expands the gas in his lungs; lung volume increases, and the box pressure rises because its gas volume decreases. Boyle's law states that pressure × volume is constant (at constant temperature).

Therefore, if the pressures in the box before and after the inspiratory effort are P_1 and P_2, respectively, V_1 is the preinspiratory box volume, and ΔV is the change in volume of the box (or lung), we can write

$$P_1 V_1 = P_2 (V_1 - \Delta V)$$

Thus, ΔV can be obtained.

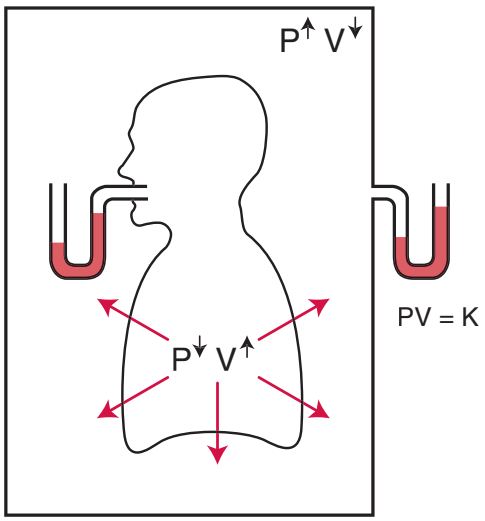


Figure 2-4. Measurement of FRC with a body plethysmograph. When the subject makes an inspiratory effort against a closed airway, he slightly increases the volume of his lung, airway pressure decreases, and box pressure increases. From Boyle's law, lung volume is obtained (see text).

Next, Boyle's law is applied to the gas in the lung. Now,

$$P_3V_2 = P_4(V_2 + \Delta V)$$

where P_3 and P_4 are the mouth pressures before and after the inspiratory effort, and V_2 is the FRC. Thus, FRC can be obtained.

The body plethysmograph measures the total volume of gas in the lung, including any that is trapped behind closed airways (an example is shown in Figure 7-9) and that therefore does not communicate with the mouth. By contrast, the helium dilution method measures only communicating gas or ventilated lung volume. In young normal subjects, these volumes are virtually the same, but in patients with lung disease, the ventilated volume may be considerably less than the total volume because of gas trapped behind obstructed airways.

Lung Volumes

- Tidal volume and vital capacity can be measured with a simple spirometer
- Total lung capacity, functional residual capacity, and residual volume need an additional measurement by helium dilution or the body plethysmograph
- Helium is used because of its very low solubility in blood
- The use of the body plethysmograph depends on Boyle's law, PV = K, at constant temperature

Ventilation

Suppose the volume exhaled with each breath is 500 ml (Figure 2-1) and there are 15 breaths·min^{-1}. Then the total volume leaving the lung each minute is 500 × 15 = 7500 ml·min^{-1}. This is known as the *total ventilation*. The volume of air entering the lung is very slightly greater because more oxygen is taken in than carbon dioxide is given out.

However, not all the air that passes the lips reaches the alveolar gas compartment where gas exchange occurs. Of each 500 ml inhaled in Figure 2-1, 150 ml remains behind in the anatomic dead space. Thus, the volume of fresh gas entering the respiratory zone each minute is (500 – 150) × 15 or 5250 ml·min^{-1}. This is called the *alveolar ventilation* and is of key importance because it represents the amount of fresh inspired air available for gas exchange (strictly, the alveolar ventilation is also measured on expiration, but the volume is almost the same).

The total ventilation can be measured easily by having the subject breathe through a valve box that separates the inspired from the expired gas, and

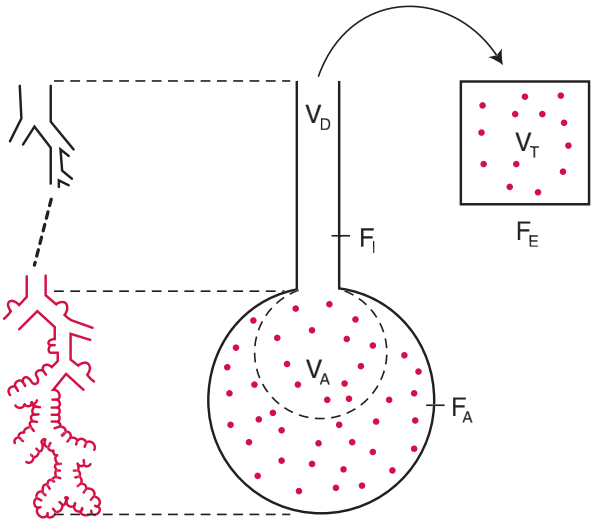


Figure 2-5. The tidal volume (V_T) is a mixture of gas from the anatomic dead space (V_D) and a contribution from the alveolar gas (V_A). The concentrations of CO_2 are shown by the *dots*. F, fractional concentration; I, inspired; E, expired. Compare Figure 1-4.

collecting all the expired gas in a bag. The alveolar ventilation is more difficult to determine. One way is to measure the volume of the anatomic dead space (see below) and calculate the dead space ventilation (volume × respiratory frequency). This is then subtracted from the total ventilation.

We can summarize this conveniently with symbols (Figure 2-5). Using V to denote volume, and the subscripts T, D, and A to denote tidal, dead space, and alveolar, respectively,

$$V_T = V_D + V_A^*$$

therefore,

$$V_T \cdot n = V_D \cdot n + V_A \cdot n$$

where n is the respiratory frequency.

Therefore,

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

where $\dot{V}$ means volume per unit time, $\dot{V}_E$ is expired total ventilation, and $\dot{V}_D$ and $\dot{V}_A$ are the dead space and alveolar ventilations, respectively (see Appendix A for a summary of symbols).

Thus,

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

*Note that V_A here means the volume of alveolar gas in the tidal volume, not the total volume of alveolar gas in the lung.

A difficulty with this method is that the anatomic dead space is not easy to measure, although a value for it can be assumed with little error. Note that alveolar ventilation can be increased by raising either tidal volume or respiratory frequency (or both). Increasing tidal volume is often more effective because this reduces the proportion of each breath occupied by the anatomic dead space.

Another way of measuring alveolar ventilation in normal subjects is from the concentration of CO_2 in expired gas (Figure 2-5). Because no gas exchange occurs in the anatomic dead space, there is no CO_2 there at the end of inspiration (we can neglect the small amount of CO_2 in the air). Thus, because all the expired CO_2 comes from the alveolar gas,

$$\dot{V}_{CO_2} = \dot{V}_A \times \frac{\%CO_2}{100}$$

The $\%CO_2/100$ is often called the fractional concentration and is denoted by Fco_2.

Therefore,

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

and rearranging gives

$$\dot{V}_A = \frac{\dot{V}_{CO_2}}{F_{CO_2}}$$

Thus, the alveolar ventilation can be obtained by dividing the CO_2 output by the alveolar fractional concentration of this gas.

Note that the partial pressure of CO_2 (denoted Pco_2) is proportional to the fractional concentration of the gas in the alveoli, or $Pco_2 = Fco_2 \times K$, where K is a constant.

Therefore,

$$\dot{V}_A = \frac{\dot{V}_{CO_2}}{P_{CO_2}} \times K$$

This is called the alveolar ventilation equation.

Because in normal subjects the Pco_2 of alveolar gas and arterial blood are virtually identical, the arterial Pco_2 can be used to determine alveolar ventilation. The relation between alveolar ventilation and Pco_2 is of crucial importance. If the alveolar ventilation is halved (and CO_2 production remains unchanged), for example, the alveolar and arterial Pco_2 will double.

Anatomic Dead Space

This is the volume of the conducting airways (Figures 1-3 and 1-4). The normal value is about 150 ml, and it increases with large inspirations because of the traction or pull exerted on the bronchi by the surrounding lung parenchyma. The dead space also depends on the size and posture of the subject.

The volume of the anatomic dead space can be measured by *Fowler's method*. The subject breathes through a valve box, and the sampling tube of a rapid nitrogen analyzer continuously samples gas at the lips (Figure 2-6A). Following a single inspiration of 100% O_2, the N_2 concentration rises as the dead space gas is increasingly washed out by alveolar gas. Finally, an almost uniform gas concentration is seen, representing pure alveolar gas. This phase is often called the alveolar "plateau," although in normal subjects it is not quite flat, and in patients with lung disease it may rise steeply. Expired volume is also recorded.

The dead space is found by plotting N_2 concentration against expired volume and drawing a vertical line such that area A is equal to area B in Figure 2-6B. The dead space is the volume expired up to the vertical line. In effect, this method measures the volume of the conducting airways down to the midpoint of the transition from dead space to alveolar gas.

Physiologic Dead Space

Another way of measuring dead space is *Bohr's method*. Figure 2-5 shows that all the expired CO_2 comes from the alveolar gas and none from the dead space. Therefore, we can write

$$V_T \cdot F_E = V_A \cdot F_A$$

Now,

$$V_T = V_A + V_D$$

Therefore,

$$V_A = V_T - V_D$$

substituting

$$V_T \cdot F_E = (V_T - V_D) \cdot F_A$$

whence

$$\frac{V_D}{V_T} = \frac{P_{A_{CO_2}} - P_{E_{CO_2}}}{P_{A_{CO_2}}} \quad \text{(Bohr equation)}$$

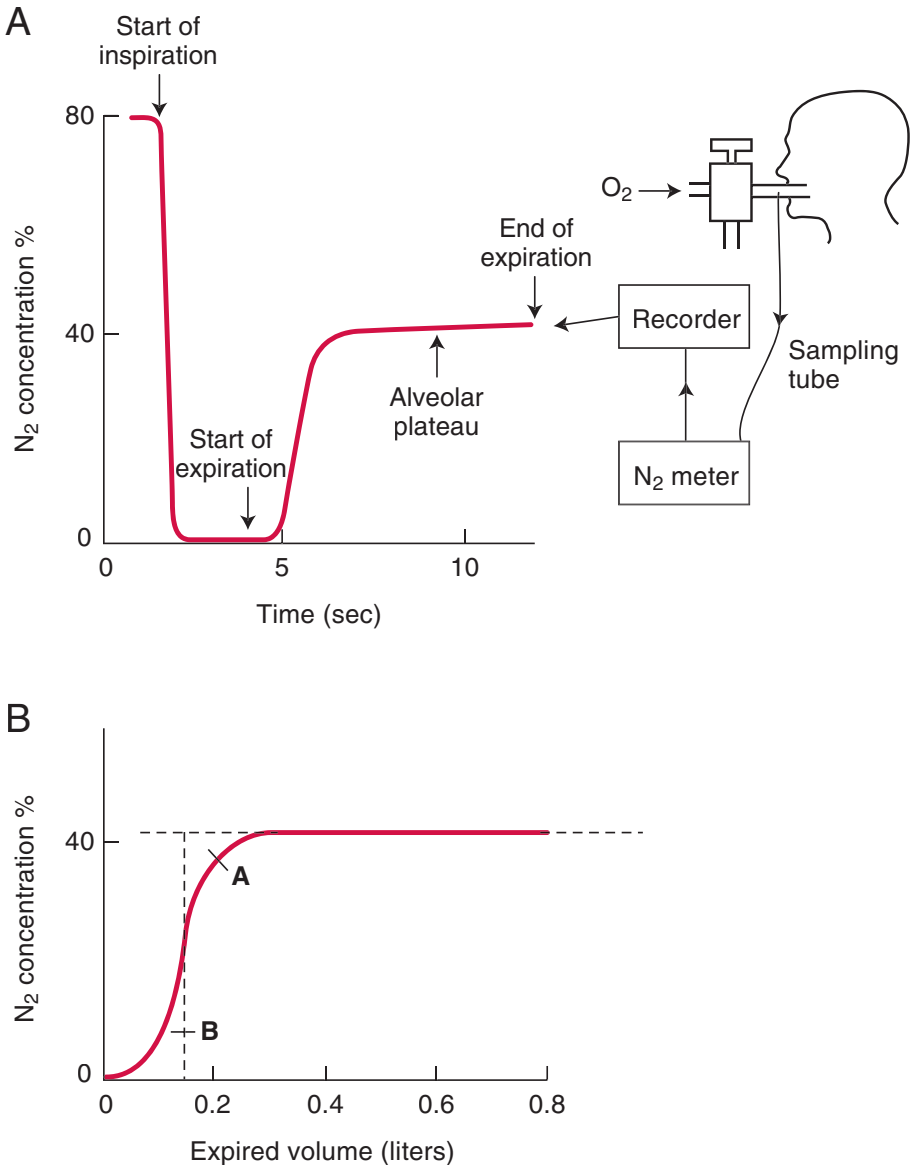


Figure 2-6. Fowler's method of measuring the anatomic dead space with a rapid N_2 analyzer. **A** shows that following a test inspiration of 100% O_2, the N_2 concentration rises during expiration to an almost level "plateau" representing pure alveolar gas. In **(B),** N_2 concentration is plotted against expired volume, and the dead space is the volume up to the *vertical dashed line*, which makes the areas *A* and *B* equal.

where A and E refer to alveolar and mixed expired, respectively (see Appendix A). The normal ratio of dead space to tidal volume is in the range of 0.2 to 0.35 during resting breathing. In normal subjects, the P_{CO_2} in alveolar gas and that in arterial blood are virtually identical so that the equation is therefore often written

$$\frac{V_D}{V_T} = \frac{P_{A_{CO_2}} - P_{E_{CO_2}}}{P_{A_{CO_2}}}$$

It should be noted that Fowler's and Bohr's methods measure somewhat different things. Fowler's method measures the volume of the conducting airways down to the level where the rapid dilution of inspired gas occurs with gas already in the lung. This volume is determined by the geometry of the rapidly expanding airways (Figure 1-5), and because it reflects the morphology of the lung, it is called the *anatomic dead space*. Bohr's method measures the volume of the lung that does not eliminate CO_2. Because this is a functional measurement, the volume is called the *physiologic dead space*. In normal subjects, the volumes are very nearly the same. However, in patients with lung disease, the physiologic dead space may be considerably larger because of inequality of blood flow and ventilation within the lung (see Chapter 5).

Ventilation

- Total ventilation is tidal volume × respiratory frequency
- Alveolar ventilation is the amount of fresh gas getting to the alveoli, or $(V_T – V_D) \times n$
- Anatomic dead space is the volume of the conducting airways, about 150 ml
- Physiologic dead space is the volume of gas that does not eliminate CO_2
- The two dead spaces are almost the same in normal subjects, but the physiologic dead space is increased in many lung diseases

Regional Differences in Ventilation

So far, we have been assuming that all regions of the normal lung have the same ventilation. However, it has been shown that the lower regions of the lung ventilate better than do the upper zones. This can be demonstrated if a subject inhales radioactive xenon gas (Figure 2-7). When the xenon-133 enters the counting field, its radiation penetrates the chest wall and can be recorded by a bank of counters or a radiation camera. In this way, the volume of the inhaled xenon going to various regions can be determined.

Figure 2-7 shows the results obtained in a series of normal volunteers using this method. It can be seen that ventilation per unit volume is greatest near the bottom of the lung and becomes progressively smaller toward the top. Other measurements show that when the subject is in the supine position, this difference disappears, with the result that apical and basal ventilations become the same. However, in that posture, the ventilation of the lowermost (posterior) lung exceeds that of the uppermost (anterior) lung. Again, in the lateral position (subject on his side), the dependent lung is best ventilated. The cause of these regional differences in ventilation is dealt with in Chapter 7.

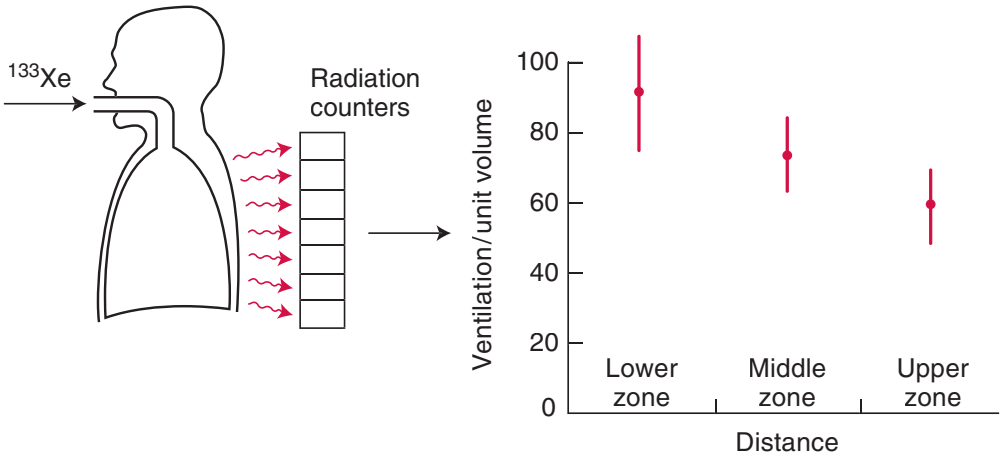


Figure 2-7. Measurement of regional differences in ventilation with radioactive xenon. When the gas is inhaled, its radiation can be detected by counters outside the chest. Note that the ventilation decreases from the lower to upper regions of the upright lung.

KEY CONCEPTS

1. Lung volumes that cannot be measured with a simple spirometer include the total lung capacity, the functional residual capacity, and the residual volume. These can be determined by helium dilution or the body plethysmograph.
2. Alveolar ventilation is the volume of fresh (non–dead space) gas entering the respiratory zone per minute. It can be determined from the alveolar ventilation equation, that is, the CO_2 output divided by the fractional concentration of CO_2 in the expired gas.
3. The concentration of CO_2 (and therefore its partial pressure) in alveolar gas and arterial blood is inversely related to the alveolar ventilation.
4. The anatomic dead space is the volume of the conducting airways and can be measured from the nitrogen concentration following a single inspiration of oxygen.
5. The physiologic dead space is the volume of lung that does not eliminate CO_2. It is measured by Bohr's method using arterial and expired CO_2.
6. The lower regions of the lung are better ventilated than the upper regions because of the effects of gravity on the lung.

Questions

For each question, choose the one best answer.

1. The only variable in the following list that cannot be measured with a simple spirometer and stopwatch is

   A. Tidal volume.
   B. Functional residual capacity.
   C. Vital capacity.
   D. Total ventilation.
   E. Respiratory frequency.

2. Concerning the pulmonary acinus,

A. Less than 90% oxygen uptake of the lung occurs in the acini.
B. Percentage change in volume of the acini during inspiration is less than that of the whole lung.
C. Volume of the acini is less than 90% of the total volume of the lung at FRC.
D. Each acinus is supplied by a terminal bronchiole.
E. The ventilation of the acini at the base of the upright human lung at FRC is less than those at the apex.

3. In a measurement of FRC by helium dilution, the original and final helium concentrations were 10% and 6%, and the spirometer volume was kept at 5 liters. What was the volume of the FRC in liters?

A. 2.5
B. 3.0
C. 3.3
D. 3.8
E. 5.0

4. A patient sits in a body plethysmograph (body box) and makes an expiratory effort against his closed glottis. What happens to the following: pressure in the lung airways, lung volume, box pressure, box volume?

	Airway Pressure	Lung Volume	Box Pressure	Box Volume
A.	↓	↑	↑	↓
B.	↓	↑	↓	↑
C.	↑	↓	↑	↓
D.	↑	↓	↓	↑
E.	↑	↑	↓	↓

5. If CO_2 production remains constant and alveolar ventilation is increased threefold, the alveolar P_{CO_2} after a steady state is reached will be what percentage of its former value?

A. 25
B. 33
C. 50
D. 100
E. 300

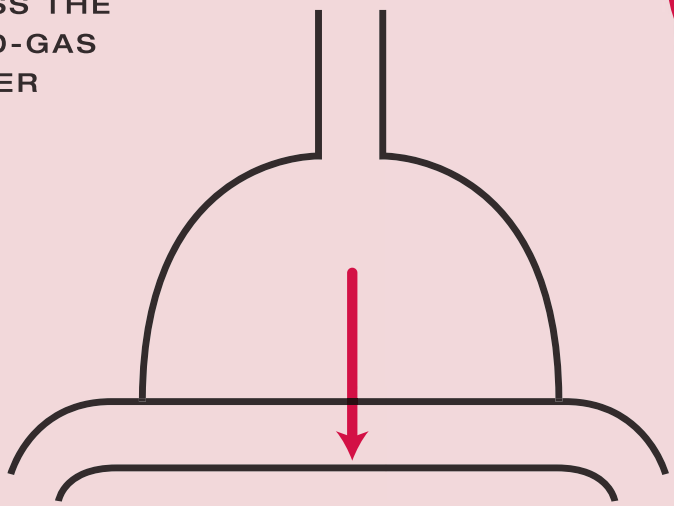
6. In a measurement of physiologic dead space using Bohr's method, the alveolar and mixed expired P_{CO_2} were 40 and 30 mm Hg, respectively. What was the ratio of dead space to tidal volume?

A. 0.20
B. 0.25
C. 0.30
D. 0.35
E. 0.40

Diffusion

3

HOW GAS GETS ACROSS THE BLOOD-GAS BARRIER



We now consider how gases move across the blood-gas barrier by diffusion. First, the basic laws of diffusion are introduced. Next, we distinguish between diffusion- and perfusion-limited gases. Oxygen uptake along the pulmonary capillary is then analyzed, and there is a section on the measurement of diffusing capacity using carbon monoxide. The finite reaction rate of oxygen with hemoglobin is conveniently considered with diffusion. Finally, there is a brief reference to the interpretation of measurements of diffusing capacity and possible limitations of carbon dioxide diffusion.

In the last chapter, we looked at how gas is moved from the atmosphere to the alveoli, or in the reverse direction. We now come to the transfer of gas across the blood-gas barrier. This process occurs by *diffusion*. Only 70 years ago, some physiologists believed that the lung secreted oxygen into the capillaries, that is, the oxygen was moved from a region of lower to one of higher partial pressure. Such a process was thought to occur in the swim bladder of fish, and it requires energy. But more accurate measurements showed that this does not occur in the lung and that all gases move across the alveolar wall by passive diffusion.

Laws of Diffusion

Diffusion through tissues is described by Fick's law (Figure 3-1). This states that the rate of transfer of a gas through a sheet of tissue is proportional to the tissue area and the difference in gas partial pressure between the two sides, and inversely proportional to the tissue thickness. As we have seen, the area of the blood-gas barrier in the lung is enormous (50 to 100 square meters), and the thickness is only 0.3 μm in many places (Figure 1-1), so the dimensions of the barrier are ideal for diffusion. In addition, the rate of transfer is proportional to a diffusion constant, which depends on the properties of the tissue and the particular gas. The constant is proportional to the solubility of the gas and inversely proportional to the square root of the molecular weight (Figure 3-1). This means that CO_2 diffuses about 20 times more rapidly than does O_2 through tissue sheets because it has a much higher solubility but not a very different molecular weight.

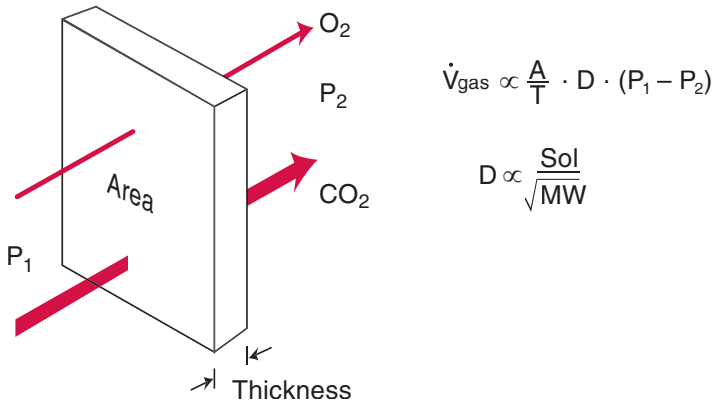


Figure 3-1. Diffusion through a tissue sheet. The amount of gas transferred is proportional to the area (A), a diffusion constant (D), and the difference in partial pressure ($P_1 - P_2$), and is inversely proportional to the thickness (T). The constant is proportional to the gas solubility (Sol) but inversely proportional to the square root of its molecular weight (MW).

Fick's Law of Diffusion

- The rate of diffusion of a gas through a tissue slice is proportional to the area but inversely proportional to the thickness
- Diffusion rate is proportional to the partial pressure difference
- Diffusion rate is proportional to the solubility of the gas in the tissue but inversely proportional to the square root of the molecular weight

Diffusion and Perfusion Limitations

Suppose a red blood cell enters a pulmonary capillary of an alveolus that contains a foreign gas such as carbon monoxide or nitrous oxide. How rapidly will the partial pressure in the blood rise? Figure 3-2 shows the time courses as the red blood cell moves through the capillary, a process that takes about 0.75 second. Look first at carbon monoxide. When the red cell enters the

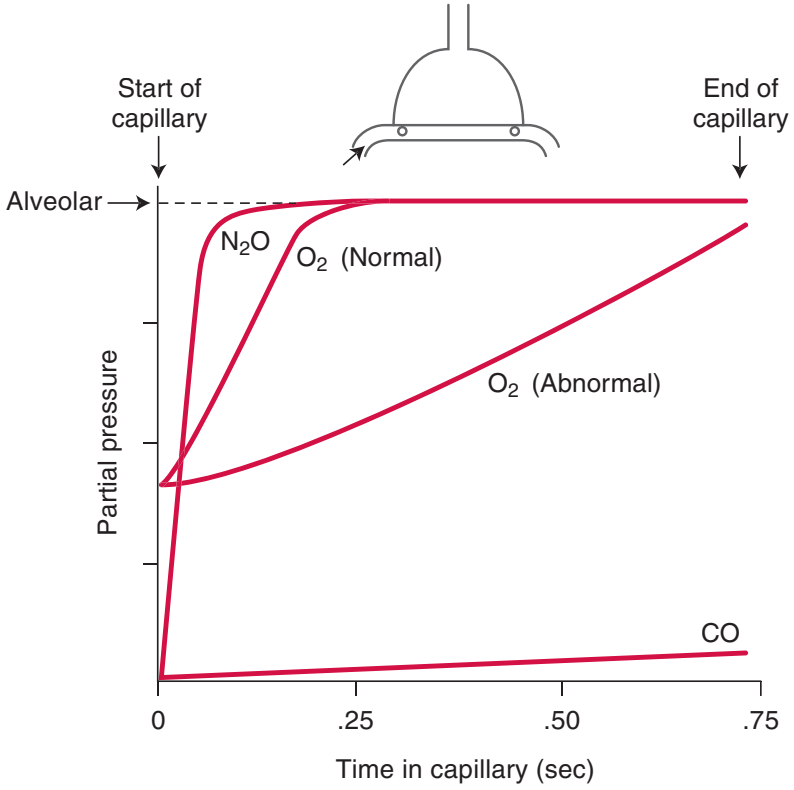


Figure 3-2. Uptake of carbon monoxide, nitrous oxide, and O_2 along the pulmonary capillary. Note that the blood partial pressure of nitrous oxide virtually reaches that of alveolar gas very early in the capillary, so the transfer of this gas is perfusion limited. By contrast, the partial pressure of carbon monoxide in the blood is almost unchanged, so its transfer is diffusion limited. O_2 transfer can be perfusion limited or partly diffusion limited, depending on the conditions.

capillary, carbon monoxide moves rapidly across the extremely thin blood-gas barrier from the alveolar gas into the cell. As a result, the content of carbon monoxide in the cell rises. However, because of the tight bond that forms between carbon monoxide and hemoglobin within the cell, a large amount of carbon monoxide can be taken up by the cell with almost no increase in partial pressure. Thus, as the cell moves through the capillary, the carbon monoxide partial pressure in the blood hardly changes, so that no appreciable back pressure develops, and the gas continues to move rapidly across the alveolar wall. It is clear, therefore, that the amount of carbon monoxide that gets into the blood is limited by the diffusion properties of the blood-gas barrier and not by the amount of blood available.* The transfer of carbon monoxide is therefore said to be *diffusion limited*.

Contrast the time course of nitrous oxide. When this gas moves across the alveolar wall into the blood, no combination with hemoglobin takes place. As a result, the blood has nothing like the avidity for nitrous oxide that it has for carbon monoxide, and the partial pressure rises rapidly. Indeed, Figure 3-2 shows that the partial pressure of nitrous oxide in the blood has virtually reached that of the alveolar gas by the time the red cell is only one-tenth of the way along the capillary. After this point, almost no nitrous oxide is transferred. Thus, the amount of this gas taken up by the blood depends entirely on the amount of available blood flow and not at all on the diffusion properties of the blood-gas barrier. The transfer of nitrous oxide is therefore *perfusion limited*.

What of O_2? Its time course lies between those of carbon monoxide and nitrous oxide. O_2 combines with hemoglobin (unlike nitrous oxide) but with nothing like the avidity of carbon monoxide. In other words, the rise in partial pressure when O_2 enters a red blood cell is much greater than is the case for the same number of molecules of carbon monoxide. Figure 3-2 shows that the Po_2 of the red blood cell as it enters the capillary is already about four-tenths of the alveolar value because of the O_2 in mixed venous blood. Under typical resting conditions, the capillary Po_2 virtually reaches that of alveolar gas when the red cell is about one-third of the way along the capillary. Under these conditions, O_2 transfer is perfusion limited like nitrous oxide. However, in some abnormal circumstances when the diffusion properties of the lung are impaired, for example, because of thickening of the blood-gas barrier, the blood Po_2 does not reach the alveolar value by the end of the capillary, and now there is some diffusion limitation as well.

A more detailed analysis shows that whether a gas is diffusion limited or not depends essentially on its solubility in the blood-gas barrier compared with its "solubility" in blood (actually the slope of the dissociation curve; see Chapter 6). For a gas like carbon monoxide, these are very different, whereas for a gas like nitrous oxide, they are the same. An analogy is the rate at which sheep can enter a field through a gate. If the gate is narrow but the field is

*This introductory description of carbon monoxide transfer is not completely accurate because of the rate of reaction of carbon monoxide with hemoglobin (see later).

large, the number of sheep that can enter in a given time is limited by the size of the gate. However, if both the gate and the field are small (or both are big), the number of sheep is limited by the size of the field.

Oxygen Uptake Along the Pulmonary Capillary

Let us take a closer look at the uptake of O_2 by blood as it moves through a pulmonary capillary. Figure 3-3A shows that the Po_2 in a red blood cell entering the capillary is normally about 40 mm Hg. Across the blood-gas barrier, only 0.3 μm away, is the alveolar Po_2 of 100 mm Hg. Oxygen floods down

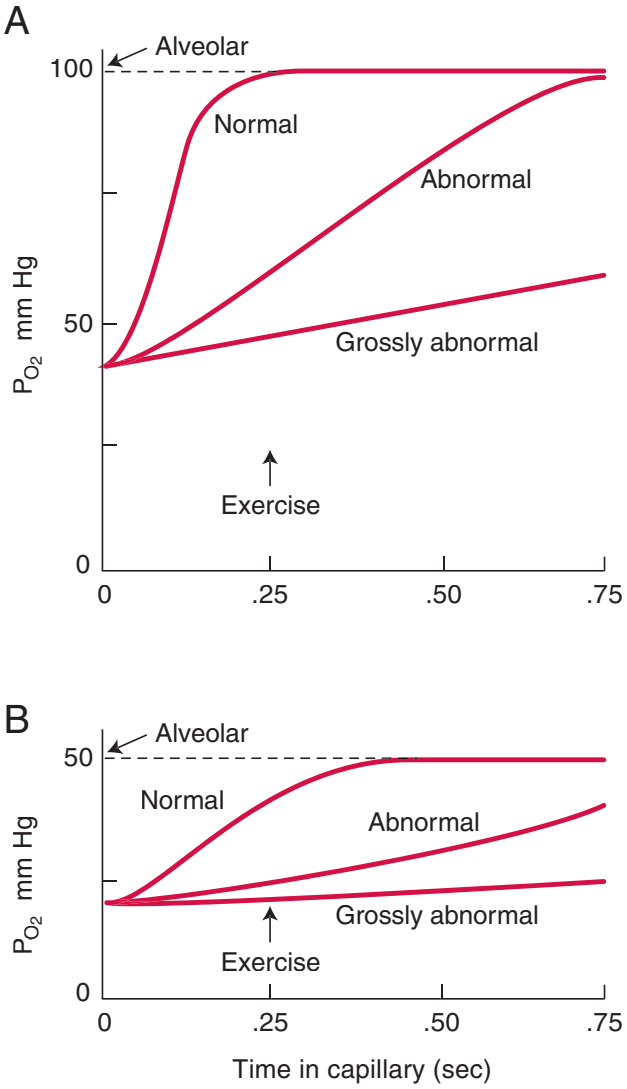


Figure 3-3. Oxygen time courses in the pulmonary capillary when diffusion is normal and abnormal (e.g., because of thickening of the blood-gas barrier by disease). **A** shows time courses when the alveolar Po_2 is normal. **B** shows slower oxygenation when the alveolar Po_2 is abnormally low. Note that in both cases, severe exercise reduces the time available for oxygenation.

this large pressure gradient, and the Po_2 in the red cell rapidly rises; indeed, as we have seen, it very nearly reaches the Po_2 of alveolar gas by the time the red cell is only one-third of its way along the capillary. Thus, under normal circumstances, the difference in Po_2 between alveolar gas and end-capillary blood is immeasurably small—a mere fraction of an mm Hg. In other words, the diffusion reserves of the normal lung are enormous.

With severe exercise, the pulmonary blood flow is greatly increased, and the time normally spent by the red cell in the capillary, about 0.75 second, may be reduced to as little as one-third of this. Therefore, the time available for oxygenation is less, but in normal subjects breathing air, there is generally still no measurable fall in end-capillary Po_2. However, if the blood-gas barrier is markedly thickened by disease so that oxygen diffusion is impeded, the rate of rise of Po_2 in the red blood cells is correspondingly slow, and the Po_2 may not reach that of alveolar gas before the time available for oxygenation in the capillary has run out. In this case, a measurable difference between alveolar gas and end-capillary blood for Po_2 may occur.

Another way of stressing the diffusion properties of the lung is to lower the alveolar Po_2 (Figure 3-3B). Suppose that this has been reduced to 50 mm Hg, by the subject either going to high altitude or inhaling a low O_2 mixture. Now, although the Po_2 in the red cell at the start of the capillary may only be about 20 mm Hg, the partial pressure difference responsible for driving the O_2 across the blood-gas barrier has been reduced from 60 mm Hg (Figure 3-3A) to only 30 mm Hg. O_2 therefore moves across more slowly. In addition, the rate of rise of Po_2 for a given increase in O_2 concentration in the blood is less than it was because of the steep slope of the O_2 dissociation curve when the Po_2 is low (see Chapter 6). For both of these reasons, therefore, the rise in Po_2 along the capillary is relatively slow, and failure to reach the alveolar Po_2 is more likely. Thus, severe exercise at very high altitude is one of the few situations in which diffusion impairment of O_2 transfer in normal subjects can be convincingly demonstrated. By the same token, patients with a thickened blood-gas barrier will be most likely to show evidence of diffusion impairment if they breathe a low oxygen mixture, especially if they exercise as well.

Diffusion of Oxygen Across the Blood-Gas Barrier

- At rest, the Po_2 of the blood virtually reaches that of the alveolar gas after about one-third of its time in the capillary
- Blood spends only about 0.75 second in the capillary at rest
- On exercise, the time is reduced to perhaps 0.25 second
- The diffusion process is challenged by exercise, alveolar hypoxia, and thickening of the blood-gas barrier

Measurement of Diffusing Capacity

We have seen that oxygen transfer into the pulmonary capillary is normally limited by the amount of blood flow available, although under some circumstances diffusion limitation also occurs (Figure 3-2). By contrast, the transfer of carbon monoxide is limited solely by diffusion, and it is therefore the gas of choice for measuring the diffusion properties of the lung. At one time O_2 was employed under hypoxic conditions (Figure 3-3B), but this technique is no longer used.

The laws of diffusion (Figure 3-1) state that the amount of gas transferred across a sheet of tissue is proportional to the area, a diffusion constant, and the difference in partial pressure, and inversely proportional to the thickness, or

$$\dot{V}_{gas} = \frac{A}{T} \cdot D \cdot (P_1 - P_2)$$

Now, for a complex structure like the blood-gas barrier of the lung, it is not possible to measure the area and thickness during life. Instead, the equation is rewritten

$$\dot{V}_{gas} = D_L \cdot (P_1 - P_2)$$

where D_L is called the *diffusing capacity of the lung* and includes the area, thickness, and diffusion properties of the sheet and the gas concerned. Thus, the diffusing capacity for carbon monoxide is given by

$$D_L = \frac{\dot{V}_{CO}}{P_1 - P_2}$$

where P_1 and P_2 are the partial pressures of alveolar gas and capillary blood, respectively. But as we have seen (Figure 3-2), the partial pressure of carbon monoxide in capillary blood is extremely small and can generally be neglected. Thus,

$$D_L = \frac{\dot{V}_{CO}}{P_{A_{CO}}}$$

or, in words, the diffusing capacity of the lung for carbon monoxide is the volume of carbon monoxide transferred in milliliters per minute per mm Hg of alveolar partial pressure.

Measurement of Diffusing Capacity

- Carbon monoxide is used because the uptake of this gas is diffusion limited
- Normal diffusing capacity is about 25 ml·min^{-1}·mm Hg^{-1}
- Diffusing capacity increases on exercise

A frequently used test is the *single-breath method*, in which a single inspiration of a dilute mixture of carbon monoxide is made and the rate of disappearance of carbon monoxide from the alveolar gas during a 10-second breathhold is calculated. This is usually done by measuring the inspired and expired concentrations of carbon monoxide with an infrared analyzer. The alveolar concentration of carbon monoxide is not constant during the breath-holding period, but allowance can be made for that. Helium is also added to the inspired gas to give a measurement of lung volume by dilution.

The normal value of the diffusing capacity for carbon monoxide at rest is about 25 ml·min^{-1}·mm Hg^{-1}, and it increases to two or three times this value on exercise because of recruitment and distension of pulmonary capillaries (see Chapter 4).

Reaction Rates with Hemoglobin

So far we have assumed that all the resistance to the movement of O_2 and CO resides in the barrier between blood and gas. However, Figure 1-1 shows that the path length from the alveolar wall to the center of a red blood cell exceeds that in the wall itself, so that some of the diffusion resistance is located within the capillary. In addition, there is another type of resistance to gas transfer that is most conveniently discussed with diffusion, that is, the resistance caused by the finite rate of reaction of O_2 or CO with hemoglobin inside the red blood cell.

When O_2 (or CO) is added to blood, its combination with hemoglobin is quite fast, being well on the way to completion in 0.2 second. However, oxygenation occurs so rapidly in the pulmonary capillary (Figure 3-3) that even this rapid reaction significantly delays the loading of O_2 by the red cell. Thus, the uptake of O_2 (or CO) can be regarded as occurring in two stages: (1) diffusion of O_2 through the blood-gas barrier (including the plasma and red cell interior) and (2) reaction of the O_2 with hemoglobin (Figure 3-4). In fact, it is possible to sum the two resultant resistances to produce an overall "diffusion" resistance.

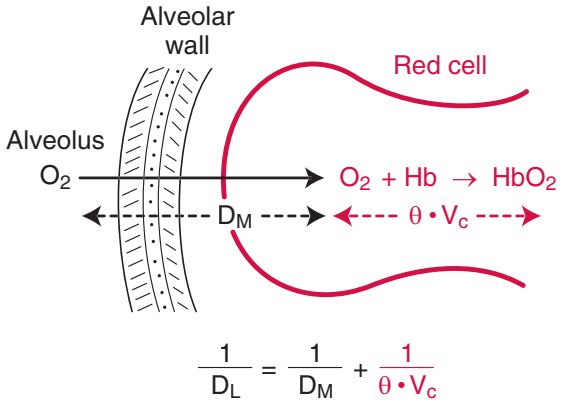


Figure 3-4. The diffusing capacity of the lung (D_L) is made up of two components: that due to the diffusion process itself and that attributable to the time taken for O_2 (or CO) to react with hemoglobin.

We saw that the diffusing capacity of the lung is defined as $D_L = \dot{V}_{gas}/(P_1 - P_2)$, that is, as the flow of gas divided by a pressure difference. Thus, the inverse of D_L is pressure difference divided by flow and is therefore analogous to electrical resistance. Consequently, the resistance of the blood-gas barrier in Figure 3-4 is shown as $1/D_M$, where M means membrane. Now, the rate of reaction of O_2 (or CO) with hemoglobin can be described by θ, which gives the rate in milliliters per minute of O_2 (or CO) that combine with 1 ml of blood per mm Hg partial pressure of O_2 (or CO). This is analogous to the "diffusing capacity" of 1 ml of blood and, when multiplied by the volume of capillary blood (V_c), gives the effective "diffusing capacity" of the rate of reaction of O_2 with hemoglobin. Again its inverse, $1/(\theta \cdot V_c)$, describes the resistance of this reaction. We can add the resistances offered by the membrane and the blood to obtain the total diffusion resistance. Thus, the complete equation is

$$\frac{1}{D_L} = \frac{1}{D_M} + \frac{1}{\theta \cdot V_c}$$

In practice, the resistances offered by the membrane and blood components are approximately equal, so that a reduction of capillary blood volume by disease can reduce the measured diffusing capacity of the lung. θ for CO is reduced if a subject breathes a high O_2 mixture, because the O_2 competes with the CO for hemoglobin. As a result, the measured diffusing capacity is reduced by O_2 breathing. In fact, it is possible to separately determine D_M and V_c by measuring the diffusing capacity for CO at different alveolar Po_2 values.

Reaction Rates of O_2 and CO with Hemoglobin

- The reaction rate of O_2 is fast, but because so little time is available in the capillary, this rate can become a limiting factor.
- The resistance to the uptake of O_2 attributable to reaction rate is probably about the same as that due to diffusion across the blood-gas barrier.
- The reaction rate of CO can be altered by changing the alveolar P_{O_2}. In this way, the separate contributions of the diffusion properties of the blood-gas barrier and the volume of capillary blood can be derived.

Interpretation of Diffusing Capacity for CO

It is clear that the measured diffusing capacity of the lung for CO depends not only on the area and thickness of the blood-gas barrier but also on the volume of blood in the pulmonary capillaries. Furthermore, in the diseased lung, the measurement is affected by the distribution of diffusion properties, alveolar volume, and capillary blood. For these reasons, the term *transfer factor* is sometimes used (particularly in Europe) to emphasize that the measurement does not solely reflect the diffusion properties of the lung.

CO_2 Transfer Across the Pulmonary Capillary

We have seen that diffusion of CO_2 through tissue is about 20 times faster than that of O_2 because of the much higher solubility of CO_2 (Figure 3-1). At first sight, therefore, it seems unlikely that CO_2 elimination could be affected by diffusion difficulties, and indeed, this has been the general belief. However, the reaction of CO_2 with blood is complex (see Chapter 6), and although there is some uncertainty about the rates of the various reactions, it is possible that a difference between end-capillary blood and alveolar gas can develop if the blood-gas barrier is diseased.

KEY CONCEPTS

1. Fick's law states that the rate of diffusion of a gas through a tissue sheet is proportional to the area of the sheet and the partial pressure difference across it, and inversely proportional to the thickness of the sheet.
2. Examples of diffusion- and perfusion-limited gases are carbon monoxide and nitrous oxide, respectively. Oxygen transfer is normally perfusion limited, but

some diffusion limitation may occur under some conditions, including intense exercise, thickening of the blood-gas barrier, and alveolar hypoxia.

3. The diffusing capacity of the lung is measured using inhaled carbon monoxide. The value increases markedly on exercise.
4. The finite reaction rate of oxygen with hemoglobin can reduce its transfer rate into the blood, and the effect is similar to that of reducing the diffusion rate.
5. Carbon dioxide transfer across the blood-gas barrier is probably not diffusion limited.

QUESTIONS

For each question, choose the one best answer.

1. Using Fick's law of diffusion of gases through a tissue slice, if gas X is 4 times as soluble and 4 times as dense as gas Y, what is the ratio of the diffusion rates of X to Y?

   A. 0.25
   B. 0.5
   C. 2
   D. 4
   E. 8

2. An exercising subject breathes a low concentration of CO in a steady state. If the alveolar P_{CO} is 0.5 mm Hg and the CO uptake is 30 ml·min^{-1}, what is the diffusing capacity of the lung for CO in ml·min^{-1}·mm·Hg^{-1}?

   A. 20
   B. 30
   C. 40
   D. 50
   E. 60

3. In a normal person, doubling the diffusing capacity of the lung would be expected to

   A. Decrease arterial P_{CO_2} during resting breathing.
   B. Increase resting oxygen uptake when the subject breathes 10% oxygen.
   C. Increase the uptake of nitrous oxide during anesthesia.
   D. Increase the arterial P_{O_2} during resting breathing.
   E. Increase maximal oxygen uptake at extreme altitude.

4. If a subject inhales several breaths of a gas mixture containing low concentrations of carbon monoxide and nitrous oxide,

   A. The partial pressures of carbon monoxide in alveolar gas and end-capillary blood will be virtually the same.
   B. The partial pressures of nitrous oxide in alveolar gas and end-capillary blood will be very different.
   C. Carbon monoxide is transferred into the blood along the whole length of the capillary.
   D. Little of the nitrous oxide will be taken up in the early part of the capillary.
   E. The uptake of nitrous oxide can be used to measure the diffusing capacity of the lung.

5. Concerning the diffusing capacity of the lung,

A. It is best measured with carbon monoxide because this gas diffuses very slowly across the blood-gas barrier.
B. Diffusion limitation of oxygen transfer during exercise is more likely to occur at sea level than at high altitude.
C. Breathing oxygen reduces the measured diffusing capacity for carbon monoxide compared with air breathing.
D. It is decreased by exercise.
E. It is increased in pulmonary fibrosis, which thickens the blood-gas barrier.

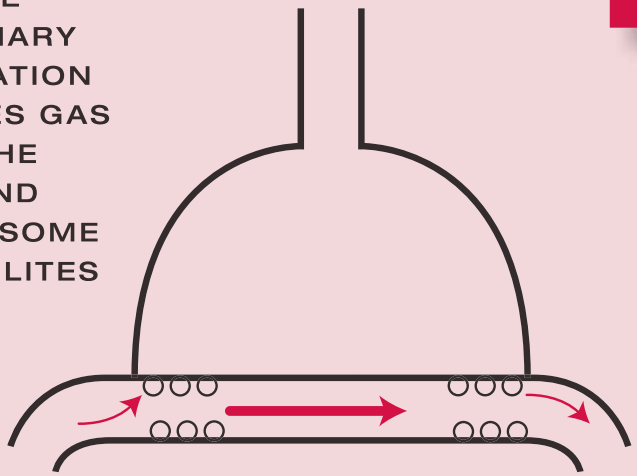
6. The diffusing capacity of the lung for carbon monoxide is increased by

A. Emphysema, which causes loss of pulmonary capillaries.
B. Asbestosis, which causes thickening of the blood-gas barrier.
C. Pulmonary embolism, which cuts off the blood supply to part of the lung.
D. Exercise in a normal subject.
E. Severe anemia.

Blood Flow and Metabolism

4

HOW THE PULMONARY CIRCULATION REMOVES GAS FROM THE LUNG AND ALTERS SOME METABOLITES



We now turn to how the respiratory gases are removed from the lung. First the pressures inside and outside the pulmonary blood vessels are considered, and then pulmonary vascular resistance is introduced. Next, we look at the measurement of total pulmonary blood flow and its uneven distribution caused by gravity. Active control of the circulation is then addressed, followed by fluid balance in the lung. Finally, other functions of the pulmonary circulation are dealt with, particularly the metabolic functions of the lung.

The pulmonary circulation begins at the main pulmonary artery, which receives the mixed venous blood pumped by the right ventricle. This artery then branches successively like the system of airways (Figure 1-3), and, indeed, the pulmonary arteries accompany the airways as far as the terminal bronchioles. Beyond that, they break up to supply the capillary bed that lies in the walls of the alveoli (Figures 1-6 and 1-7). The pulmonary capillaries form a dense network in the alveolar wall that makes an exceedingly efficient arrangement for gas exchange (Figures 1-1, 1-6, and 1-7). So rich is the mesh that some physiologists feel that it is misleading to talk of a network of individual capillary segments, and they prefer to regard the capillary bed as a sheet of flowing blood interrupted in places by posts (Figure 1-6), rather like an underground parking garage. The oxygenated blood is then collected from the capillary bed by the small pulmonary veins that run between the lobules and eventually unite to form the four large veins (in humans), which drain into the left atrium.

At first sight, this circulation appears to be simply a small version of the systemic circulation, which begins at the aorta and ends in the right atrium. However, there are important differences between the two circulations, and confusion frequently results from attempts to emphasize similarities between them.

Pressures Within Pulmonary Blood Vessels

The pressures in the pulmonary circulation are remarkably low. The mean pressure in the main pulmonary artery is only about 15 mm Hg; the systolic and diastolic pressures are about 25 and 8 mm Hg, respectively (Figure 4-1). The pressure is therefore very pulsatile. By contrast, the mean pressure in

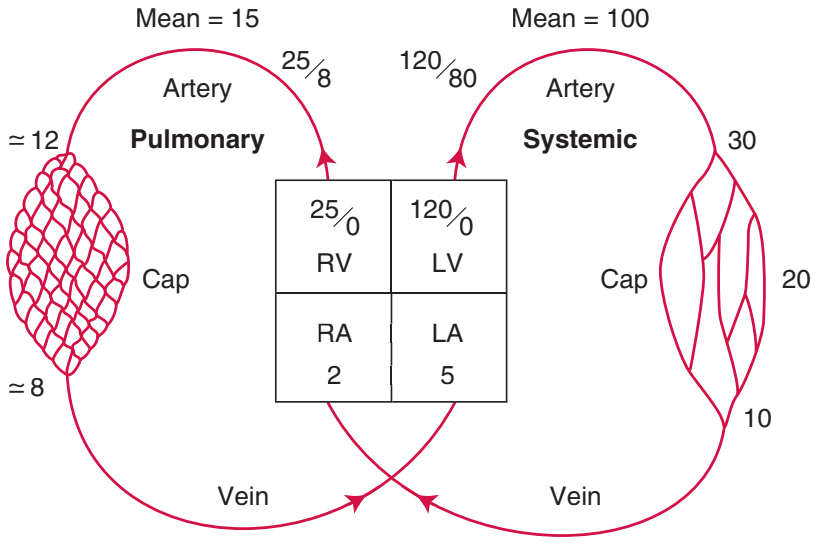


Figure 4-1. Comparison of pressures (mm Hg) in the pulmonary and systemic circulations. Hydrostatic differences modify these.

the aorta is about 100 mm Hg—about six times more than in the pulmonary artery. The pressures in the right and left atriums are not very dissimilar—about 2 and 5 mm Hg, respectively. Thus, the pressure differences from inlet to outlet of the pulmonary and systemic systems are about (15 – 5) = 10 and (100 – 2) = 98 mm Hg, respectively—a factor of 10.

In keeping with these low pressures, the walls of the pulmonary artery and its branches are remarkably thin and contain relatively little smooth muscle (they are easily mistaken for veins). This is in striking contrast to the systemic circulation, where the arteries generally have thick walls and the arterioles in particular have abundant smooth muscle.

The reasons for these differences become clear when the functions of the two circulations are compared. The systemic circulation regulates the supply of blood to various organs, including those which may be far above the level of the heart (the upstretched arm, for example). By contrast, the lung is required to accept the whole of the cardiac output at all times. It is rarely concerned with directing blood from one region to another (an exception is localized alveolar hypoxia; see below), and its arterial pressure is therefore as low as is consistent with lifting blood to the top of the lung. This keeps the work of the right heart as small as is feasible for efficient gas exchange to occur in the lung.

The pressure within the pulmonary capillaries is uncertain. The best evidence suggests that it lies about halfway between pulmonary arterial and venous pressure, and that probably much of the pressure drop occurs within the capillary bed itself. Certainly the distribution of pressures along the pulmonary circulation is far more symmetrical than in its systemic counterpart, where most of the pressure drop is just upstream of the capillaries (Figure 4-1). In addition, the pressure within the pulmonary capillaries varies considerably throughout the lung because of hydrostatic effects (see below).

Pressures Around Pulmonary Blood Vessels

The pulmonary capillaries are unique in that they are virtually surrounded by gas (Figures 1-1 and 1-7). It is true that there is a very thin layer of epithelial cells lining the alveoli, but the capillaries receive little support from this and, consequently, are liable to collapse or distend, depending on the pressures within and around them. The latter is very close to alveolar pressure. (The pressure in the alveoli is usually close to atmospheric pressure; indeed, during breath-holding with the glottis open, the two pressures are identical.) Under some special conditions, the effective pressure around the capillaries is reduced by the surface tension of the fluid lining the alveoli. But usually, the effective pressure is alveolar pressure, and when this rises above the pressure inside the capillaries, they collapse. The pressure difference between the inside and outside of the capillaries is often called the *transmural pressure*.

What is the pressure around the pulmonary arteries and veins? This can be considerably less than alveolar pressure. As the lung expands, these larger

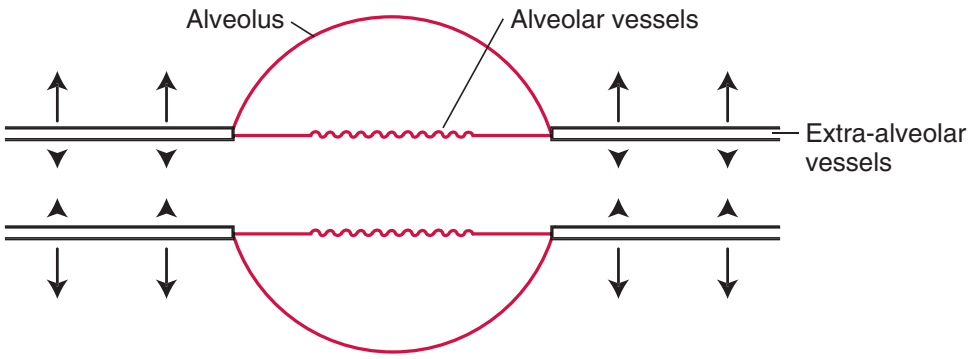


Figure 4-2. "Alveolar" and "extra-alveolar" vessels. The first are mainly the capillaries and are exposed to alveolar pressure. The second are pulled open by the radial traction of the surrounding lung parenchyma, and the effective pressure around them is therefore lower than alveolar pressure.

blood vessels are pulled open by the radial traction of the elastic lung parenchyma that surrounds them (Figures 4-2 and 4-3). Consequently, the effective pressure around them is low; in fact, there is some evidence that this pressure is even less than the pressure around the whole lung (intrapleural pressure). This paradox can be explained by the mechanical advantage that develops when a relatively rigid structure such as a blood vessel or bronchus is surrounded by a rapidly expanding elastic material such as lung parenchyma. In any event, both the arteries and veins increase their caliber as the lung expands.

The behavior of the capillaries and the larger blood vessels is so different they are often referred to as alveolar and extra-alveolar vessels, respectively (Figure 4-2). Alveolar vessels are exposed to alveolar pressure and include

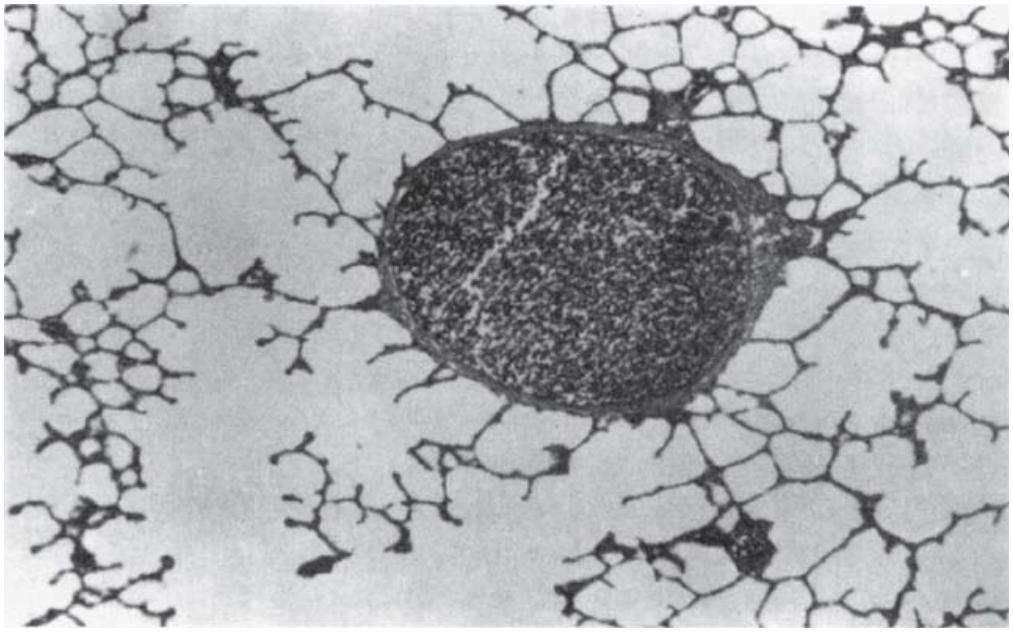


Figure 4-3. Section of lung showing many alveoli and an extra-alveolar vessel (in this case, a small vein) with its perivascular sheath.

the capillaries and the slightly larger vessels in the corners of the alveolar walls. Their caliber is determined by the relationship between alveolar pressure and the pressure within them. Extra-alveolar vessels include all the arteries and veins that run through the lung parenchyma. Their caliber is greatly affected by lung volume because this determines the expanding pull of the parenchyma on their walls. The very large vessels near the hilum are outside the lung substance and are exposed to intrapleural pressure.

Alveolar and Extra-alveolar Vessels

- Alveolar vessels are exposed to alveolar pressure and are compressed if this increases
- Extra-alveolar vessels are exposed to a pressure less than alveolar and are pulled open by the radial traction of the surrounding parenchyma

Pulmonary Vascular Resistance

It is useful to describe the resistance of a system of blood vessels as follows:

$$\text{Vascular resistance} = \frac{\text{input pressure} - \text{output pressure}}{\text{blood flow}}$$

This is analogous to electrical resistance, which is (input voltage – output voltage) divided by current. The number for vascular resistance is certainly not a complete description of the pressure-flow properties of the system. For example, the number usually depends on the magnitude of the blood flow. Nevertheless, it often allows a helpful comparison of different circulations or the same circulation under different conditions.

We have seen that the total pressure drop from pulmonary artery to left atrium in the pulmonary circulation is only some 10 mm Hg, against about 100 mm Hg for the systemic circulation. Because the blood flows through the two circulations are virtually identical, it follows that the pulmonary vascular resistance is only one-tenth that of the systemic circulation. The pulmonary blood flow is about 6 liters·min^{-1}, so that, in numbers, the pulmonary vascular resistance is 5 (15 – 5)/6 or about 1.7 mm Hg·liter^{-1}·min.* The high resistance of the systemic circulation is largely caused by very muscular arterioles that allow the regulation of blood flow to various organs of the body. The pulmonary circulation has no such vessels and appears to have as low a resistance as is compatible with distributing the blood in a thin film over a vast area in the alveolar walls.

Although the normal pulmonary vascular resistance is extraordinarily small, it has a remarkable facility for becoming even smaller as the pressure

*Cardiologists sometimes express pulmonary vascular resistance in the units dyne·s·cm^{-5}. The normal value is then in the region of 100.

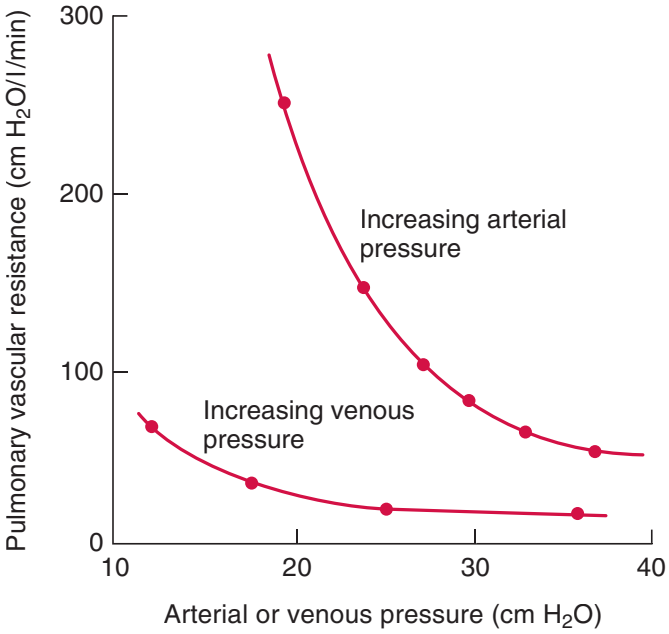


Figure 4-4. Fall in pulmonary vascular resistance as the pulmonary arterial or venous pressure is raised. When the arterial pressure was changed, the venous pressure was held constant at 12 cm water, and when the venous pressure was changed, the arterial pressure was held at 37 cm water. (Data from an excised animal lung preparation.)

within the vessels rises. Figure 4-4 shows that an increase in either pulmonary arterial or venous pressure causes pulmonary vascular resistance to fall. Two mechanisms are responsible for this. Under normal conditions, some capillaries are either closed or open but with no blood flow. As the pressure rises, these vessels begin to conduct blood, thus lowering the overall resistance. This is termed *recruitment* (Figure 4-5) and is apparently the chief mechanism for the fall in pulmonary vascular resistance that occurs as the pulmonary artery pressure is raised from low levels. The reason some vessels are unper-

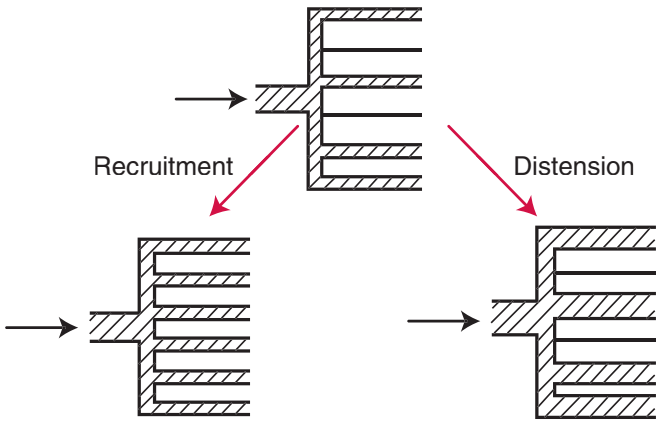


Figure 4-5. Recruitment (opening of previously closed vessels) and distension (increase in caliber of vessels). These are the two mechanisms for the decrease in pulmonary vascular resistance that occurs as vascular pressures are raised.

fused at low perfusing pressures is not fully understood but perhaps is caused by random differences in the geometry of the complex network (Figure 1-6), which result in preferential channels for flow.

At higher vascular pressures, widening of individual capillary segments occurs. This increase in caliber, or *distension*, is hardly surprising in view of the very thin membrane that separates the capillary from the alveolar space (Figure 1-1). Distension is probably chiefly a change in shape of the capillaries from near-flattened to more circular. There is evidence that the capillary wall strongly resists stretching. Distension is apparently the predominant mechanism for the fall in pulmonary vascular resistance at relatively high vascular pressures. However, recruitment and distension often occur together.

Another important determinant of pulmonary vascular resistance is *lung volume*. The caliber of the extra-alveolar vessels (Figure 4-2) is determined by a balance between various forces. As we have seen, they are pulled open as the lung expands. As a result, their vascular resistance is low at large lung volumes. On the other hand, their walls contain smooth muscle and elastic tissue, which resist distension and tend to reduce the caliber of the vessels. Consequently, they have a high resistance when lung volume is low (Figure 4-6). Indeed, if the lung is completely collapsed, the smooth muscle tone of these vessels is so effective that the pulmonary artery pressure has to be raised several centimeters of water above downstream pressure before any flow at all occurs. This is called a *critical opening pressure*.

Is the vascular resistance of the capillaries influenced by lung volume? This depends on whether alveolar pressure changes with respect to the pressure

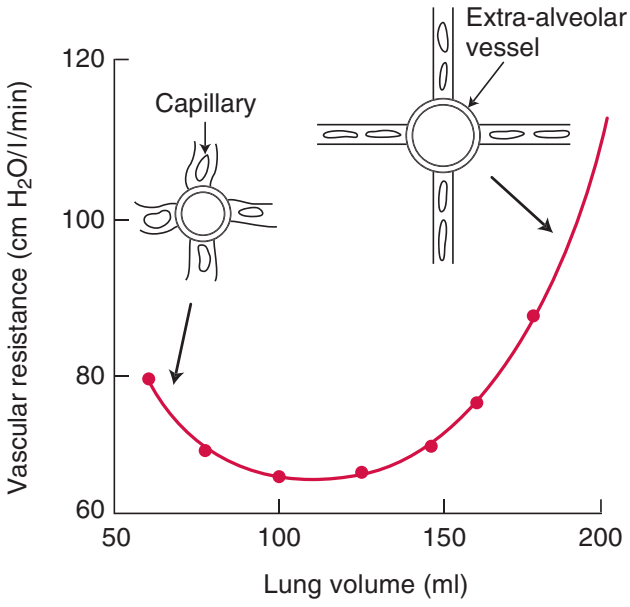


Figure 4-6. Effect of lung volume on pulmonary vascular resistance when the transmural pressure of the capillaries is held constant. At low lung volumes, resistance is high because the extra-alveolar vessels become narrow. At high volumes, the capillaries are stretched, and their caliber is reduced. (Data from an animal lobe preparation.)

inside the capillaries, that is, whether their transmural pressure alters. If alveolar pressure rises with respect to capillary pressure, the vessels tend to be squashed, and their resistance rises. This usually occurs when a normal subject takes a deep inspiration, because the vascular pressures fall. (The heart is surrounded by intrapleural pressure, which falls on inspiration.) However, the pressures in the pulmonary circulation do not remain steady after such a maneuver. An additional factor is that the caliber of the capillaries is reduced at large lung volumes because of stretching and consequent thinning of the alveolar walls. Thus, even if the transmural pressure of the capillaries is not changed with large lung inflations, their vascular resistance increases (Figure 4-6).

Because of the role of smooth muscle in determining the caliber of the extra-alveolar vessels, drugs that cause contraction of the muscle increase pulmonary vascular resistance. These include serotonin, histamine, and norepinephrine. These drugs are particularly effective vasoconstrictors when the lung volume is low and the expanding forces on the vessels are weak. Drugs that can relax smooth muscle in the pulmonary circulation include acetylcholine and isoproterenol.

Pulmonary Vascular Resistance

- Is normally very small
- Decreases on exercise because of recruitment and distension of capillaries
- Increases at high and low lung volumes
- Increases with alveolar hypoxia because of constriction of small pulmonary arteries

Measurement of Pulmonary Blood Flow

The volume of blood passing through the lungs each minute ($\dot{Q}$) can be calculated using the *Fick principle*. This states that the O_2 consumption per minute ($\dot{V}o_2$) measured at the mouth is equal to the amount of O_2 taken up by the blood in the lungs per minute. Because the O_2 concentration in the blood entering the lungs is $C\bar{v}_{O_2}$ and that in the blood leaving is Ca_{O_2}, we have

$$\dot{V}_{O_2} = \dot{Q}(Ca_{O_2} - C\bar{v}_{O_2})$$

or

$$\dot{Q} = \frac{\dot{V}_{O_2}}{Ca_{O_2} - C\bar{v}_{O_2}}$$

$\dot{V}o_2$ is measured by collecting the expired gas in a large spirometer and measuring its O_2 concentration. Mixed venous blood is taken via a catheter in the pulmonary artery, and arterial blood by puncture of the brachial or radial artery. Pulmonary blood flow can also be measured by the indicator dilution technique, in which a dye or other indicator is injected into the venous circulation and its concentration in arterial blood is recorded. Both these methods are of great importance, but they will not be considered in more detail here because they fall within the province of cardiovascular physiology.

Distribution of Blood Flow

So far, we have been assuming that all parts of the pulmonary circulation behave identically. However, considerable inequality of blood flow exists within the upright human lung. This can be shown by a modification of the radioactive xenon method that was used to measure the distribution of ventilation (Figure 2-7). For the measurement of blood flow, the xenon is dissolved in saline and injected into a peripheral vein (Figure 4-7). When it reaches the pulmonary capillaries, it is evolved into alveolar gas because of its low solubility, and the distribution of radioactivity can be measured by counters over the chest during breath-holding.

In the upright human lung, blood flow decreases almost linearly from bottom to top, reaching very low values at the apex (Figure 4-7). This distribution is affected by change of posture and exercise. When the

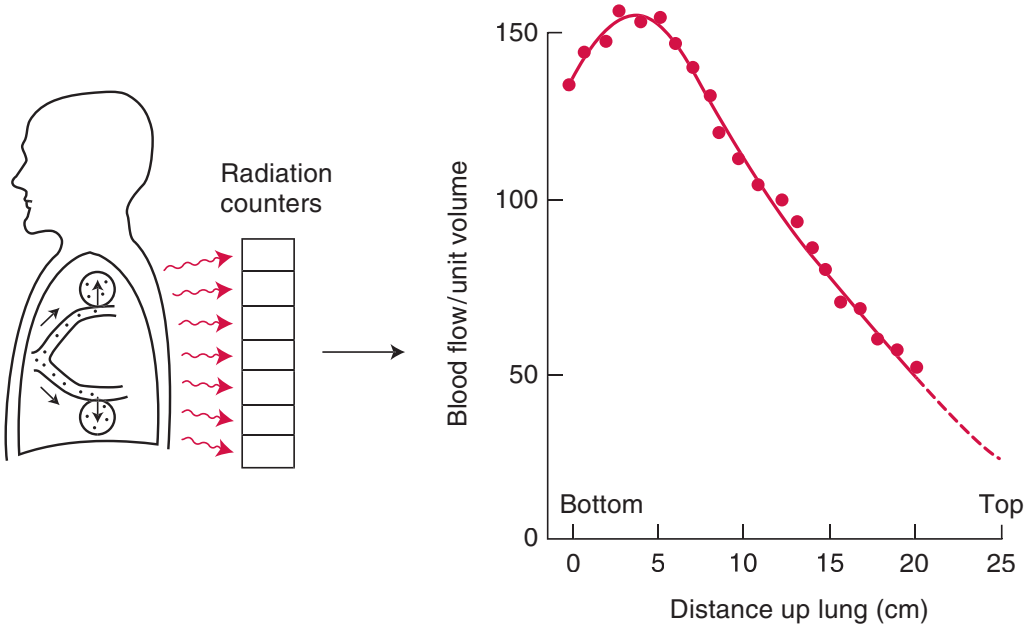


Figure 4-7. Measurement of the distribution of blood flow in the upright human lung, using radioactive xenon. The dissolved xenon is evolved into alveolar gas from the pulmonary capillaries. The units of blood flow are such that if flow were uniform, all values would be 100. Note the small flow at the apex.

subject lies supine, the apical zone blood flow increases, but the basal zone flow remains virtually unchanged, with the result that the distribution from apex to base becomes almost uniform. However, in this posture, blood flow in the posterior (lower or dependent) regions of the lung exceeds flow in the anterior parts. Measurements on subjects suspended upside down show that apical blood flow may exceed basal flow in this position. On mild exercise, both upper and lower zone blood flows increase, and the regional differences become less.

The uneven distribution of blood flow can be explained by the hydrostatic pressure differences within the blood vessels. If we consider the pulmonary arterial system as a continuous column of blood, the difference in pressure between the top and bottom of a lung 30 cm high will be about 30 cm water, or 23 mm Hg. This is a large pressure difference for such a low-pressure system as the pulmonary circulation (Figure 4-1), and its effects on regional blood flow are shown in Figure 4-8.

There may be a region at the top of the lung (*zone 1*) where pulmonary arterial pressure falls below alveolar pressure (normally close to atmospheric pressure). If this occurs, the capillaries are squashed flat, and no flow is possible. Zone 1 does *not* occur under normal conditions, because the pulmonary arterial pressure is just sufficient to raise blood to the top of the lung, but may be present if the arterial pressure is reduced (following severe hemorrhage, for example) or if alveolar pressure is raised (during positive pressure

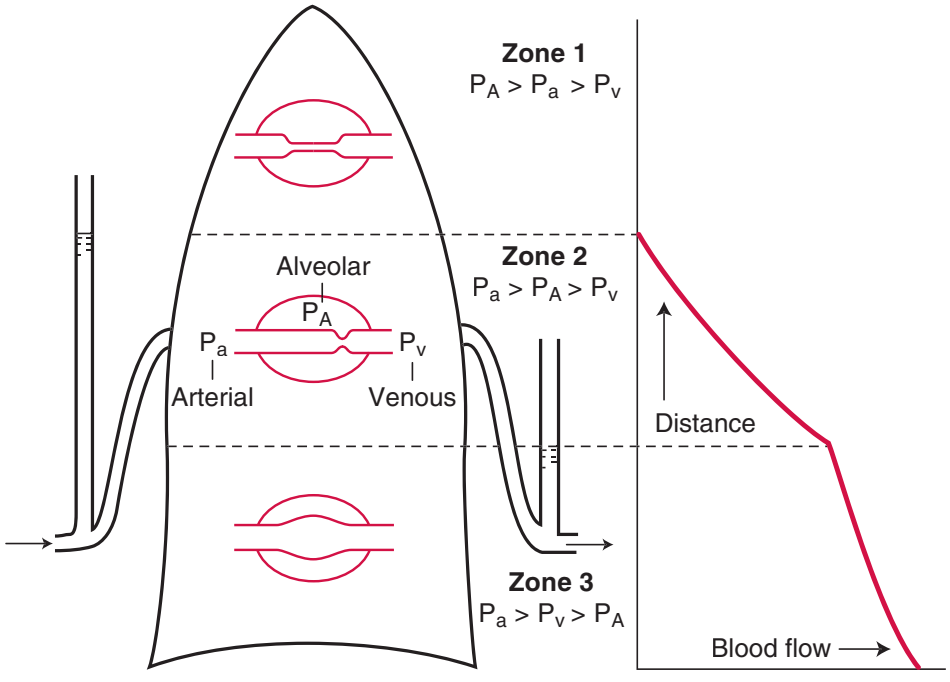


Figure 4-8. Explanation of the uneven distribution of blood flow in the lung, based on the pressures affecting the capillaries. See text for details.

ventilation). This ventilated but unperfused lung is useless for gas exchange and is called *alveolar dead space*.

Farther down the lung (*zone 2*), pulmonary arterial pressure increases because of the hydrostatic effect and now exceeds alveolar pressure. However, venous pressure is still very low and is less than alveolar pressure, which leads to remarkable pressure-flow characteristics. Under these conditions, blood flow is determined by the difference between arterial and alveolar pressures (not the usual arterial-venous pressure difference). Indeed, venous pressure has no influence on flow unless it exceeds alveolar pressure.

This behavior can be modeled with a flexible rubber tube inside a glass chamber (Figure 4-9). When chamber pressure is greater than downstream pressure, the rubber tube collapses at its downstream end, and the pressure inside the tube at this point limits flow. The pulmonary capillary bed is clearly very different from a rubber tube. Nevertheless, the overall behavior is similar and is often called the Starling resistor, sluice, or waterfall effect. Because arterial pressure is increasing down the zone but alveolar pressure is the same throughout the lung, the pressure difference responsible for flow increases. In addition, increasing recruitment of capillaries occurs down this zone.

In *zone 3*, venous pressure now exceeds alveolar pressure, and flow is determined in the usual way by the arterial-venous pressure difference. The increase in blood flow down this region of the lung is apparently caused chiefly by distension of the capillaries. The pressure within them (lying between arterial and venous) increases down the zone while the pressure outside (alveolar) remains constant. Thus, their transmural pressure rises and, indeed, measurements show that their mean width increases. Recruitment of previously closed vessels may also play some part in the increase in blood flow down this zone.

The scheme shown in Figure 4-8 summarizes the role played by the capillaries in determining the distribution of blood flow. At low lung volumes, the

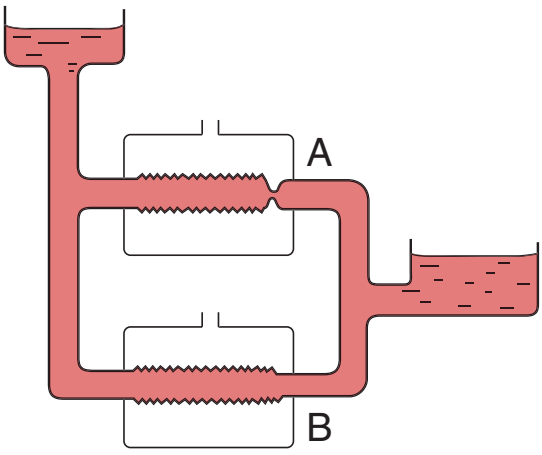


Figure 4-9. Two Starling resistors, each consisting of a thin rubber tube inside a container. When chamber pressure exceeds downstream pressure as in *A,* flow is independent of downstream pressure. However, when downstream pressure exceeds chamber pressure as in *B,* flow is determined by the upstream-downstream difference.

resistance of the extra-alveolar vessels becomes important, and a reduction of regional blood flow is seen, starting first at the base of the lung, where the parenchyma is least expanded (see Figure 7-8). This region of reduced blood flow is sometimes called *zone 4* and can be explained by the narrowing of the extra-alveolar vessels, which occurs when the lung around them is poorly inflated (Figure 4-6).

There are other factors causing unevenness of blood flow in the lung. The complex, partly random arrangement of blood vessels and capillaries (Figure 1-6) causes some inequality of blood flow at any given level in the lung. There is also evidence that blood flow decreases along the acinus, with peripheral parts less well supplied with blood. Some measurements suggest that the peripheral regions of the whole lung receive less blood flow than the central regions. In some animals, some regions of the lung appear to have an intrinsically higher vascular resistance.

Active Control of the Circulation

We have seen that passive factors dominate the vascular resistance and the distribution of flow in the pulmonary circulation under normal conditions. However, a remarkable active response occurs when the Po_2 of alveolar gas is reduced. This is known as *hypoxic pulmonary vasoconstriction* and consists of contraction of smooth muscle in the walls of the small arterioles in the hypoxic region. The precise mechanism of this response is not known, but it occurs in excised isolated lung and so does not depend on central nervous connections. Excised segments of pulmonary artery constrict if their environment is made hypoxic, so there is a local action of the hypoxia on the artery itself. The Po_2 of the alveolar gas, not the pulmonary arterial blood, chiefly determines the response. This can be proved by perfusing a lung with blood of a high Po_2 while keeping the alveolar Po_2 low. Under these conditions, the response occurs.

The vessel wall becomes hypoxic as a result of diffusion of oxygen over the very short distance from the wall to the surrounding alveoli. Recall that a small pulmonary artery is very closely surrounded by alveoli (compare the proximity of alveoli to the small pulmonary vein in Figure 4-3). The stimulus-response curve of this constriction is very nonlinear (Figure 4-10). When the alveolar Po_2 is altered in the region above 100 mm Hg, little change in vascular resistance is seen. However, when the alveolar Po_2 is reduced below approximately 70 mm Hg, marked vasoconstriction may occur, and at a very low Po_2, the local blood flow may be almost abolished.

The mechanism of hypoxic pulmonary vasoconstriction is the subject of a great deal of research. Recent studies show that inhibition of voltage-gated potassium channels and membrane depolarization are involved, leading to increased calcium ion concentrations in the cytoplasm. An increase in cytoplasmic calcium ion concentration is the major trigger for smooth muscle contraction.

Endothelium-derived vasoactive substances play a role. Nitric oxide (NO) has been shown to be an endothelium-derived relaxing factor for blood vessels. It is formed from L-arginine via catalysis by endothelial NO synthase (eNOS) and is a final common pathway for a variety of biological processes. NO activates soluble guanylate cyclase and increases the synthesis of guanosine 3',5'-cyclic monophosphate (cyclic GMP), which leads to smooth muscle relaxation. Inhibitors of NO synthase augment hypoxic pulmonary vasoconstriction in animal preparations, and inhaled NO reduces hypoxic pulmonary vasoconstriction in humans. The required inhaled concentration of NO is extremely low (about 20 ppm), and the gas is very toxic at high concentrations. Disruption of the eNOS gene has been shown to cause pulmonary hypertension in animal models.

Hypoxic Pulmonary Vasoconstriction

- Alveolar hypoxia constricts small pulmonary arteries
- Probably a direct effect of the low P_{O_2} on vascular smooth muscle
- Its release is critical at birth in the transition from placental to air breathing
- Directs blood flow away from poorly ventilated areas of the diseased lung in the adult

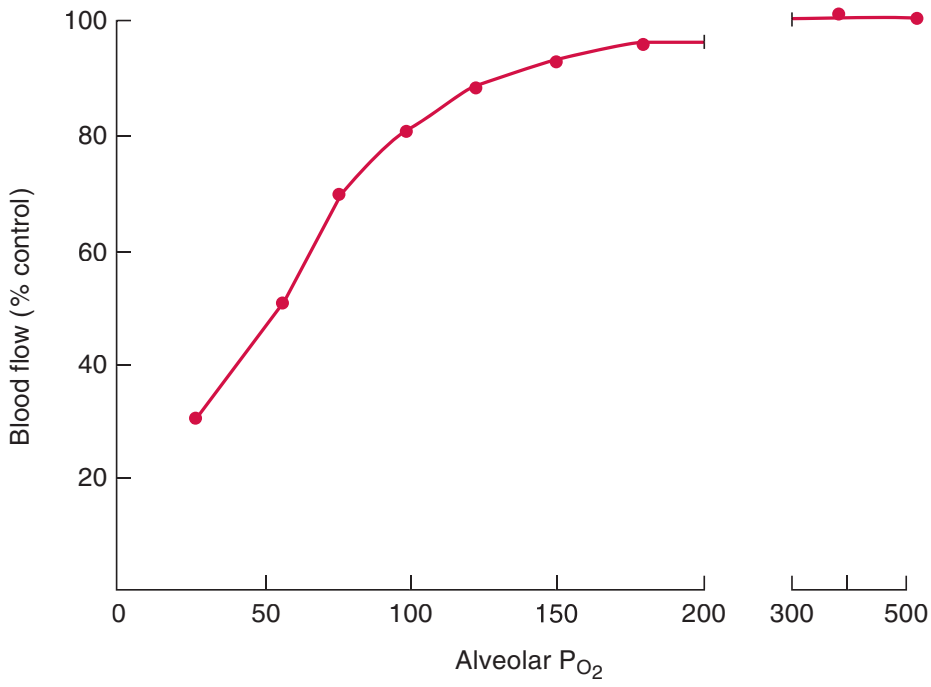


Figure 4-10. Effect of reducing alveolar P_{O_2} on pulmonary blood flow. (Data from anesthetized cat.)

Pulmonary vascular endothelial cells also release potent vasoconstrictors such as endothelin-1 (ET-1) and thromboxane A_2 (TXA_2). Their roles in normal physiology and disease are the subject of intense study. Blockers of endothelin receptors have been used clinically to treat patients with pulmonary hypertension.

Hypoxic vasoconstriction has the effect of directing blood flow away from hypoxic regions of lung. These regions may result from bronchial obstruction, and by diverting blood flow, the deleterious effects on gas exchange are reduced. At high altitude, generalized pulmonary vasoconstriction occurs, leading to a rise in pulmonary arterial pressure. But probably the most important situation in which this mechanism operates is at birth. During fetal life, the pulmonary vascular resistance is very high, partly because of hypoxic vasoconstriction, and only some 15% of the cardiac output goes through the lungs (see Figure 9-5). When the first breath oxygenates the alveoli, the vascular resistance falls dramatically because of relaxation of vascular smooth muscle, and the pulmonary blood flow increases enormously.

Other active responses of the pulmonary circulation have been described. A low blood pH causes vasoconstriction, especially when alveolar hypoxia is present. The autonomic nervous system exerts a weak control, an increase in sympathetic outflow causing stiffening of the walls of the pulmonary arteries and vasoconstriction.

Water Balance in the Lung

Because only 0.3 μm of tissue separates the capillary blood from the air in the lung (Figure 1-1), the problem of keeping the alveoli free of fluid is critical. Fluid exchange across the capillary endothelium obeys Starling's law. The force tending to push fluid *out* of the capillary is the capillary hydrostatic pressure minus the hydrostatic pressure in the interstitial fluid, or $P_c - P_i$. The force tending to pull fluid in is the colloid osmotic pressure of the proteins of the blood minus that of the proteins of the interstitial fluid, or $\pi_c - \pi_i$. This force depends on the reflection coefficient σ, which is a measure of the effectiveness of the capillary wall in preventing the passage of proteins across it. Thus,

$$\text{net fluid out} = K[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$$

where K is a constant called the filtration coefficient.

Unfortunately, the practical use of this equation is limited because of our ignorance of many of the values. The colloid osmotic pressure within the capillary is about 25–28 mm Hg. The capillary hydrostatic pressure is probably about halfway between arterial and venous pressure and is much higher at the bottom of the lung than at the top. The colloid osmotic pressure of the

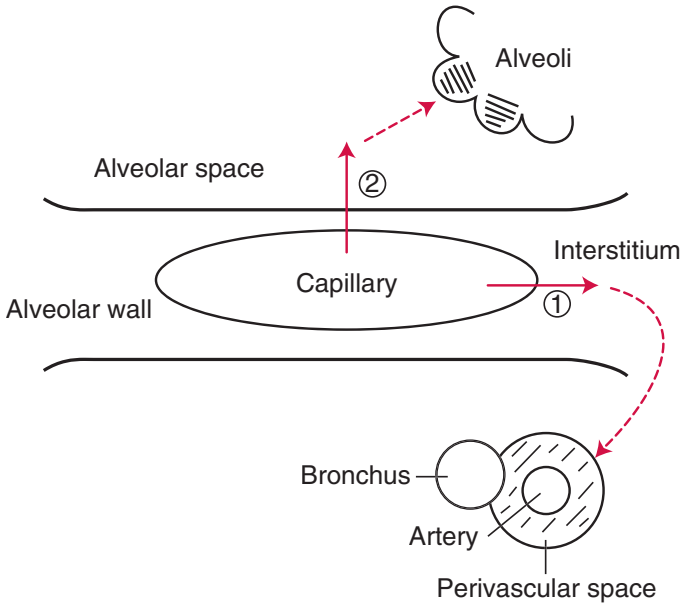


Figure 4-11. Two possible paths for fluid that moves out of pulmonary capillaries. Fluid that enters the interstitium initially finds its way into the perivascular and peribronchial spaces. Later, fluid may cross the alveolar wall, filling alveolar spaces.

interstitial fluid is not known but is about 20 mm Hg in lung lymph. However, this value may be higher than that in the interstitial fluid around the capillaries. The interstitial hydrostatic pressure is unknown, but some measurements show it is substantially below atmospheric pressure. It is probable that the net pressure of the Starling equation is outward, causing a small lymph flow of perhaps 20 $ml \cdot h^{-1}$ in humans under normal conditions.

Where does fluid go when it leaves the capillaries? Figure 4-11 shows that fluid that leaks out into the interstitium of the alveolar wall tracks through the interstitial space to the perivascular and peribronchial space within the lung. Numerous lymphatics run in the perivascular spaces, and these help to transport the fluid to the hilar lymph nodes. In addition, the pressure in these perivascular spaces is low, thus forming a natural sump for the drainage of fluid (compare Figure 4-2). The earliest form of pulmonary edema[†] is characterized by engorgement of these peribronchial and perivascular spaces and is known as interstitial edema. The rate of lymph flow from the lung increases considerably if the capillary pressure is raised over a long period.

In a later stage of pulmonary edema, fluid may cross the alveolar epithelium into the alveolar spaces (Figure 4-11). When this occurs, the alveoli fill with fluid one by one, and because they are then unventilated, no oxygenation of the blood passing through them is possible. What prompts fluid to start moving across into the alveolar spaces is not known, but it may be that

[†]For a more extensive discussion of pulmonary edema, see the companion volume, JB West, *Pulmonary Pathophysiology: The Essentials*, 7th ed. (Baltimore, MD: Lippincott Williams & Wilkins, 2007).

this occurs when the maximal drainage rate through the interstitial space is exceeded and the pressure there rises too high. Fluid that reaches the alveolar spaces is actively pumped out by a sodium-potassium ATPase pump in epithelial cells. Alveolar edema is much more serious than interstitial edema because of the interference with pulmonary gas exchange.

Other Functions of the Pulmonary Circulation

The chief function of the pulmonary circulation is to move blood to and from the blood-gas barrier so that gas exchange can occur. However, it has other important functions. One is to act as a reservoir for blood. We saw that the lung has a remarkable ability to reduce its pulmonary vascular resistance as its vascular pressures are raised through the mechanisms of recruitment and distension (Figure 4-5). The same mechanisms allow the lung to increase its blood volume with relatively small rises in pulmonary arterial or venous pressures. This occurs, for example, when a subject lies down after standing. Blood then drains from the legs into the lung.

Another function of the lung is to filter blood. Small blood thrombi are removed from the circulation before they can reach the brain or other vital organs. Many white blood cells are trapped by the lung and later released, although the value of this is not clear.

Metabolic Functions of the Lung

The lung has important metabolic functions in addition to gas exchange. A number of vasoactive substances are metabolized by the lung (Table 4-1). Because the lung is the only organ except the heart that receives the whole circulation, it is uniquely suited to modifying bloodborne substances. A substantial fraction of all the vascular endothelial cells in the body are located in the lung. The metabolic functions of the vascular endothelium are only briefly dealt with here because many fall within the province of pharmacology.

The only known example of biological activation by passage through the pulmonary circulation is the conversion of the relatively inactive polypeptide angiotensin I to the potent vasoconstrictor angiotensin II. The latter, which is up to 50 times more active than its precursor, is unaffected by passage through the lung. The conversion of angiotensin I is catalyzed by angiotensin-converting enzyme, or ACE, which is located in small pits in the surface of the capillary endothelial cells.

Table 4.1 Fate of Substances in the Pulmonary Circulation

Substance	Fate
Peptides	
Angiotensin I	Converted to angiotensin II by ACE
Angiotensin II	Unaffected
Vasporessin	Unaffected
Bradykinin	Up to 80% inactivated
Amines	
Serotonin	Almost completely removed
Norepinephrine	Up to 30% removed
Histamine	Not affected
Dopamine	Not affected
Arachidonic acid metabolites	
Prostaglandins E_2 and $F_{2\alpha}$	Almost completely removed
Prostaglandin A_2	Not affected
Prostacyclin (PGI_2)	Not affected
Leukotrienes	Almost completely removed

Many vasoactive substances are completely or partially inactivated during passage through the lung. Bradykinin is largely inactivated (up to 80%), and the enzyme responsible is ACE. The lung is the major site of inactivation of serotonin (5-hydroxytryptamine), but this is not by enzymatic degradation but by an uptake and storage process (Table 4-1). Some of the serotonin may be transferred to platelets in the lung or stored in some other way and released during anaphylaxis. The prostaglandins E_1, E_2, and $F_{2\alpha}$ are also inactivated in the lung, which is a rich source of the responsible enzymes. Norepinephrine is also taken up by the lung to some extent (up to 30%). Histamine appears not to be affected by the intact lung but is readily inactivated by slices.

Some vasoactive materials pass through the lung without significant gain or loss of activity. These include epinephrine, prostaglandins A_1 and A_2, angiotensin II, and vasopressin (ADH).

Several vasoactive and bronchoactive substances are metabolized in the lung and may be released into the circulation under certain conditions. Important among these are the arachidonic acid metabolites (Figure 4-12). Arachidonic acid is formed through the action of the enzyme phospholipase A_2 on phospholipid bound to cell membranes. There are two major synthetic pathways, the initial reactions being catalyzed by the enzymes lipoxygenase and cyclooxygenase, respectively. The first produces the leukotrienes, which include the mediator originally described as slow-reacting substance of anaphylaxis (SRS-A). These compounds cause airway constriction and may have an important role in asthma.[‡] Other leukotrienes are involved in inflammatory responses.

The prostaglandins are potent vasoconstrictors or vasodilators. Prostaglandin E_2 plays an important role in the fetus because it helps to relax the

[‡]For more details, see JB West, *Pulmonary Pathophysiology: The Essentials*, 7th ed. (Baltimore, MD: Lippincott Williams & Wilkins, 2007).

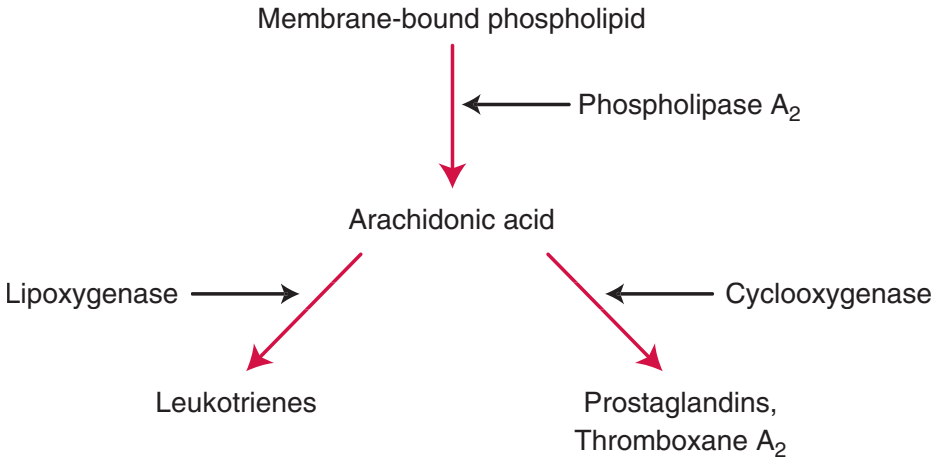


Figure 4-12. Two pathways of arachidonic acid metabolism. The leukotrienes are generated by the lipoxygenase pathway, whereas the prostaglandins and thromboxane A_2 come from the cyclooxygenase pathway.

patent ductus arteriosus. Prostaglandins also affect platelet aggregation and are active in other systems, such as the kallikrein-kinin clotting cascade. They also may have a role in the bronchoconstriction of asthma.

There is also evidence that the lung plays a role in the clotting mechanism of blood under normal and abnormal conditions. For example, there are a large number of mast cells containing heparin in the interstitium. In addition, the lung is able to secrete special immunoglobulins, particularly IgA, in the bronchial mucus that contribute to its defenses against infection.

Synthetic functions of the lung include the synthesis of phospholipids such as dipalmitoyl phosphatidylcholine, which is a component of pulmonary surfactant (see Chapter 7). Protein synthesis is also clearly important because collagen and elastin form the structural framework of the lung. Under some conditions, proteases are apparently liberated from leukocytes in the lung, causing breakdown of collagen and elastin, and this may result in emphysema. Another significant area is carbohydrate metabolism, especially the elaboration of mucopolysaccharides of bronchial mucus.

KEY CONCEPTS

1. The pressures within the pulmonary circulation are much lower than in the systemic circulation. Also the capillaries are exposed to alveolar pressure, whereas the pressures around the extra-alveolar vessels are lower.
2. Pulmonary vascular resistance is low and falls even more when cardiac output increases because of recruitment and distension of the capillaries. Pulmonary vascular resistance increases at very low or high lung volumes.

3. Blood flow is unevenly distributed in the upright lung. There is a higher flow at the base than at the apex as a result of gravity. If capillary pressure is less than alveolar pressure at the top of the lung, the capillaries collapse and there is no blood flow (zone 1). There is also uneven blood flow at any given level in the lung because of random variations of the blood vessels.
4. Hypoxic pulmonary vasoconstriction reduces the blood flow to poorly ventilated regions of the lung. Release of this mechanism is responsible for a large increase in blood flow to the lung at birth.
5. Fluid movement across the capillary endothelium is governed by the Starling equilibrium.
6. The pulmonary circulation has many metabolic functions, notably the conversion of angiotensin I to angiotensin II by angiotensin-converting enzyme.

QUESTIONS

For each question, choose the one best answer.

1. The ratio of total systemic vascular resistance to pulmonary vascular resistance is about

   A. 2: 1
   B. 3: 1
   C. 5: 1
   D. 10: 1
   E. 20: 1

2. Concerning the extra-alveolar vessels of the lung,

   A. Tension in the surrounding alveolar walls tends to narrow them.
   B. Their walls contain smooth muscle and elastic tissue.
   C. They are exposed to alveolar pressure.
   D. Their constriction in response to alveolar hypoxia mainly takes place in the veins.
   E. Their caliber is reduced by lung inflation.

3. A patient with pulmonary vascular disease has mean pulmonary arterial and venous pressures of 55 and 5 mm Hg, respectively, while the cardiac output is 3 liters·min^{-1}. What is his pulmonary vascular resistance in mm Hg·liters^{-1}·min?

   A. 0.5
   B. 1.7
   C. 2.5
   D. 5
   E. 17

4. The fall in pulmonary vascular resistance on exercise is caused by

   A. Decrease in pulmonary arterial pressure.
   B. Decrease in pulmonary venous pressure.
   C. Increase in alveolar pressure.
   D. Distension of pulmonary capillaries.
   E. Alveolar hypoxia.

5. In a measurement of cardiac output using the Fick principle, the O_2 concentrations of mixed venous and arterial blood are 16 and 20 ml·100 ml^{-1}, respectively, and the O_2 consumption is 300 ml·min^{-1}. The cardiac output in liters·min^{-1} is

A. 2.5
B. 5
C. 7.5
D. 10
E. 75

6. In zone 2 of the lung,

A. Alveolar pressure exceeds arterial pressure.
B. Venous pressure exceeds alveolar pressure.
C. Venous pressure exceeds arterial pressure.
D. Blood flow is determined by arterial pressure minus alveolar pressure.
E. Blood flow is unaffected by arterial pressure.

7. Pulmonary vascular resistance is reduced by

A. Removal of one lung.
B. Breathing a 10% oxygen mixture.
C. Exhaling from functional residual capacity to residual volume.
D. Acutely increasing pulmonary venous pressure.
E. Mechanically ventilating the lung with positive pressure.

8. Hypoxic pulmonary vasoconstriction

A. Depends more on the P_{O_2} of mixed venous blood than alveolar gas.
B. Is released in the transition from placental to air respiration.
C. Involves CO_2 uptake in vascular smooth muscle.
D. Partly diverts blood flow from well-ventilated regions of diseased lungs.
E. Is increased by inhaling low concentrations of nitric oxide.

9. If the pressures in the capillaries and interstitial space at the top of the lung are 3 and 0 mm Hg, respectively, and the colloid osmotic pressures of the blood and interstitial fluid are 25 and 5 mm Hg, respectively, what is the net pressure in mm Hg moving fluid into the capillaries?

A. 17
B. 20
C. 23
D. 27
E. 33

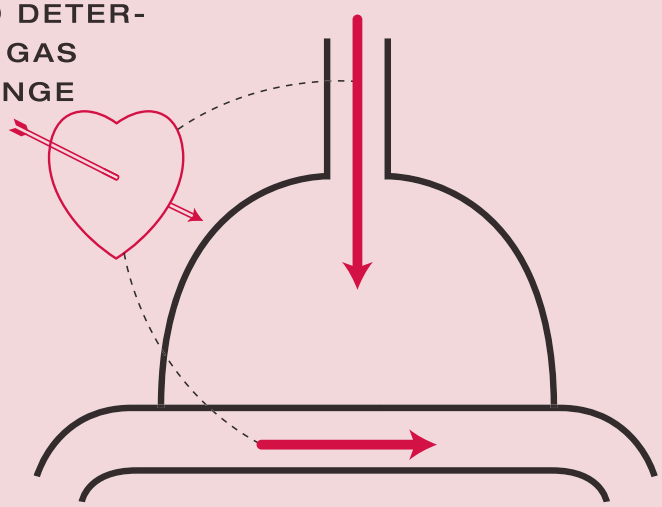
10. The metabolic functions of the lung include

A. Converting angiotensin II to angiotensin I.
B. Producing bradykinin.
C. Secreting serotonin.
D. Removing leukotrienes.
E. Generating erythropoietin.

Ventilation-Perfusion Relationships

5

HOW MATCHING OF GAS AND BLOOD DETERMINES GAS EXCHANGE



This chapter is devoted to the primary function of the lung, that is, gas exchange. First, a theoretical ideal lung is considered. Then we review three mechanisms of hypoxemia: hypoventilation, diffusion limitation, and shunt. The difficult concept of ventilation-perfusion inequality is then introduced, and to illustrate this the regional differences of gas exchange in the upright human lung are described. Then we examine how ventilation-perfusion inequality impairs overall gas exchange. It is emphasized that this is true not only of oxygen but also of carbon dioxide. Methods of measuring ventilation-perfusion inequality are then briefly discussed.

So far we have considered the movement of air to and from the blood-gas interface, the diffusion of gas across it, and the movement of blood to and from the barrier. It would be natural to assume that if all these processes were adequate, normal gas exchange within the lung would be assured. Unfortunately, this is not so because the matching of ventilation and blood flow within various regions of the lung is critical for adequate gas exchange. Indeed, mismatching of ventilation and blood flow is responsible for most of the defective gas exchange in pulmonary diseases.

In this chapter, we shall look closely at the important (but difficult) subject of how the relations between ventilation and blood flow determine gas exchange. First, however, we shall examine two relatively simple causes of impairment of gas exchange—hypoventilation and shunt. Because all of these situations result in *hypoxemia*, that is, in an abnormally low Po_2 in arterial blood, it is useful to take a preliminary look at normal O_2 transfer.

Oxygen Transport from Air to Tissues

Figure 5-1 shows how the Po_2 falls as the gas moves from the atmosphere in which we live to the mitochondria where it is utilized. The Po_2 of air is 20.93% of the total dry gas pressure (that is, excluding water vapor). At sea level, the barometric pressure is 760 mm Hg, and at the body temperature of 37°C, the water vapor pressure of moist inspired gas (which is fully saturated with water vapor) is 47 mm Hg. Thus, the Po_2 of inspired air is (20.93/100) × (760 – 47), or 149 mm Hg (say 150).

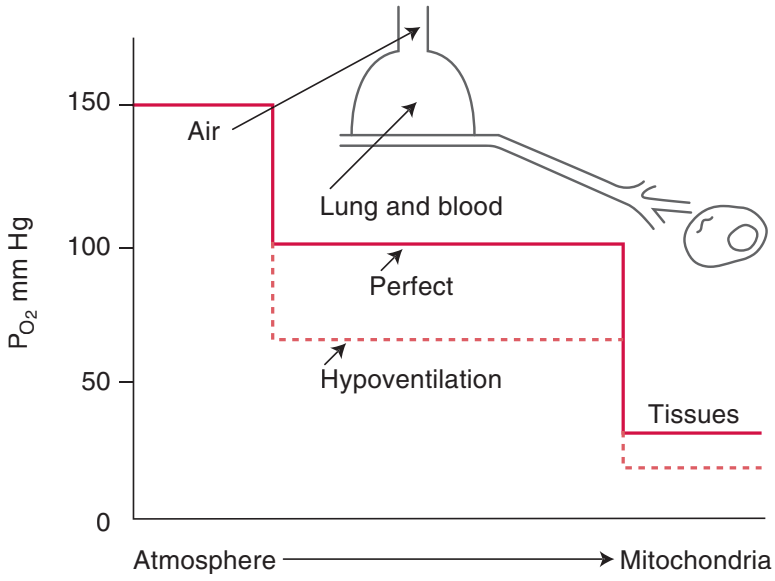


Figure 5-1. Scheme of the O_2 partial pressures from air to tissues. The *solid line* shows a hypothetical perfect situation, and the *broken line* depicts hypoventilation. Hypoventilation depresses the Po_2 in the alveolar gas and, therefore, in the tissues.

Figure 5-1 is drawn for a hypothetical perfect lung, and it shows that by the time the O_2 has reached the alveoli, the Po_2 has fallen to about 100 mm Hg, that is, by one-third. This is because the Po_2 of alveolar gas is determined by a balance between two processes: the removal of O_2 by pulmonary capillary blood on the one hand and its continual replenishment by alveolar ventilation on the other. (Strictly, alveolar ventilation is not continuous but is breath by breath. However, the fluctuation in alveolar Po_2 with each breath is only about 3 mm Hg, because the tidal volume is small compared with the volume of gas in the lung, so the process can be regarded as continuous.) The rate of removal of O_2 from the lung is governed by the O_2 consumption of the tissues and varies little under resting conditions. In practice, therefore, the alveolar Po_2 is largely determined by the level of alveolar ventilation. The same applies to the alveolar Pco_2, which is normally about 40 mm Hg.

Four Causes of Hypoxemia

- Hypoventilation
- Diffusion limitation
- Shunt
- Ventilation-perfusion inequality

When the systemic arterial blood reaches the tissue capillaries, O_2 diffuses to the mitochondria, where the Po_2 is much lower. The "tissue" Po_2 probably differs considerably throughout the body, and in some cells at least, the Po_2 is as low as 1 mm Hg. However, the lung is an essential link in the chain of O_2 transport, and any decrease of Po_2 in arterial blood must result in a lower tissue Po_2, other things being equal. For the same reasons, impaired pulmonary gas exchange causes a rise in tissue Pco_2.

Hypoventilation

We have seen that the level of alveolar Po_2 is determined by a balance between the rate of removal of O_2 by the blood (which is set by the metabolic demands of the tissues) and the rate of replenishment of O_2 by alveolar ventilation. Thus, if the alveolar ventilation is abnormally low, the alveolar Po_2 falls. For similar reasons, the Pco_2 rises. This is known as hypoventilation (Figure 5-1).

Causes of hypoventilation include such drugs as morphine and barbiturates that depress the central drive to the respiratory muscles, damage to the chest wall or paralysis of the respiratory muscles, and a high resistance to breathing (for example, very dense gas at great depth underwater). Hypoventilation always causes an increased alveolar and, therefore,

arterial P_{CO_2}. The relationship between alveolar ventilation and P_{CO_2} was derived on p. 20 in the alveolar ventilation equation:

$$P_{CO_2} = \frac{\dot{V}_{CO_2}}{\dot{V}_A} \times K$$

where $\dot{V}_{CO_2}$ is the CO_2 production, $\dot{V}_A$ is the alveolar ventilation, and K is a constant. This means that if the alveolar ventilation is halved, the P_{CO_2} is doubled, once a steady state has been established.

Hypoventilation

- Always increases the alveolar and arterial P_{CO_2}
- Decreases the P_{O_2} unless additional O_2 is inspired
- Hypoxemia is easy to reverse by adding O_2 to the inspired gas

The relationship between the fall in P_{O_2} and the rise in P_{CO_2} that occurs in hypoventilation can be calculated from the *alveolar gas equation* if we know the composition of inspired gas and the respiratory exchange ratio R. The latter is given by the CO_2 production/O_2 consumption and is determined by the metabolism of the tissues in a steady state. It is sometimes known as the respiratory quotient. A simplified form of the alveolar gas equation is

$$P_{A_{O_2}} = P_{I_{O_2}} - \frac{P_{A_{CO_2}}}{R} + F$$

where F is a small correction factor (typically about 2 mm Hg for air breathing), which we can ignore. This equation shows that if R has its normal value of 0.8, the fall in alveolar P_{O_2} is slightly greater than is the rise in P_{CO_2} during hypoventilation. The full version of the equation is given in Appendix A.

Hypoventilation always reduces the alveolar and arterial P_{O_2} except when the subject breathes an enriched O_2 mixture. In this case, the added amount of O_2 per breath can easily make up for the reduced flow of inspired gas (try question 3 on p. 75).

If alveolar ventilation is suddenly increased (for example, by voluntary hyperventilation), it may take several minutes for the alveolar P_{O_2} and P_{CO_2} to assume their new steady-state values. This is because of the different O_2 and CO_2 stores in the body. The CO_2 stores are much greater than the O_2 stores because of the large amount of CO_2 in the form of bicarbonate in the blood and interstitial fluid (see Chapter 6). Therefore, the alveolar P_{CO_2} takes longer to come to equilibrium, and during the nonsteady state, the R value of expired gas is high as the CO_2 stores are washed out. Opposite changes occur with the onset of hypoventilation.

Diffusion

Figure 5-1 shows that in a perfect lung, the Po_2 of arterial blood would be the same as that in alveolar gas. In real life, this is not so. One reason is that although the Po_2 of the blood rises closer and closer to that of alveolar gas as the blood traverses the pulmonary capillary (Figure 3-3), it can never quite reach it. Under normal conditions, the Po_2 difference between alveolar gas and end-capillary blood resulting from incomplete diffusion is immeasurably small but is shown schematically in Figure 5-2. As we have seen, the difference can become larger during exercise, or when the blood-gas barrier is thickened, or if a low O_2 mixture is inhaled (Figure 3-3B).

Shunt

Another reason why the Po_2 of arterial blood is less than that in alveolar gas is shunted blood. *Shunt* refers to blood that enters the arterial system without going through ventilated areas of the lung. In the normal lung, some of the bronchial artery blood is collected by the pulmonary veins after it has perfused the bronchi and its O_2 has been partly depleted. Another source is a small amount of coronary venous blood that drains directly into the cavity of the left ventricle through the thebesian veins. The effect of the addition of this poorly oxygenated blood is to depress the arterial Po_2. Some patients have an abnormal vascular connection between a small pulmonary artery and vein (pulmonary arteriovenous fistula). In patients with heart disease, there

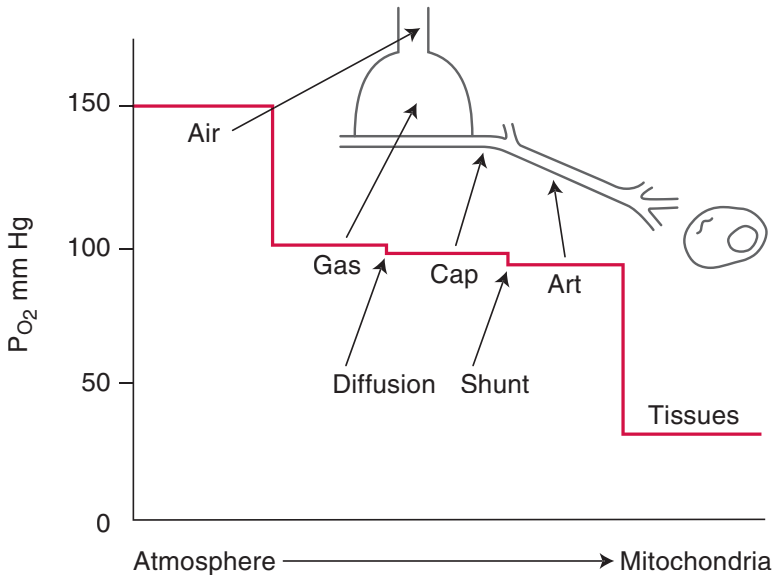


Figure 5-2. Scheme of O_2 transfer from air to tissues showing the depression of arterial Po_2 caused by diffusion and shunt.

may be a direct addition of venous blood to arterial blood across a defect between the right and left sides of the heart.

When the shunt is caused by the addition of mixed venous blood to blood draining from the capillaries, it is possible to calculate the amount of the shunt flow (Figure 5-3). The total amount of O_2 leaving the system is the total blood flow $\dot{Q}_T$ multiplied by the O_2 concentration in the arterial blood Ca_{O_2}, or $\dot{Q}_T \times Ca_{O_2}$. This must equal the sum of the amounts of O_2 in the shunted blood, $\dot{Q}_S \times C\bar{v}_{O_2}$, and end-capillary blood, $(\dot{Q}_T - \dot{Q}_S) \times Cc'_O$. Thus,

$$\dot{Q}_T \times Ca_{O_2} = \dot{Q}_S \times C\bar{v}_{O_2} + (\dot{Q}_T - \dot{Q}_S) \times Cc'_{O_2}$$

Rearranging gives

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{Cc'_{O_2} - Ca_{O_2}}{Cc'_{O_2} - C\bar{v}_{O_2}}$$

The O_2 concentration of end-capillary blood is usually calculated from the alveolar Po_2 and the oxygen dissociation curve (see Chapter 6).

When the shunt is caused by blood that does not have the same O_2 concentration as mixed venous blood (for example, bronchial vein blood), it is generally not possible to calculate its true magnitude. However, it is often useful to calculate an "as if" shunt, that is, what the shunt *would* be if the observed depression of arterial O_2 concentration were caused by the addition of mixed venous blood.

An important feature of a shunt is that the hypoxemia cannot be abolished by giving the subject 100% O_2 to breathe. This is because the shunted blood that bypasses ventilated alveoli is never exposed to the higher alveolar Po_2, so it continues to depress the arterial Po_2. However, some elevation of the arterial Po_2 occurs because of the O_2 added to the capillary blood of ventilated lung. Most of the added O_2 is in the dissolved form, rather than attached to hemoglobin, because the blood that is perfusing ventilated alveoli is nearly

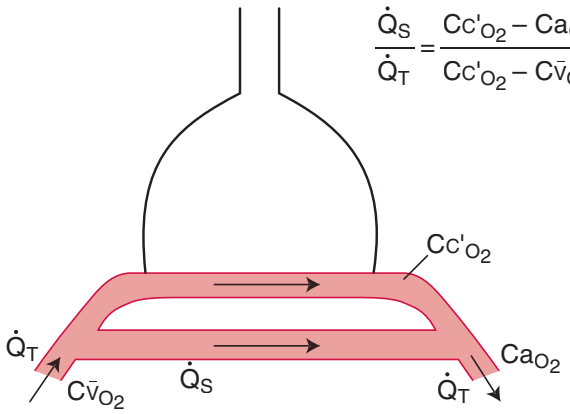


Figure 5-3. Measurement of shunt flow. The oxygen carried in the arterial blood equals the sum of the oxygen carried in the capillary blood and that in the shunted blood (see text).

fully saturated (see Chapter 6). Giving the subject 100% O_2 to breathe is a very sensitive measurement of shunt because when the Po_2 is high, a small depression of arterial O_2 concentration causes a relatively large fall in Po_2 due to the almost flat slope of the O_2 dissociation curve in this region (Figure 5-4).

A shunt usually does not result in a raised Pco_2 in arterial blood, even though the shunted blood is rich in CO_2. The reason is that the chemoreceptors sense any elevation of arterial Pco_2 and they respond by increasing the ventilation. This reduces the Pco_2 of the unshunted blood until the arterial Pco_2 is normal. Indeed, in some patients with a shunt, the arterial Pco_2 is low because the hypoxemia increases respiratory drive (see Chapter 8).

Shunt

- Hypoxemia responds poorly to added inspired O_2
- When 100% O_2 is inspired, the arterial Po_2 does not rise to the expected level—a useful diagnostic test
- If the shunt is caused by mixed venous blood, its size can be calculated from the shunt equation

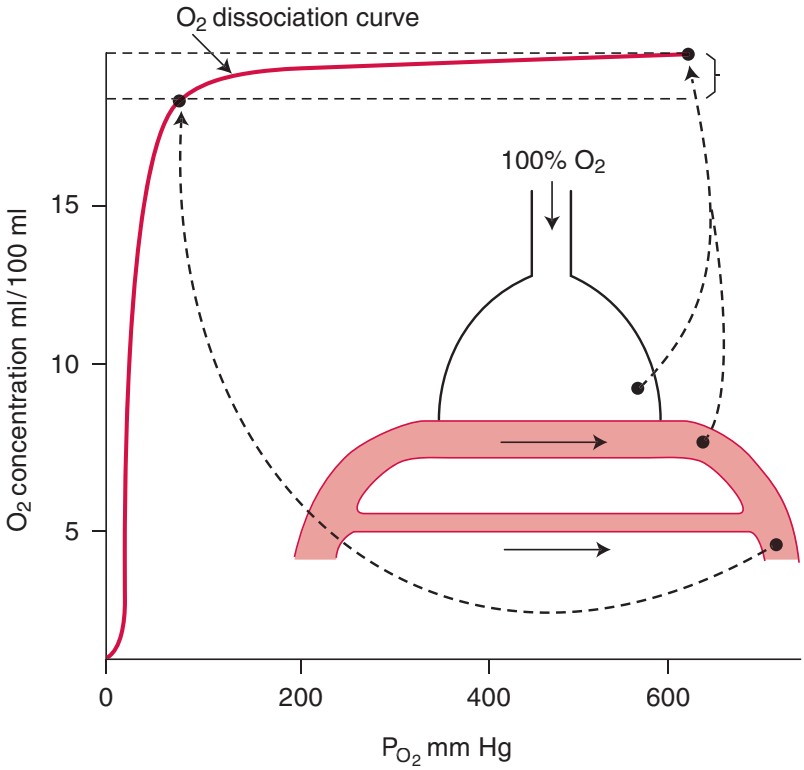


Figure 5-4. Depression of arterial Po_2 by shunt during 100% O_2 breathing. The addition of a small amount of shunted blood with its low O_2 concentration greatly reduces the Po_2 of arterial blood. This is because the O_2 dissociation curve is nearly flat when the Po_2 is very high.

The Ventilation-Perfusion Ratio

So far, we have considered three of the four causes of hypoxemia: hypoventilation, diffusion, and shunt. We now come to the last cause, which is both the most common and the most difficult to understand, namely, ventilation-perfusion inequality. It turns out that if ventilation and blood flow are mismatched in various regions of the lung, impairment of both O_2 and CO_2 transfer results. The key to understanding how this happens is the ventilation-perfusion ratio.

Consider a model of a lung unit (Figure 2-1) in which the uptake of O_2 is being mimicked using dye and water (Figure 5-5). Powdered dye is continuously poured into the unit to represent the addition of O_2 by alveolar ventilation. Water is pumped continuously through the unit to represent the blood flow that removes the O_2. A stirrer mixes the alveolar contents, a process normally accomplished by gaseous diffusion. The key question is: What determines the concentration of dye (or O_2) in the alveolar compartment and, therefore, in the effluent water (or blood)?

It is clear that both the rate at which the dye is added (ventilation) and the rate at which water is pumped (blood flow) will affect the concentration of dye in the model. What may not be intuitively clear is that the concentration of dye is determined by the ratio of these rates. In other words, if dye is added at the rate of V g·min^{-1} and water is pumped through at Q liters·min^{-1},

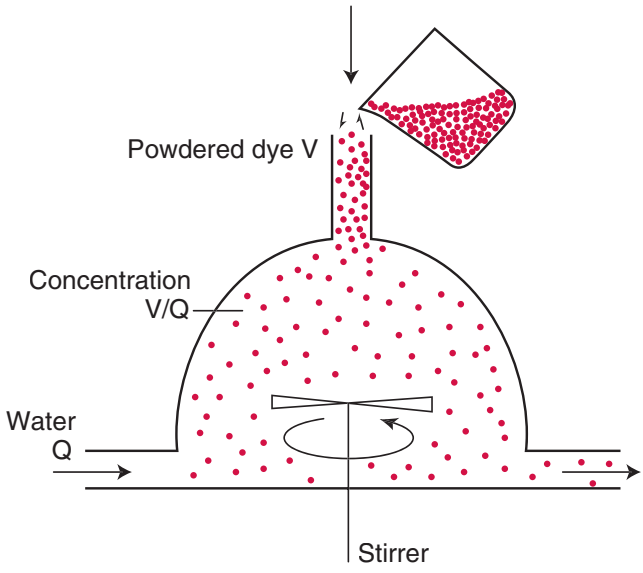


Figure 5-5. Model to illustrate how the ventilation-perfusion ratio determines the P_{O_2} in a lung unit. Powdered dye is added by ventilation at the rate V and removed by blood flow Q to represent the factors controlling alveolar P_{O_2}. The concentration of dye is given by V/Q.

the concentration of dye in the alveolar compartment and effluent water is V/Q g·liter^{-1}.

In exactly the same way, the concentration of O_2 (or, better, P_{O_2}) in any lung unit is determined by the ratio of ventilation to blood flow. This is true not only for O_2 but CO_2, N_2, and any other gas that is present under steady-state conditions. This is why the ventilation-perfusion ratio plays such a key role in pulmonary gas exchange.

Effect of Altering the Ventilation-Perfusion Ratio of a Lung Unit

Let us take a closer look at the way alterations in the ventilation-perfusion ratio of a lung unit affect its gas exchange. Figure 5-6A shows the P_{O_2} and P_{CO_2} in a unit with a normal ventilation-perfusion ratio (about 1, see Figure 2-1). The inspired air has a P_{O_2} of 150 mm Hg (Figure 5-1) and a P_{CO_2} of 0. The mixed venous blood entering the unit has a P_{O_2} of 40 mm Hg and a P_{CO_2} of 45 mm Hg. The alveolar P_{O_2} of 100 mm Hg is determined by a balance between the addition of O_2 by ventilation and its removal by blood flow. The normal alveolar P_{CO_2} of 40 mm Hg is set similarly.

Now suppose that the ventilation-perfusion ratio of the unit is gradually reduced by obstructing its ventilation, leaving its blood flow unchanged (Figure 5-6B). It is clear that the O_2 in the unit will fall and the CO_2

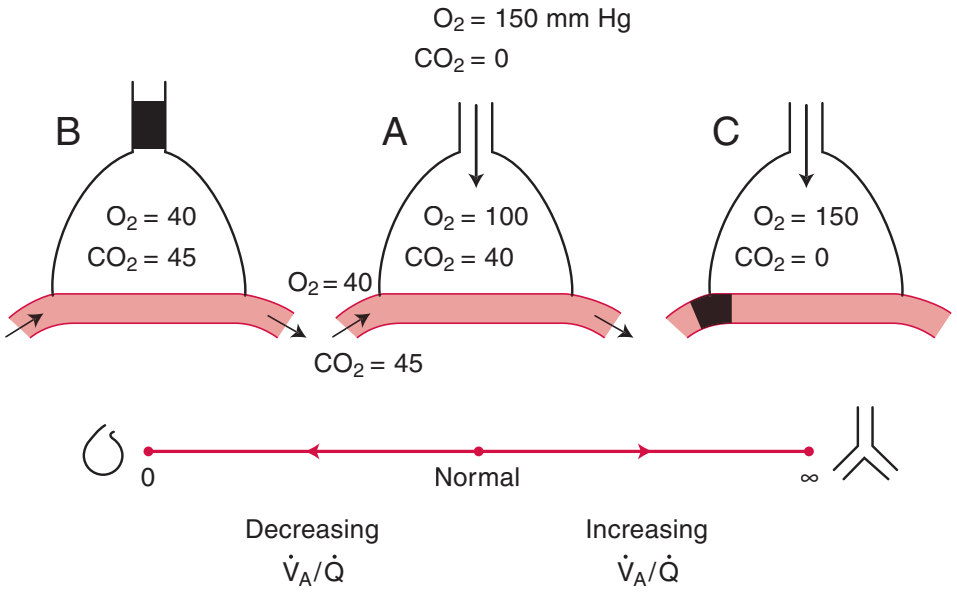


Figure 5-6. Effect of altering the ventilation-perfusion ratio on the P_{O_2} and P_{CO_2} in a lung unit.

will rise, although the relative changes of these two are not immediately obvious.* However, we can easily predict what will eventually happen when the ventilation is completely abolished (ventilation-perfusion ratio of 0). Now the O_2 and CO_2 of alveolar gas and end-capillary blood must be the same as those of mixed venous blood. (In practice, completely obstructed units eventually collapse, but we can neglect such long-term effects at the moment.) Note that we are assuming that what happens in one lung unit out of a very large number does not affect the composition of the mixed venous blood.

Suppose instead that the ventilation-perfusion ratio is increased by gradually obstructing blood flow (Figure 5-6C). Now the O_2 rises and the CO_2 falls, eventually reaching the composition of inspired gas when blood flow is abolished (ventilation-perfusion ratio of infinity). Thus, as the ventilation-perfusion ratio of the unit is altered, its gas composition approaches that of mixed venous blood or inspired gas.

A convenient way of depicting these changes is to use the O_2-CO_2 diagram (Figure 5-7). In this, P_{O_2} is plotted on the X axis, and P_{CO_2} is plotted on the Y axis. First, locate the normal alveolar gas composition, point A (P_{O_2} = 100, P_{CO_2} = 40). If we assume that blood equilibrates with alveolar gas at the end of the capillary (Figure 3-3), this point can equally well represent the end-capillary blood. Next find the mixed venous point $\bar{v}$ (P_{O_2} = 40, P_{CO_2} = 45). The bar above v means "mixed" or "mean." Finally, find the inspired point I (P_{O_2} = 150, P_{CO_2} = 0). Also, note the similarities between Figures 5-6 and 5-7.

The line joining $\bar{v}$ to I passing through A shows the changes in alveolar gas (and end-capillary blood) composition that can occur when the ventilation-perfusion ratio is either decreased below normal (A $\rightarrow \bar{v}$) or increased above normal (A $\rightarrow$ I). Indeed, this line indicates *all* the possible alveolar gas compositions in a lung that is supplied with gas of composition I and blood of composition $\bar{v}$. For example, such a lung could not contain an alveolus with a P_{O_2} of 70 and P_{CO_2} of 30 mm Hg, because this point does not lie on the ventilation-perfusion line. However, this alveolar composition *could* exist if the mixed venous blood or inspired gas were changed so that the line then passed through this point.

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*The alveolar gas equation is not applicable here because the respiratory exchange ratio is not constant. The appropriate equation is

$$\frac{\dot{V}_A}{\dot{Q}} = 8.63\ R\ \frac{Ca_{O_2} - C\bar{v}_{O_2}}{P_{A_{CO_2}}}$$

This is called the ventilation-perfusion ratio equation.

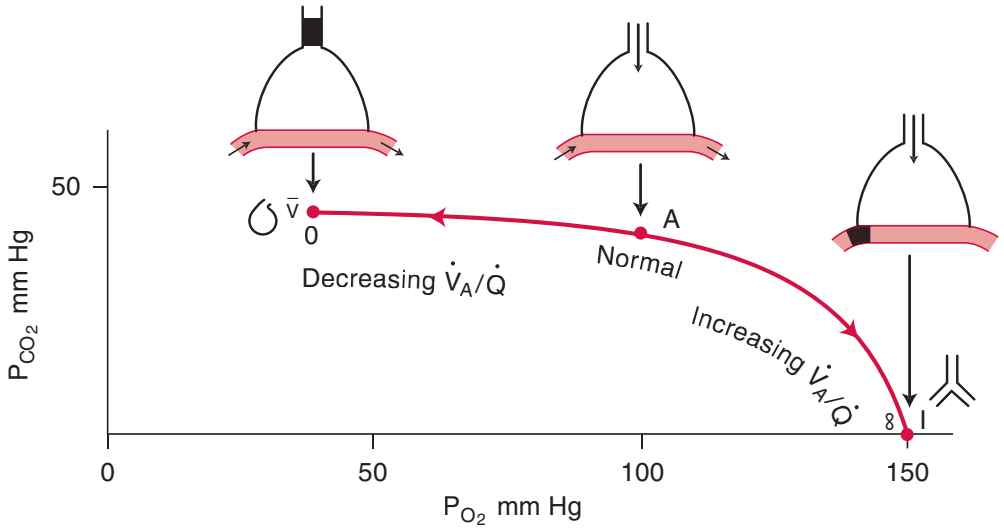

Figure 5-7. O_2-CO_2 diagram showing a ventilation-perfusion ratio line. The P_{O_2} and P_{CO_2} of a lung unit move along this line from the mixed venous point to the inspired gas point I as the ventilation-perfusion ratio is increased (compare Figure 5-6).

Regional Gas Exchange in the Lung

The way in which the ventilation-perfusion ratio of a lung unit determines its gas exchange can be graphically illustrated by looking at the differences that occur down the upright lung. We saw in Figures 2-7 and 4-7 that ventilation increases slowly from top to bottom of the lung and blood flow increases more rapidly (Figure 5-8). As a consequence, the ventilation-perfusion ratio

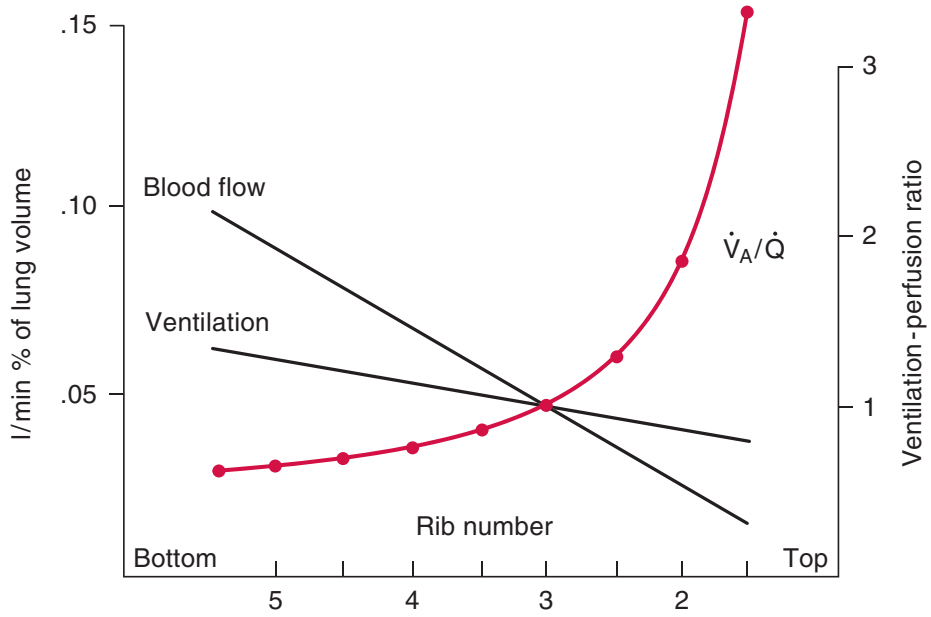

Figure 5-8. Distribution of ventilation and blood flow down the upright lung (compare Figures 2-7 and 4-7). Note that the ventilation-perfusion ratio decreases down the lung.

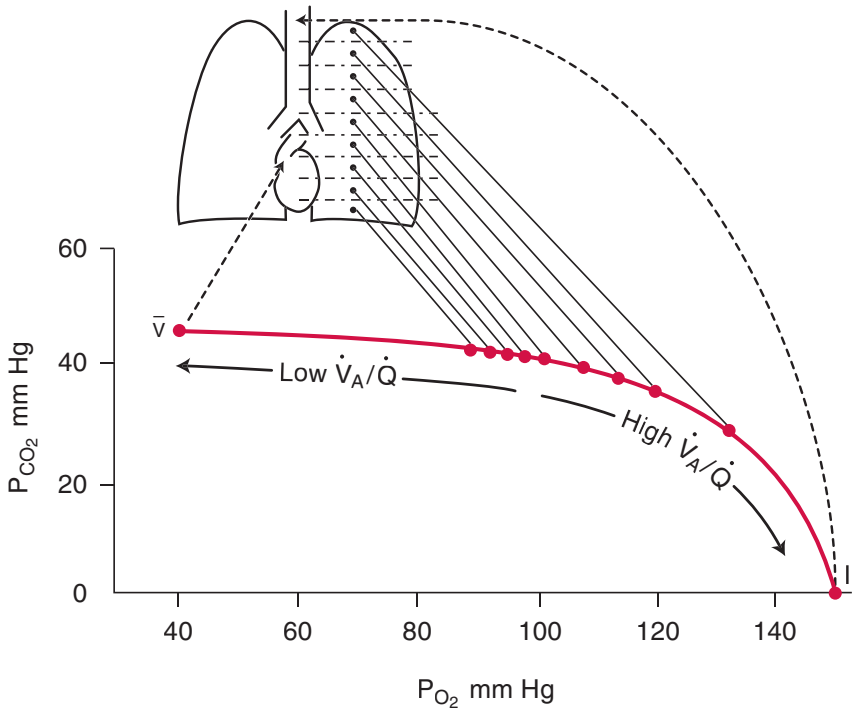

Figure 5-9. Result of combining the pattern of ventilation-perfusion ratio inequality shown in Figure 5-8 with the effects of this on gas exchange as shown in Figure 5-7. Note that the high ventilation-perfusion ratio at the apex results in a high P_{O_2} and low P_{CO_2} there. The opposite is seen at the base.

is abnormally high at the top of the lung (where the blood flow is minimal) and much lower at the bottom. We can now use these regional differences in ventilation-perfusion ratio on an O_2-CO_2 diagram (Figure 5-7) to depict the resulting differences in gas exchange.

Figure 5-9 shows the upright lung divided into imaginary horizontal "slices," each of which is located on the ventilation-perfusion line by its own ventilation-perfusion ratio. This ratio is high at the apex, so this point is found toward the right end of the line, whereas the base of the lung is to the left of normal (compare Figure 5-7). It is clear that the P_{O_2} of the alveoli (horizontal axis) decreases markedly down the lung, whereas the P_{CO_2} (vertical axis) increases much less.

Figure 5-10 illustrates the values that can be read off a diagram like Figure 5-9. (Of course, there will be variations between individuals; the chief aim of this approach is to describe the principles underlying gas exchange.) Note first that the volume of the lung in the slices is less near the apex than the base. Ventilation is less at the top than the bottom, but the differences in blood flow are more marked. Consequently, the ventilation-perfusion ratio decreases down the lung, and all the differences in gas exchange follow from this. Note that the P_{O_2} changes by over 40 mm Hg, whereas the difference in P_{CO_2} between apex and base is much less. (Incidentally, the high P_{O_2} at

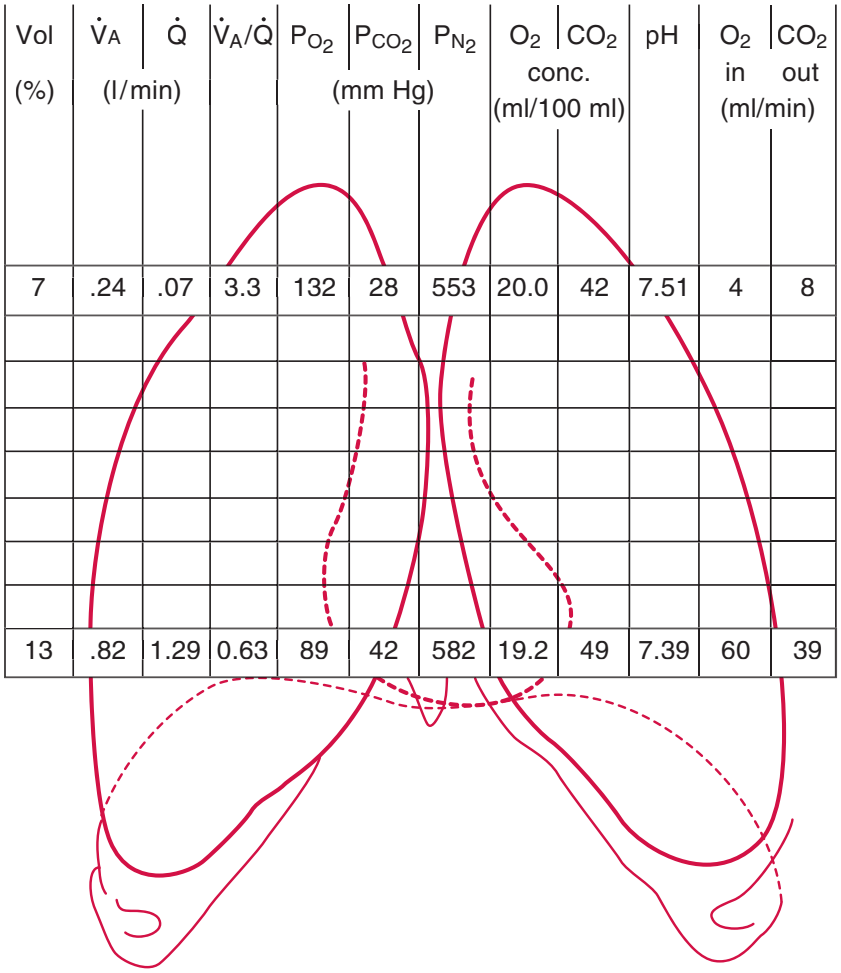

Figure 5-10. Regional differences in gas exchange down the normal lung. Only the apical and basal values are shown for clarity.

the apex probably accounts for the preference of adult tuberculosis for this region because it provides a more favorable environment for this organism.) The variation in P_{N_2} is, in effect, by default because the total pressure in the alveolar gas is the same throughout the lung.

The regional differences in P_{O_2} and P_{CO_2} imply differences in the end-capillary concentrations of these gases, which can be obtained from the appropriate dissociation curves (Chapter 6). Note the surprisingly large difference in pH down the lung, which reflects the considerable variation in P_{CO_2} of the blood. The minimal contribution to overall O_2 uptake made by the apex can be mainly attributed to the very low blood flow there. The difference in CO_2 output between apex and base is much less because this can be shown to be more closely related to ventilation. As a result, the respiratory exchange ratio (CO_2 output/O_2 uptake) is higher at the apex than at the base. On exercise, when the distribution of blood flow becomes more uniform, the apex assumes a larger share of the O_2 uptake.

Effect of Ventilation-Perfusion Inequality on Overall Gas Exchange

Although the regional differences in gas exchange discussed above are of interest, more important to the body as a whole is whether uneven ventilation and blood flow affect the overall gas exchange of the lung, that is, its ability to take up O_2 and put out CO_2. It turns out that a lung with ventilation-perfusion inequality is not able to transfer as much O_2 and CO_2 as a lung that is uniformly ventilated and perfused, other things being equal. Or if the same amounts of gas are being transferred (because these are set by the metabolic demands of the body), the lung with ventilation-perfusion inequality cannot maintain as high an arterial P_{O_2} or as low an arterial P_{CO_2} as a homogeneous lung, again other things being equal.

The reason why a lung with uneven ventilation and blood flow has difficulty oxygenating arterial blood can be illustrated by looking at the differences down the upright lung (Figure 5-11). Here the P_{O_2} at the apex is some 40 mm Hg higher than at the base of the lung. However, the major share of the blood leaving the lung comes from the lower zones, where the P_{O_2} is low. This has the result of depressing the arterial P_{O_2}. By contrast, the expired alveolar gas comes more uniformly from apex and base because the differences of ventilation are much less than those for blood flow (Figure 5-8). By the same reasoning, the arterial P_{CO_2} will be elevated because it is higher at the base of the lung than at the apex (Figure 5-10).

An additional reason that uneven ventilation and blood flow depress the arterial P_{O_2} is shown in Figure 5-12. This depicts three groups of alveoli with low, normal, and high ventilation-perfusion ratios. The O_2 concentrations of the effluent blood are 16, 19.5, and 20 ml 100 ml^{-1}, respectively. As a result, the units with the high

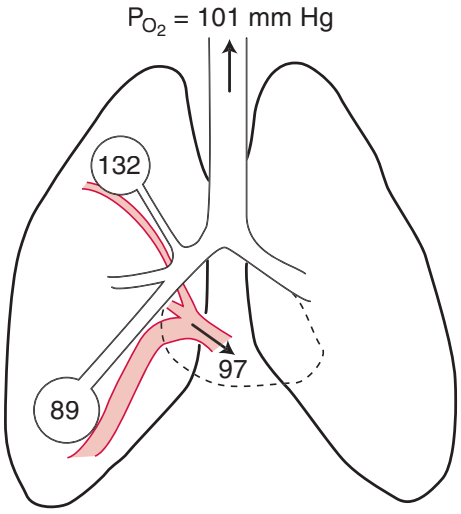

Figure 5-11. Depression of the arterial P_{O_2} by ventilation-perfusion inequality. In this diagram of the upright lung, only two groups of alveoli are shown, one at the apex and another at the base. The relative sizes of the airways and blood vessels indicate their relative ventilations and blood flows. Because most of the blood comes from the poorly oxygenated base, depression of the blood P_{O_2} is inevitable.

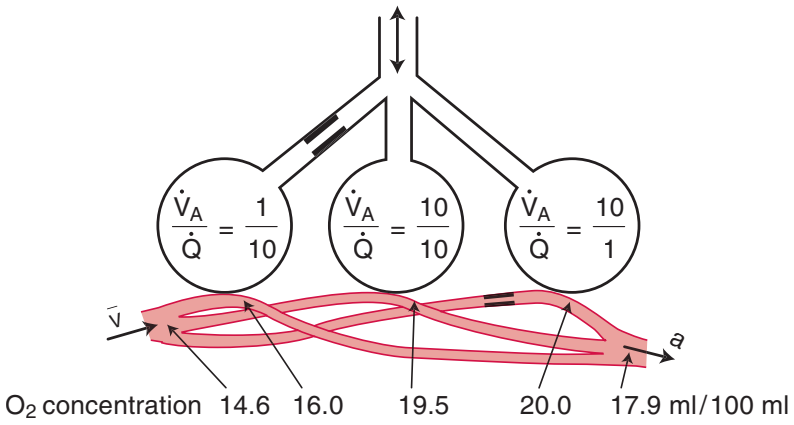

Figure 5-12. Additional reason for the depression of arterial P_{O_2} by mismatching of ventilation and blood flow. The lung units with a high ventilation-perfusion ratio add relatively little oxygen to the blood, compared with the decrement caused by alveoli with a low ventilation-perfusion ratio.

ventilation-perfusion ratio add relatively little oxygen to the blood, compared with the decrement caused by the alveoli with the low ventilation-perfusion ratio. Thus, the mixed capillary blood has a lower O_2 concentration than that from units with a normal ventilation-perfusion ratio. This can be explained by the nonlinear shape of the oxygen dissociation curve, which means that although units with a high ventilation-perfusion ratio have a relatively high P_{O_2}, this does not increase the oxygen concentration of their blood very much. This additional reason for the depression of P_{O_2} does not apply to the elevation of the P_{CO_2} because the CO_2 dissociation curve is almost linear in the working range.

The net result of these mechanisms is a depression of the arterial P_{O_2} below that of the mixed alveolar P_{O_2}—the so-called alveolar-arterial O_2 difference. In the normal upright lung, this difference is of trivial magnitude, being only about 4 mm Hg due to ventilation-perfusion inequality. Its development is described here only to illustrate how uneven ventilation and blood flow must result in depression of the arterial P_{O_2}. In lung disease, the lowering of arterial P_{O_2} by this mechanism can be extreme.

Distributions of Ventilation-Perfusion Ratios

It is possible to obtain information about the distribution of ventilation-perfusion ratios in patients with lung disease by infusing into a peripheral vein a mixture of dissolved inert gases having a range of solubilities and then measuring the concentrations of the gases in arterial blood and expired gas. The details of this technique are too complex to be described here, and it is used for research purposes rather than in the pulmonary function laboratory. The technique returns a distribution of ventilation and blood flow plotted against ventilation-perfusion ratio with 50 compartments equally spaced on a log scale.

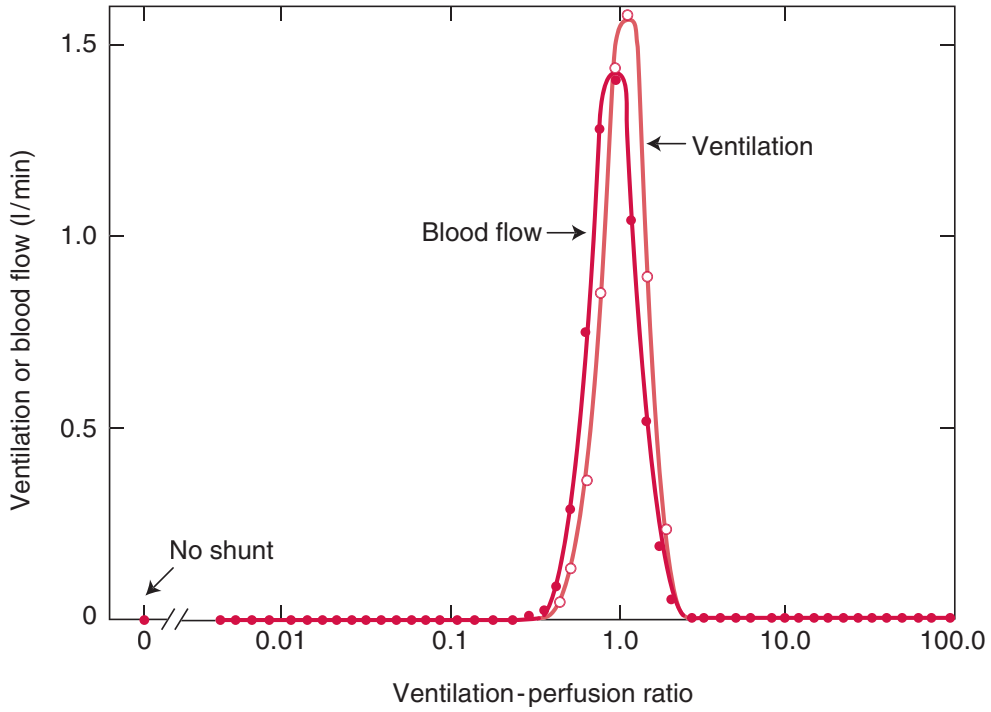

Figure 5-13. Distribution of ventilation-perfusion ratios in a young normal subject. Note the narrow dispersion and absence of shunt.

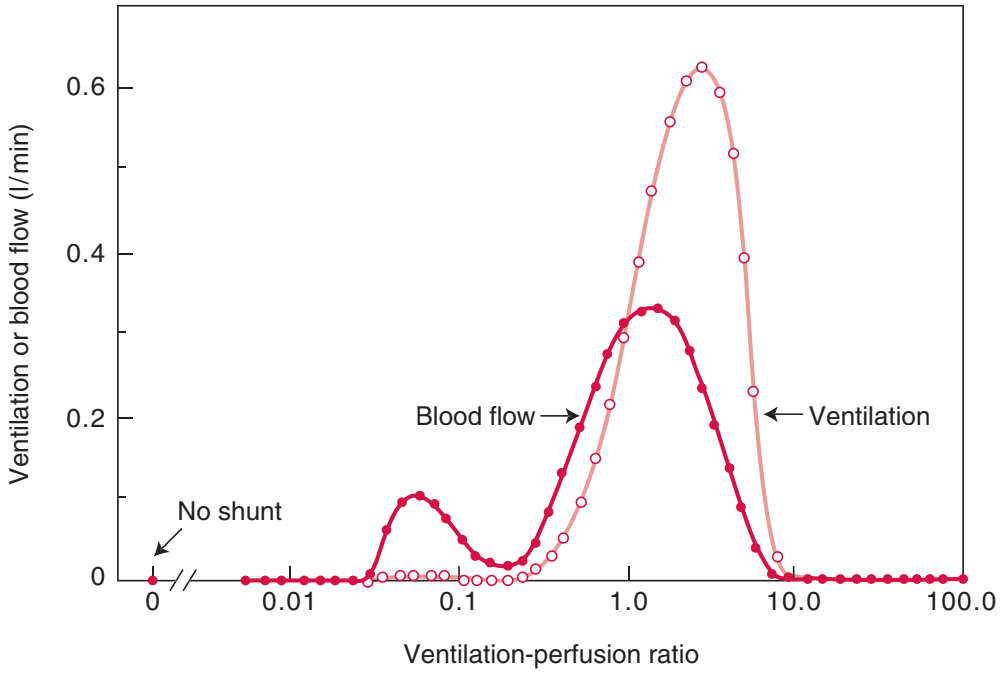

Figure 5-14. Distribution of ventilation-perfusion ratios in a patient with chronic bronchitis and emphysema. Note particularly the blood flow to lung units with very low ventilation-perfusion ratios. Compare Figure 5-13.

Figure 5-13 shows a typical result from a young normal subject. Note that all the ventilation and blood flow goes to compartments close to the normal ventilation-perfusion ratio of about 1.0, and, in particular, there is no blood flow to the unventilated compartment (shunt). The distributions in patients with lung disease are often very different. An example from a patient with chronic bronchitis and emphysema is shown in Figure 5-14. Note that although much of the ventilation and blood flow goes to compartments with ventilation-perfusion ratios near normal, considerable blood flow is going to compartments with ventilation-perfusion ratios of between 0.03 and 0.3. Blood from these units will be poorly oxygenated and will depress the arterial Po_2. There is also excessive ventilation to lung units with ventilation-perfusion ratios up to 10. These units are inefficient at eliminating CO_2. This particular patient had arterial hypoxemia but a normal arterial Pco_2 (see below). Other patterns are seen in other types of lung disease.

Ventilation-Perfusion Inequality as a Cause of CO_2 Retention

Imagine a lung that is uniformly ventilated and perfused and that is transferring normal amounts of O_2 and CO_2. Suppose that in some magical way, the matching of ventilation and blood flow is suddenly disturbed while everything else remains unchanged. What happens to gas exchange? It transpires that the effect of this "pure" ventilation-perfusion inequality (that is, everything else held constant) is to reduce *both* the O_2 uptake and CO_2 output of the lung. In other words, the lung becomes less efficient as a gas exchanger for both gases. Hence, mismatching ventilation and blood flow must cause both hypoxemia and hypercapnia (CO_2 retention), other things being equal.

Ventilation-Perfusion Inequality

- The ventilation-perfusion ratio ($\dot{V}_A / \dot{Q}$) determines the gas exchange in any single lung unit
- Regional differences of $\dot{V}_A / \dot{Q}$ in the upright human lung cause a pattern of regional gas exchange
- $\dot{V}_A / \dot{Q}$ inequality impairs the uptake or elimination of all gases by the lung
- Although the elimination of CO_2 is impaired by $\dot{V}_A / \dot{Q}$ inequality, this can be corrected by increasing the ventilation to the alveoli
- By contrast, the hypoxemia resulting from $\dot{V}_A / \dot{Q}$ inequality cannot be eliminated by increases in ventilation
- The different behavior of the two gases results from the different shapes of their dissociation curves

However, in practice, patients with undoubted ventilation-perfusion inequality often have a normal arterial P_{CO_2}. The reason for this is that whenever the chemoreceptors sense a rising P_{CO_2}, there is an increase in ventilatory drive (Chapter 8). The consequent increase in ventilation to the alveoli is usually effective in returning the arterial P_{CO_2} to normal. However, such patients can only maintain a normal P_{CO_2} at the expense of this increased ventilation to their alveoli; the ventilation in excess of what they would normally require is sometimes referred to as *wasted ventilation* and is necessary because the lung units with abnormally high ventilation-perfusion ratios are inefficient at eliminating CO_2. Such units are said to constitute an *alveolar dead space*.

While the increase in ventilation to a lung with ventilation-perfusion inequality is usually effective at reducing the arterial P_{CO_2}, it is much less effective at increasing the arterial P_{O_2}. The reason for the different behavior of the two gases lies in the shapes of the CO_2 and O_2 dissociation curves (Chapter 6). The CO_2 dissociation curve is almost straight in the physiological range, with the result that an increase in ventilation will raise the CO_2 output of lung units with both high and low ventilation-perfusion ratios. By contrast, the almost flat top of the O_2 dissociation curve means that only units with moderately low ventilation-perfusion ratios will benefit appreciably from the increased ventilation. Those units that are very high on the dissociation curve (high ventilation-perfusion ratio) increase the O_2 concentration of their effluent blood very little (Figure 5-12). Those units that have a very low ventilation-perfusion ratio continue to put out blood with an O_2 concentration close to that of mixed venous blood. The net result is that the mixed arterial P_{O_2} rises only modestly, and some hypoxemia always remains.

Measurement of Ventilation-Perfusion Inequality

How can we assess the amount of ventilation-perfusion inequality in diseased lungs? Radioactive gases can be used to define topographical differences in ventilation and blood flow in the normal upright lung (Figures 2-7 and 4-7), but in most patients large amounts of inequality exist between closely adjacent units, and this cannot be distinguished by counters over the chest. In practice, we turn to indices based on the resulting impairment of gas exchange.[†]

One useful measurement is the *alveolar-arterial* P_{O_2} *difference*, obtained by subtracting the arterial P_{O_2} from the so-called ideal alveolar P_{O_2}. The latter

[†]For more details of this difficult subject, see JB West, *Pulmonary Pathophysiology: The Essentials*, 7th ed. (Baltimore, MD: Lippincott Williams & Wilkins, 2007).

is the P_{O_2} that the lung *would* have if there were no ventilation-perfusion inequality, and it was exchanging gas at the same respiratory exchange ratio as the real lung. It is derived from the alveolar gas equation:

$$P_{A_{O_2}} = P_{I_{O_2}} - \frac{P_{A_{CO_2}}}{R} + F$$

The arterial P_{CO_2} is used for the alveolar value.

An example will clarify this. Suppose a patient who is breathing air at sea level has an arterial P_{O_2} of 50 mm Hg, an arterial P_{CO_2} of 60 mm Hg, and a respiratory exchange ratio of 0.8. Could the arterial hypoxemia be explained by hypoventilation?

From the alveolar gas equation, the ideal alveolar P_{O_2} is given by

$$P_{A_{O_2}} = 149 - \frac{60}{0.8} + F = 7.4 \text{ mm Hg}$$

where the inspired P_{O_2} is 149 mm Hg and we ignore the small factor F. Thus, the alveolar-arterial P_{O_2} difference is approximately (74 – 50) = 24 mm Hg. This is abnormally high and indicates that there is ventilation-perfusion inequality.

Additional information on the measurement of ventilation-perfusion inequality can be found in Chapter 10.

KEY CONCEPTS

1. The four causes of hypoxemia are hypoventilation, diffusion limitation, shunt, and ventilation-perfusion inequality.
2. The two causes of hypercapnia, or CO_2 retention, are hypoventilation and ventilation-perfusion inequality.
3. Shunt is the only cause of hypoxemia in which the arterial P_{O_2} does not rise to the expected level when a patient is given 100% O_2 to breathe.
4. The ventilation-perfusion ratio determines the P_{O_2} and P_{CO_2} in any lung unit. Because the ratio is high at the top of the lung, P_{O_2} is high there and the P_{CO_2} is low.
5. Ventilation-perfusion inequality reduces the gas exchange efficiency of the lung for all gases. However, many patients with ventilation-perfusion inequality have a normal arterial P_{CO_2} because they increase the ventilation to their alveoli. By contrast, the arterial P_{O_2} is always low. The different behavior of the two gases is attributable to the different shapes of the two dissociation curves.
6. The alveolar-arterial P_{O_2} difference is a useful measure of ventilation-perfusion inequality. The alveolar P_{O_2} is calculated from the alveolar gas equation using the arterial P_{CO_2}.

QUESTIONS

For each question, choose the one best answer.

1. A climber reaches an altitude of 4,500 m (14,800 ft) where the barometric pressure is 447 mm Hg. The P_{O_2} of moist inspired gas (in mm Hg) is

A. 47
B. 63
C. 75
D. 84
E. 98

2. A man with normal lungs and an arterial P_{CO_2} of 40 mm Hg takes an overdose of barbiturate that halves his alveolar ventilation but does not change his CO_2 output. If his respiratory exchange ratio is 0.8, what will be his arterial P_{O_2} (in mm Hg), approximately?

A. 40
B. 50
C. 60
D. 70
E. 80

3. In the situation described in Question 2, how much does the inspired O_2 concentration (%) have to be raised to return the arterial P_{O_2} to its original level?

A. 7
B. 11
C. 15
D. 19
E. 23

4. A patient with normal lungs but a right-to-left shunt is found at catheterization to have oxygen concentrations in his arterial and mixed venous blood of 18 and 14 ml·100 ml^{-1}, respectively. If the O_2 concentration of the blood leaving the pulmonary capillaries is calculated to be 20 ml · 100 ml^{-1}, what is his shunt as a percentage of his cardiac output?

A. 23
B. 33
C. 43
D. 53
E. 63

5. If a climber on the summit of Mt. Everest (barometric pressure 247 mm Hg) maintains an alveolar P_{O_2} of 34 mm Hg and is in a steady state ($R \leq 1$), his alveolar P_{CO_2} (in mm Hg) cannot be any higher than

A. 5
B. 8
C. 10
D. 12
E. 15

6. A patient with severe chronic obstructive pulmonary disease, which causes marked ventilation-perfusion inequality, has an arterial P_{O_2} of 50 mm Hg and an arterial P_{CO_2} of 40 mm Hg. The P_{CO_2} is normal despite the hypoxemia because

A. Ventilation-perfusion inequality does not interfere with CO_2 elimination.
B. Much of the CO_2 is carried as bicarbonate.
C. The formation of carbonic acid is accelerated by carbonic anhydrase.
D. CO_2 diffuses much faster through tissue than O_2.
E. The O_2 and CO_2 dissociation curves have different shapes.

7. The apex of the upright human lung compared with the base has

A. A higher P_{O_2}.
B. A higher ventilation.
C. A lower pH in end-capillary blood.
D. A higher blood flow.
E. Smaller alveoli.

8. If the ventilation-perfusion ratio of a lung unit is decreased by partial bronchial obstruction while the rest of the lung is unaltered, the affected lung unit will show

A. Increased alveolar P_{O_2}.
B. Decreased alveolar P_{CO_2}.
C. No change in alveolar P_{N_2}.
D. A rise in pH of end-capillary blood.
E. A fall in oxygen uptake.

9. A patient with lung disease who is breathing air has an arterial P_{O_2} and P_{CO_2} of 49 and 48 mm Hg, respectively, and a respiratory exchange ratio of 0.8. The approximate alveolar-arterial difference for P_{O_2} (in mm Hg) is

A. 10
B. 20
C. 30
D. 40
E. 50