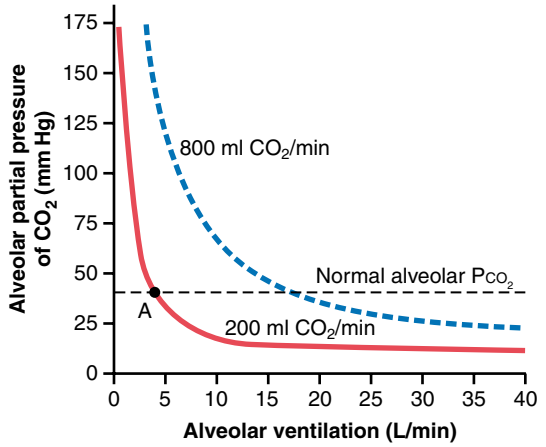

Figure 39-5 Effect of alveolar ventilation on the alveolar P_{CO_2} at two rates of carbon dioxide excretion from the blood—800 ml/min and 200 ml/min. *Point A* is the normal operating point.

Therefore, the concentrations and partial pressures of both oxygen and carbon dioxide in the alveoli are determined by the rates of absorption or excretion of the two gases and by the amount of alveolar ventilation.

Expired Air Is a Combination of Dead Space Air and Alveolar Air

The overall composition of expired air is determined by (1) the amount of the expired air that is dead space air and (2) the amount that is alveolar air. Figure 39-6 shows the progressive changes in oxygen and carbon dioxide partial pressures in the expired air during the course of expiration. The first portion of this air, the dead space air from the respiratory passageways, is typical humidified air, as shown in Table 39-1. Then, progressively more and more alveolar air becomes mixed with the dead space air until all the dead space air has finally been washed out and nothing but alveolar air is expired at the end of expiration. Therefore, the method of collecting alveolar air for study is simply to collect a sample of the last portion of the expired air after forceful expiration has removed all the dead space air.

Normal expired air, containing both dead space air and alveolar air, has gas concentrations and partial pressures approximately as shown in Table 39-1 (i.e., concentrations between those of alveolar air and humidified atmospheric air).

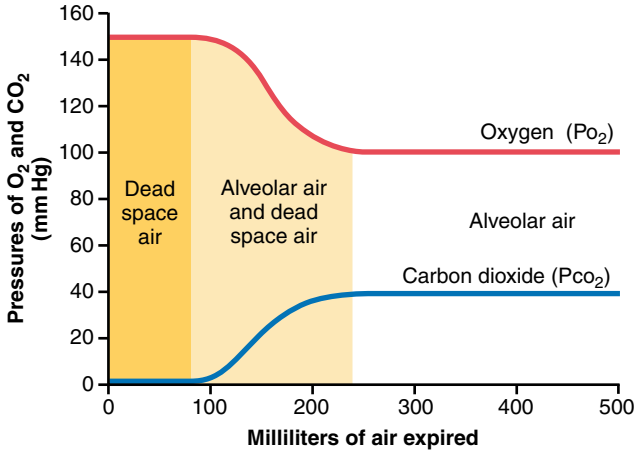

Figure 39-6 Oxygen and carbon dioxide partial pressures in the various portions of normal expired air.

Diffusion of Gases Through the Respiratory Membrane

Respiratory Unit. Figure 39-7 shows the *respiratory unit* (also called "respiratory lobule"), which is composed of a *respiratory bronchiole, alveolar ducts, atria*, and *alveoli*. There are about 300 million alveoli in the two lungs, and each alveolus has an average diameter of about 0.2 millimeter. The alveolar walls are extremely thin, and between the alveoli is an almost solid network of interconnecting capillaries, shown in Figure 39-8. Indeed, because of the extensiveness of the capillary plexus, the flow of blood in the alveolar wall has been described as a "sheet" of flowing blood. Thus, it is obvious that the alveolar gases are in very close proximity to the blood of the pulmonary capillaries. Further, gas exchange between the alveolar air and the pulmonary blood occurs through the membranes of all the terminal portions of the lungs, not merely in the alveoli themselves. All these membranes are collectively known as the *respiratory membrane*, also called the *pulmonary membrane*.

Respiratory Membrane. Figure 39-9 shows the ultrastructure of the respiratory membrane drawn in cross section on the left and a red blood cell on the right. It also shows the diffusion of oxygen from the alveolus into the red blood cell and diffusion of carbon dioxide in

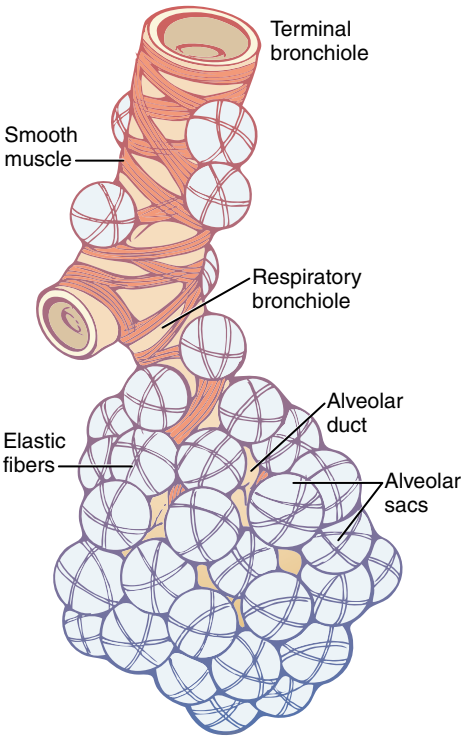

Figure 39-7 Respiratory unit.

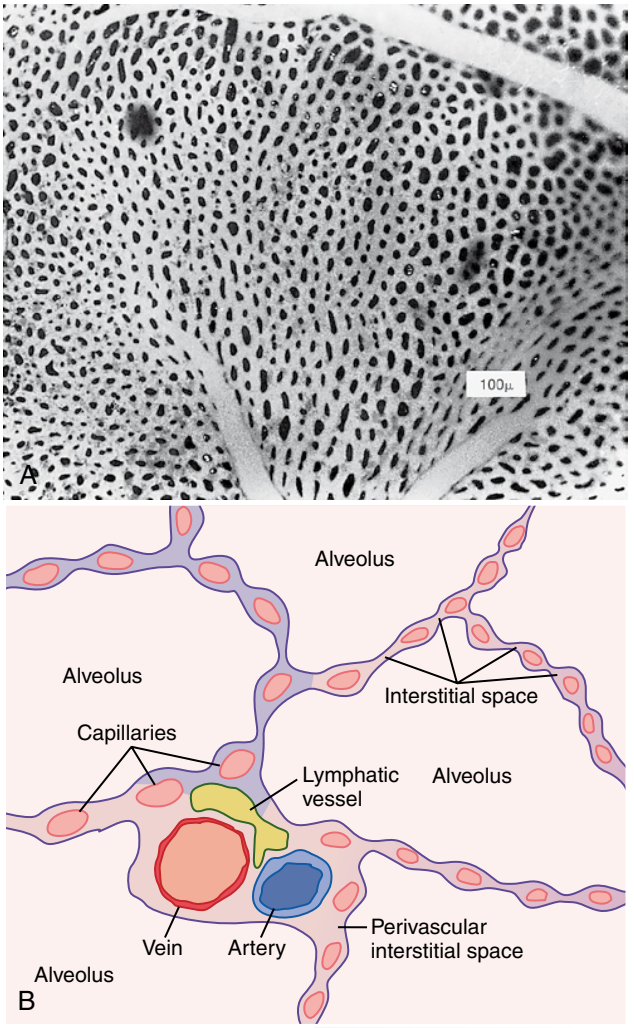

Figure 39-8 *A*, Surface view of capillaries in an alveolar wall. *B*, Cross-sectional view of alveolar walls and their vascular supply. (*A*, From Maloney JE, Castle BL: Pressure-diameter relations of capillaries and small blood vessels in frog lung. Respir Physiol 7:150, 1969. Reproduced by permission of ASP Biological and Medical Press, North-Holland Division.)

the opposite direction. Note the following different layers of the respiratory membrane:

1. A layer of fluid lining the alveolus and containing surfactant that reduces the surface tension of the alveolar fluid
2. The alveolar epithelium composed of thin epithelial cells
3. An epithelial basement membrane
4. A thin interstitial space between the alveolar epithelium and the capillary membrane
5. A capillary basement membrane that in many places fuses with the alveolar epithelial basement membrane
6. The capillary endothelial membrane

Despite the large number of layers, the overall thickness of the respiratory membrane in some areas is as little as 0.2 micrometer, and it averages about 0.6 micrometer, except where there are cell nuclei. From histological

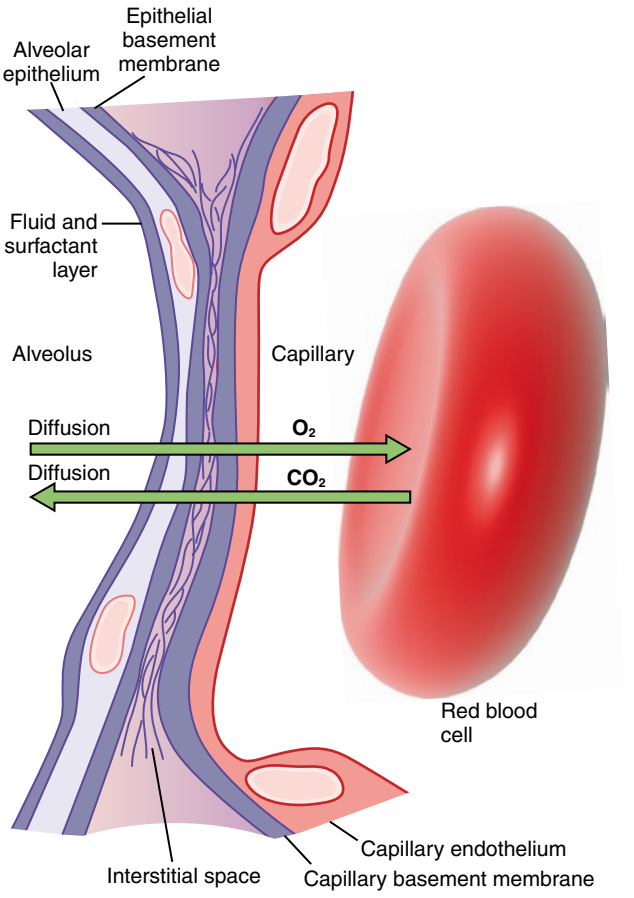

Figure 39-9 Ultrastructure of the alveolar respiratory membrane, shown in cross section.

studies, it has been estimated that the total surface area of the respiratory membrane is about 70 square meters in the normal adult human male. This is equivalent to the floor area of a 25-by-30-foot room. The total quantity of blood in the capillaries of the lungs at any given instant is 60 to 140 milliliters. Now imagine this small amount of blood spread over the entire surface of a 25-by-30-foot floor, and it is easy to understand the rapidity of the respiratory exchange of oxygen and carbon dioxide.

The average diameter of the pulmonary capillaries is only about 5 micrometers, which means that red blood cells must squeeze through them. The red blood cell membrane usually touches the capillary wall, so oxygen and carbon dioxide need not pass through significant amounts of plasma as they diffuse between the alveolus and the red cell. This, too, increases the rapidity of diffusion.

Factors That Affect the Rate of Gas Diffusion Through the Respiratory Membrane

Referring to the earlier discussion of diffusion of gases in water, one can apply the same principles and mathematical formulas to diffusion of gases through the respiratory membrane. Thus, the factors that determine how rapidly a gas will pass through the membrane are (1) the *thickness of the membrane*, (2) the *surface area of the membrane*,

(3) the *diffusion coefficient* of the gas in the substance of the membrane, and (4) the *partial pressure difference* of the gas between the two sides of the membrane.

The *thickness of the respiratory membrane* occasionally increases—for instance, as a result of edema fluid in the interstitial space of the membrane and in the alveoli—so the respiratory gases must then diffuse not only through the membrane but also through this fluid. Also, some pulmonary diseases cause fibrosis of the lungs, which can increase the thickness of some portions of the respiratory membrane. Because the rate of diffusion through the membrane is inversely proportional to the thickness of the membrane, any factor that increases the thickness to more than two to three times normal can interfere significantly with normal respiratory exchange of gases.

The *surface area of the respiratory membrane* can be greatly decreased by many conditions. For instance, removal of an entire lung decreases the total surface area to one half normal. Also, in *emphysema*, many of the alveoli coalesce, with dissolution of many alveolar walls. Therefore, the new alveolar chambers are much larger than the original alveoli, but the total surface area of the respiratory membrane is often decreased as much as fivefold because of loss of the alveolar walls. When the total surface area is decreased to about one-third to one-fourth normal, exchange of gases through the membrane is impeded to a significant degree, *even under resting conditions*, and during competitive sports and other strenuous exercise even the slightest decrease in surface area of the lungs can be a serious detriment to respiratory exchange of gases.

The *diffusion coefficient* for transfer of each gas through the respiratory membrane depends on the gas's *solubility* in the membrane and, inversely, on the *square root* of the gas's *molecular weight*. The rate of diffusion in the respiratory membrane is almost exactly the same as that in water, for reasons explained earlier. Therefore, for a given pressure difference, carbon dioxide diffuses about 20 times as rapidly as oxygen. Oxygen diffuses about twice as rapidly as nitrogen.

The *pressure difference* across the respiratory membrane is the difference between the partial pressure of the gas in the alveoli and the partial pressure of the gas in the pulmonary capillary blood. The partial pressure represents a measure of the total number of molecules of a particular gas striking a unit area of the alveolar surface of the membrane in unit time, and the pressure of the gas in the blood represents the number of molecules that attempt to escape from the blood in the opposite direction. Therefore, the difference between these two pressures is a measure of the *net tendency* for the gas molecules to move through the membrane.

When the partial pressure of a gas in the alveoli is greater than the pressure of the gas in the blood, as is true for oxygen, net diffusion from the alveoli into the blood occurs; when the pressure of the gas in the blood is greater than the partial pressure in the alveoli, as is true for carbon dioxide, net diffusion from the blood into the alveoli occurs.

Diffusing Capacity of the Respiratory Membrane

The ability of the respiratory membrane to exchange a gas between the alveoli and the pulmonary blood is expressed in quantitative terms by the *respiratory membrane's diffusing capacity*, which is defined as the *volume of a gas that will diffuse through the membrane each minute for a partial pressure difference of 1 mm Hg*. All the factors discussed earlier that affect diffusion through the respiratory membrane can affect this diffusing capacity.

Diffusing Capacity for Oxygen. In the average young man, the *diffusing capacity for oxygen* under resting conditions averages *21 ml/min/mm Hg*. In functional terms, what does this mean? The mean oxygen pressure difference across the respiratory membrane during normal, quiet breathing is about 11 mm Hg. Multiplication of this pressure by the diffusing capacity (11 × 21) gives a total of about 230 milliliters of oxygen diffusing through the respiratory membrane each minute; this is equal to the rate at which the resting body uses oxygen.

Increased Oxygen Diffusing Capacity During Exercise. During strenuous exercise or other conditions that greatly increase pulmonary blood flow and alveolar ventilation, the diffusing capacity for oxygen increases in young men to a maximum of about 65 ml/min/mm Hg, which is three times the diffusing capacity under resting conditions. This increase is caused by several factors, among which are (1) opening up of many previously dormant pulmonary capillaries or extra dilation of already open capillaries, thereby increasing the surface area of the blood into which the oxygen can diffuse; and (2) a better match between the ventilation of the alveoli and the perfusion of the alveolar capillaries with blood, called the *ventilation-perfusion ratio*, which is explained in detail later in this chapter. Therefore, during exercise, oxygenation of the blood is increased not only by increased alveolar ventilation but also by greater diffusing capacity of the respiratory membrane for transporting oxygen into the blood.

Diffusing Capacity for Carbon Dioxide. The diffusing capacity for carbon dioxide has never been measured because of the following technical difficulty: Carbon dioxide diffuses through the respiratory membrane so rapidly that the average P_{CO_2} in the pulmonary blood is not far different from the P_{CO_2} in the alveoli—the average difference is less than 1 mm Hg—and with the available techniques, this difference is too small to be measured.

Nevertheless, measurements of diffusion of other gases have shown that the diffusing capacity varies directly with the diffusion coefficient of the particular gas. Because the diffusion coefficient of carbon dioxide is slightly more than 20 times that of oxygen, one would expect a diffusing capacity for carbon dioxide under resting conditions of about 400 to 450 ml/min/mm Hg and during exercise of about 1200 to 1300 ml/min/mm Hg. Figure 39-10

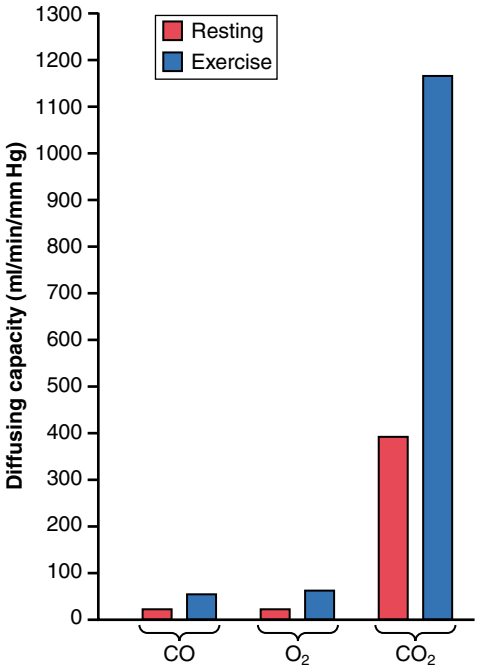

Figure 39-10 *Diffusing capacities* for carbon monoxide, oxygen, and carbon dioxide in the normal lungs under resting conditions and during exercise.

compares the measured or calculated diffusing capacities of carbon monoxide, oxygen, and carbon dioxide at rest and during exercise, showing the extreme diffusing capacity of carbon dioxide and the effect of exercise on the diffusing capacity of each of these gases.

Measurement of Diffusing Capacity—the Carbon Monoxide Method. The oxygen diffusing capacity can be calculated from measurements of (1) alveolar P_{O_2}, (2) P_{O_2} in the pulmonary capillary blood, and (3) the rate of oxygen uptake by the blood. However, measuring the P_{O_2} in the pulmonary capillary blood is so difficult and so imprecise that it is not practical to measure oxygen diffusing capacity by such a direct procedure, except on an experimental basis.

To obviate the difficulties encountered in measuring oxygen diffusing capacity directly, physiologists usually measure carbon monoxide diffusing capacity instead and then calculate the oxygen diffusing capacity from this. The principle of the carbon monoxide method is the following: A small amount of carbon monoxide is breathed into the alveoli, and the partial pressure of the carbon monoxide in the alveoli is measured from appropriate alveolar air samples. The carbon monoxide pressure in the blood is essentially zero because hemoglobin combines with this gas so rapidly that its pressure never has time to build up. Therefore, the pressure difference of carbon monoxide across the respiratory membrane is equal to its partial pressure in the alveolar air sample. Then, by measuring the volume of carbon monoxide absorbed in a short period and dividing this by the alveolar carbon monoxide partial pressure, one can determine accurately the carbon monoxide diffusing capacity.

To convert carbon monoxide diffusing capacity to oxygen diffusing capacity, the value is multiplied by a factor of 1.23 because the diffusion coefficient for oxygen is 1.23 times that for carbon monoxide. Thus, the average diffusing capacity for carbon monoxide in young men at rest is 17 ml/min/mm Hg, and the diffusing capacity for oxygen is 1.23 times this, or 21 ml/min/mm Hg.

Effect of the Ventilation-Perfusion Ratio on Alveolar Gas Concentration

In the early part of this chapter, we learned that two factors determine the P_{O_2} and the P_{CO_2} in the alveoli: (1) the rate of alveolar ventilation and (2) the rate of transfer of oxygen and carbon dioxide through the respiratory membrane. These earlier discussions made the assumption that all the alveoli are ventilated equally and that blood flow through the alveolar capillaries is the same for each alveolus. However, even normally to some extent, and especially in many lung diseases, some areas of the lungs are well ventilated but have almost no blood flow, whereas other areas may have excellent blood flow but little or no ventilation. In either of these conditions, gas exchange through the respiratory membrane is seriously impaired, and the person may suffer severe respiratory distress despite both normal *total* ventilation and normal *total* pulmonary blood flow, but with the ventilation and blood flow going to different parts of the lungs. Therefore, a highly quantitative concept has been developed to help us understand respiratory exchange when there is imbalance between alveolar ventilation and alveolar blood flow. This concept is called the *ventilation-perfusion ratio*.

In quantitative terms, the ventilation-perfusion ratio is expressed as $\dot{V}_A/\dot{Q}$. When $\dot{V}_A$ (alveolar ventilation) is normal for a given alveolus and $\dot{Q}$ (blood flow) is also normal for the same alveolus, the ventilation-perfusion ratio ($\dot{V}_A/\dot{Q}$) is also said to be normal. When the ventilation ($\dot{V}_A$) is zero, yet there is still perfusion ($\dot{Q}$) of the alveolus, the $\dot{V}_A/\dot{Q}$ is zero. Or, at the other extreme, when there is adequate ventilation ($\dot{V}_A$) but zero perfusion ($\dot{Q}$), the ratio $\dot{V}_A/\dot{Q}$ is infinity. At a ratio of either zero or infinity, there is no exchange of gases through the respiratory membrane of the affected alveoli, which explains the importance of this concept. Therefore, let us explain the respiratory consequences of these two extremes.

Alveolar Oxygen and Carbon Dioxide Partial Pressures When $\dot{V}_A/\dot{Q}$ Equals Zero. When $\dot{V}_A/\dot{Q}$ is equal to zero—that is, without any alveolar ventilation—the air in the alveolus comes to equilibrium with the blood oxygen and carbon dioxide because these gases diffuse between the blood and the alveolar air. Because the blood that perfuses the capillaries is venous blood returning to the lungs from the systemic circulation, it is the gases in this blood with which the alveolar gases equilibrate. In Chapter 40, we describe how the normal venous blood ($\bar{v}$) has a P_{O_2} of 40 mm Hg and a P_{CO_2} of 45 mm Hg. Therefore, these are also the normal partial pressures of these two gases in alveoli that have blood flow but no ventilation.

Alveolar Oxygen and Carbon Dioxide Partial Pressures When $\dot{V}_A/\dot{Q}$ Equals Infinity. The effect on the alveolar gas partial pressures when $\dot{V}_A/\dot{Q}$ equals infinity is entirely different from the effect when $\dot{V}_A/\dot{Q}$ equals zero because now there is no capillary blood flow to carry oxygen away or to bring carbon dioxide to the alveoli. Therefore, instead of the alveolar gases coming to equilibrium with the venous blood, the alveolar air becomes equal to the humidified inspired air.

That is, the air that is inspired loses no oxygen to the blood and gains no carbon dioxide from the blood. And because normal inspired and humidified air has a P_{O_2} of 149 mm Hg and a P_{CO_2} of 0 mm Hg, these will be the partial pressures of these two gases in the alveoli.

Gas Exchange and Alveolar Partial Pressures When $\dot{V}_A/\dot{Q}$ Is Normal. When there is both normal alveolar ventilation and normal alveolar capillary blood flow (normal alveolar perfusion), exchange of oxygen and carbon dioxide through the respiratory membrane is nearly optimal, and alveolar P_{O_2} is normally at a level of 104 mm Hg, which lies between that of the inspired air (149 mm Hg) and that of venous blood (40 mm Hg). Likewise, alveolar P_{CO_2} lies between two extremes; it is normally 40 mm Hg, in contrast to 45 mm Hg in venous blood and 0 mm Hg in inspired air. Thus, under normal conditions, the alveolar air P_{O_2} averages 104 mm Hg and the P_{CO_2} averages 40 mm Hg.

P_{O_2}-P_{CO_2}, $\dot{V}_A/\dot{Q}$ Diagram

The concepts presented in the preceding sections can be shown in graphical form, as demonstrated in Figure 39-11, called the P_{O_2}-P_{CO_2}, $\dot{V}_A/\dot{Q}$ diagram. The curve in the diagram represents all possible P_{O_2} and P_{CO_2} combinations between the limits of $\dot{V}_A/\dot{Q}$ equals zero and $\dot{V}_A/\dot{Q}$ equals infinity when the gas pressures in the venous blood are normal and the person is breathing air at sea-level pressure. Thus, point $\bar{v}$ is the plot of P_{O_2} and P_{CO_2} when $\dot{V}_A/\dot{Q}$ equals zero. At this point, the P_{O_2} is 40 mm Hg and the P_{CO_2} is 45 mm Hg, which are the values in normal venous blood.

At the other end of the curve, when $\dot{V}_A/\dot{Q}$ equals infinity, point I represents inspired air, showing P_{O_2} to be 149 mm Hg while P_{CO_2} is zero. Also plotted on the curve is the point that represents normal alveolar air when $\dot{V}_A/\dot{Q}$ is normal. At this point, P_{O_2} is 104 mm Hg and P_{CO_2} is 40 mm Hg.

Concept of "Physiologic Shunt" (When $\dot{V}_A/\dot{Q}$ Is Below Normal)

Whenever $\dot{V}_A/\dot{Q}$ is below normal, there is inadequate ventilation to provide the oxygen needed to fully oxygenate the blood flowing through the alveolar capillaries. Therefore, a certain fraction of the venous blood passing through the pulmonary capillaries does not become oxygenated. This fraction is called *shunted blood*. Also, some additional blood flows through bronchial vessels rather than through alveolar capillaries, normally about 2 percent of the cardiac output; this, too, is unoxygenated, shunted blood.

The total quantitative amount of shunted blood per minute is called the *physiologic shunt*. This physiologic shunt is measured in clinical pulmonary function laboratories by analyzing the concentration of oxygen in both mixed venous blood and arterial blood, along with simultaneous measurement of cardiac output. From these values, the physiologic shunt can be calculated by the following equation:

$$\frac{\dot{Q}_{PS}}{\dot{Q}_T} = \frac{Ci_{O_2} - Ca_{O_2}}{Ci_{O_2} - C\bar{v}_{O_2}}.$$

in which $\dot{Q}_{PS}$ is the physiologic shunt blood flow per minute, $\dot{Q}_T$ is cardiac output per minute, Ci_{O_2} is the concentration of oxygen in the arterial blood if there is an "ideal" ventilation-perfusion ratio, Ca_{O_2} is the measured concentration of oxygen in the arterial blood, and $C\bar{v}_{O_2}$ is the measured concentration of oxygen in the mixed venous blood.

The greater the physiologic shunt, the greater the *amount of blood that fails to be oxygenated* as it passes through the lungs.

Concept of the "Physiologic Dead Space" (When $\dot{V}_A/\dot{Q}$ Is Greater Than Normal)

When ventilation of some of the alveoli is great but alveolar blood flow is low, there is far more available oxygen in the alveoli than can be transported away from the alveoli by the flowing blood. Thus, the ventilation of these alveoli is said to be *wasted*. The ventilation of the anatomical dead space areas of the respiratory passageways is also wasted. The sum of these two types of wasted ventilation is called the *physiologic dead space*. This is measured in the clinical pulmonary function laboratory by making appropriate blood and expiratory gas measurements and using the following equation, called the Bohr equation:

$$\frac{\dot{V}_{D_{phys}}}{\dot{V}_T} = \frac{Pa_{CO_2} - P\bar{e}_{CO_2}}{Pa_{CO_2}},$$

in which $\dot{V}_{D_{phys}}$ is the physiologic dead space, $\dot{V}_T$ is the tidal volume, Pa_{CO_2} is the partial pressure of carbon dioxide in the arterial blood, and $P\bar{e}_{CO_2}$ is the average partial pressure of carbon dioxide in the entire expired air.

When the physiologic dead space is great, much of the *work of ventilation* is wasted effort because so much of the ventilating air never reaches the blood.

Abnormalities of Ventilation-Perfusion Ratio

Abnormal $\dot{V}_A/\dot{Q}$ in the Upper and Lower Normal Lung. In a normal person in the upright position, both pulmonary capillary blood flow and alveolar ventilation are considerably less in the upper part of the lung than in the lower part; however, blood flow is decreased considerably more than ventilation is. Therefore, at the top of the lung, $\dot{V}_A/\dot{Q}$ is as much as 2.5 times as great as the ideal value, which causes a moderate degree of *physiologic dead space* in this area of the lung.

At the other extreme, in the bottom of the lung, there is slightly too little ventilation in relation to blood flow, with $\dot{V}_A/\dot{Q}$ as low as 0.6 times the ideal value. In this area, a small fraction of the blood fails to become normally oxygenated, and this represents a *physiologic shunt*.

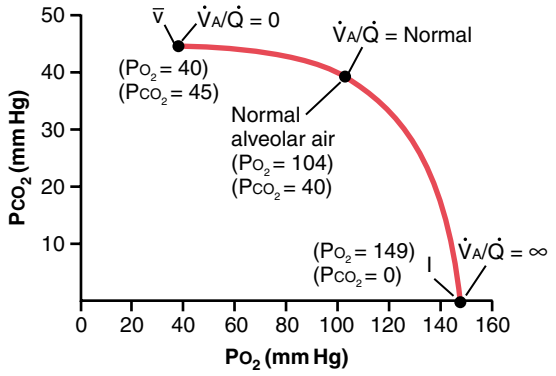

Figure 39-11 Normal P_{O_2}-P_{CO_2}, $\dot{V}_A/\dot{Q}$ diagram.

In both extremes, inequalities of ventilation and perfusion decrease slightly the lung's effectiveness for exchanging oxygen and carbon dioxide. However, during exercise, blood flow to the upper part of the lung increases markedly, so far less physiologic dead space occurs, and the effectiveness of gas exchange now approaches optimum.

Abnormal $\dot{V}_A/\dot{Q}$ in Chronic Obstructive Lung Disease. Most people who smoke for many years develop various degrees of bronchial obstruction; in a large share of these persons, this condition eventually becomes so severe that they develop serious alveolar air trapping and resultant *emphysema.* The emphysema in turn causes many of the alveolar walls to be destroyed. Thus, two abnormalities occur in smokers to cause abnormal $\dot{V}_A/\dot{Q}$. First, because many of the small bronchioles are obstructed, the alveoli beyond the obstructions are unventilated, causing a $\dot{V}_A/\dot{Q}$ that approaches zero. Second, in those areas of the lung where the alveolar walls have been mainly destroyed but there is still alveolar ventilation, most of the ventilation is wasted because of inadequate blood flow to transport the blood gases.

Thus, in chronic obstructive lung disease, some areas of the lung exhibit *serious physiologic shunt*, and other areas exhibit *serious physiologic dead space.* Both conditions tremendously decrease the effectiveness of the lungs as gas exchange organs, sometimes reducing their effectiveness to as little as one-tenth normal. In fact, this is the most prevalent cause of pulmonary disability today.

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