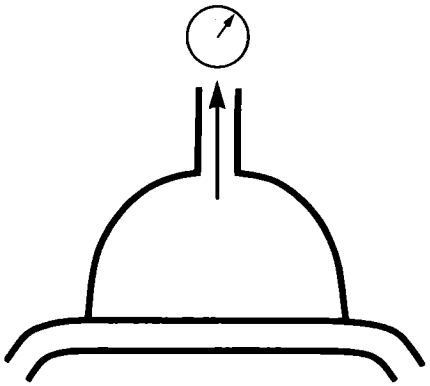


1 Ventilation

The simplest test of lung function is a forced expiration. It is also one of the most informative tests and it requires minimal equipment and trivial calculations. The majority of patients with lung disease have an abnormal forced expiration volume and, very often, the information obtained from this test is useful in their management. In spite of this, the test is not used as often as it should be. For example, it can be valuable in detecting early airway disease, an extremely common and important condition. This chapter also discusses a simple test of uneven ventilation.

■ TESTS OF VENTILATORY CAPACITY

Forced Expiratory Volume

The *forced expiratory volume* (FEV) is the volume of gas exhaled in *one second* by a forced expiration from full inspiration. The *vital capacity* is the *total* volume of gas that can be exhaled after a full inspiration.

A simple way of making these measurements is shown in Figure 1-1. The patient is comfortably seated in front of a spirometer having a low resistance. He or she breathes in maximally and then exhales as hard and as far as possible. As the spirometer bell moves up, the kymograph pen moves down, thus indicating the expired volume against time.

Figure 1-2A shows a normal tracing. The volume exhaled in 1 second was 4.0 liters and the total volume exhaled was 5.0 liters. These two volumes are therefore the forced expiratory volume in 1 second (FEV_1) and the vital capacity. The vital capacity measured with a forced expiration may be less than that measured with a slower exhalation, so that the term *forced vital capacity* (FVC) is generally used. Note that the normal ratio of FEV_1 to FVC is approximately 80% but it decreases with age. (See Appendix A for normal values.)

The FEV can be measured over other times, such as 2 or 3 seconds, but the 1-second value is most informative. When the subscript is omitted, the period is 1 second.

Figure 1-2*B* shows the type of tracing obtained from a patient with chronic obstructive pulmonary disease (COPD). Note that the rate at which the air was exhaled was much slower, so that only 1.3 liters were blown out in the first second. In addition, the total volume exhaled was only 3.1 liters. FEV_1/FVC was reduced to 42%. These figures are typical of an *obstructive* pattern.

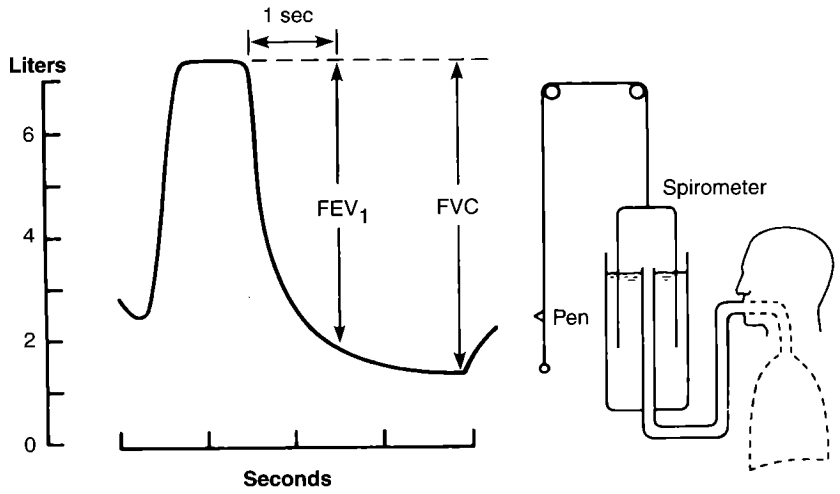


FIGURE 1-1 Measurement of Forced Expiratory Volume (FEV_1) and Vital Capacity (FVC).

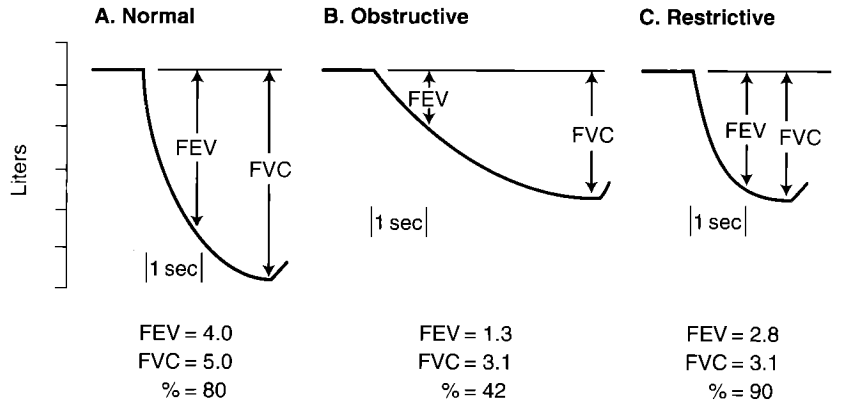


FIGURE 1-2 Normal, Obstructive, and Restrictive Patterns of a Forced Expiration.

Contrast this pattern with that of Figure 1-2C, which shows the type of tracing obtained from a patient with pulmonary fibrosis. Here the vital capacity was reduced to 3.1 liters, but a large percentage (90%) was exhaled in the first second. These figures mean *restrictive* disease.

The simple water-filled spirometer shown in Figure 1-1 is now seldom used and has been replaced by electronic spirometers, which often provide a graph to be filed with the patient's chart. Careful calibration is important and criteria have been published. (1)

The patient should loosen tight clothing, and the mouthpiece should be at a convenient height. One accepted procedure is to allow two practice blows and then record three good test breaths. The highest FEV_1 and FVC from these three breaths are then used. The volumes should be converted to body temperature and pressure (see Appendix A). Further practical details can be found elsewhere. (1)

The test is often valuable in assessing the efficacy of bronchodilator drugs. If reversible airway obstruction is suspected, the test should be carried out before and after administering the drug (for example, 0.5% albuterol by nebulizer for 3 minutes). Both the FEV_1 and FVC usually increase in a patient with bronchospasm.

FEV_1 and FVC

The one-second forced expiratory volume together with the forced vital capacity is

- a simple test.
- often informative.
- abnormal in many patients with lung disease.
- often valuable in assessing the progress of disease.

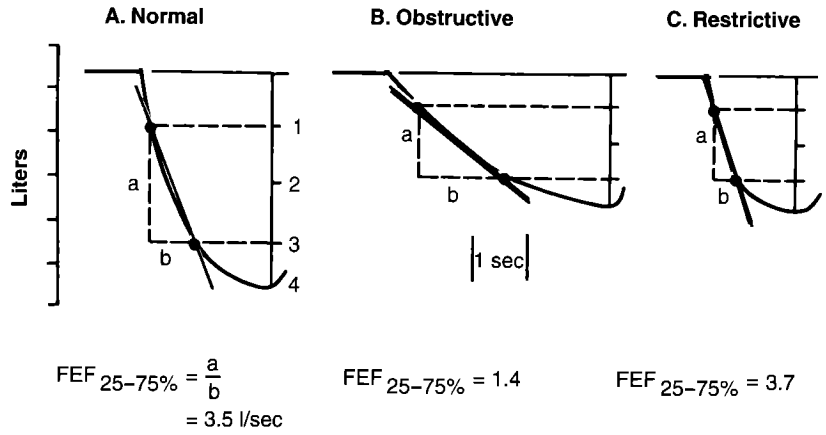


FIGURE 1-3 Calculation of Forced Expiratory Flow ($FEF_{25-75\%}$) from a Forced Expiration.

Forced Expiratory Flow

This index is calculated from a forced expiration, as shown in Figure 1-3. The middle half (by volume) of the total expiration is marked and its duration is measured. The $FEF_{25-75\%}$ is the volume in liters divided by the time in seconds. (l)

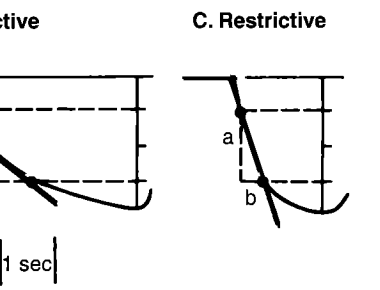
The correlation between $FEF_{25-75\%}$ and FEV_1 is generally close in patients with obstructive pulmonary disease. The changes in $FEF_{25-75\%}$ are often more striking, but the range of normal values is greater.

Interpretation of Tests of Forced Expiration

In some respects, the lungs and thorax can be regarded as a simple air pump (Fig. 1-4). The output of such a pump depends on the stroke volume, the resistance of the airways, and the force applied to the piston. The last factor is relatively unimportant in a forced expiration, as we shall presently see.

The *vital capacity* (or forced vital capacity) is a measure of the stroke volume, and any reduction of it affects the ventilatory capacity. Causes of stroke volume reduction include diseases of the thoracic cage, such as kyphoscoliosis, ankylosing spondylitis, and acute injuries; diseases affecting the nerve supply to the respiratory muscles or the muscles themselves, such as poliomyelitis and muscular dystrophy; abnormalities of the pleural cavity, such as pneumothorax and pleural thickening; disease in the lung itself, such as fibrosis, which reduces its distensibility; space-occupying lesions, such as cysts; or an increased pulmonary blood volume, as in left heart failure. In addition, there are diseases of the airways that cause them to close prematurely during expiration, thus limiting the volume that can be exhaled. This occurs in asthma and bronchitis.

The *forced expiratory volume* (and related indices such as the $FEF_{25-75\%}$) is affected by the airway resistance during forced expiration. Any increase in resistance reduces the ventilatory capacity. Causes include bronchoconstriction, as in asthma or following the inhalation of irritants such as cigarette smoke; structural changes in the airways, as in chronic bronchitis; obstructions within the airways,



= 1.4 $FEF_{25-75\%}$ = 3.7

w ($FEF_{25-75\%}$) from a Forced Expiration.

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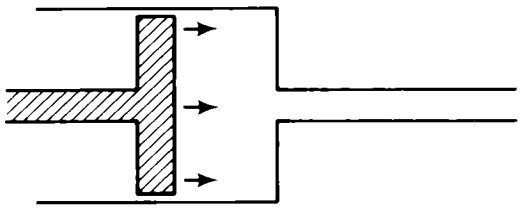


↓Stroke volume

Kyphoscoliosis
Interstitial lung disease
Poliomyelitis
Muscular dystrophy
Pleural disease

↑Airway resistance

Asthma
Bronchitis

FIGURE 1-4 Simple Model of Factors that May Reduce the Ventilatory Capacity. The stroke volume may be reduced by diseases of the chest wall, lung parenchyma, respiratory muscles, and pleura. Airway resistance is increased in asthma and bronchitis.

such as an inhaled foreign body or excess bronchial secretions; and destructive processes in the lung parenchyma, which interfere with the radial traction that normally holds the airways open.

The simple model of Figure 1-4 introduces the factors limiting the ventilatory capacity of the diseased lung, but we need to refine the model to obtain a better understanding. For example, the airways are actually *inside*, not *outside*, the pump, as shown in Figure 1-4. Useful additional information comes from the flow-volume curve.

Expiratory Flow-Volume Curve

If we record flow rate and volume during a maximal forced expiration, we obtain a pattern like that shown in Figure 1-5A. A curious feature of the flow-volume curve is that it is virtually impossible to get outside it. For example, if we begin by exhaling slowly and then exert maximum effort, the flow rate increases to the envelope but not beyond. Clearly, something very powerful is limiting the maximum flow rate at a given volume. This factor is *dynamic compression of the airways*.

Figure 1-5B shows typical patterns found in obstructive and restrictive lung disease. In obstructive diseases, such as chronic bronchitis and emphysema, the maximal expiration typically begins and ends at abnormally high lung volumes, and the flow rates are much lower than normal. In addition, the curve may have a scooped-out appearance. By contrast, patients with restrictive disease, such as interstitial fibrosis, operate at low lung volumes. Their flow envelope is flattened compared with a normal curve; but if flow rate is related to lung volume, the flow is seen to be higher than normal (Figure 1-5B). Note that the figure shows absolute lung volumes, although these cannot be obtained from a forced expiration. They require an additional measurement of residual volume.

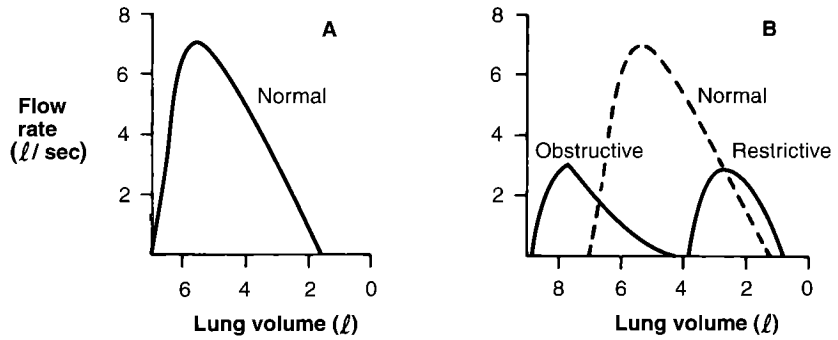


FIGURE 1-5 Expiratory Flow-Volume Curves. *(A)* Normal. *(B)* Obstructive and restrictive patterns.

To understand these patterns, consider the pressures inside and outside the airways (Fig. 1-6) (see *Respiratory Physiology: The Essentials*, 7th ed., p. 114). Before inspiration (A), the pressures in the mouth, airways, and alveoli are all atmospheric because there is no flow. Intrapleural pressure is, say, 5 cm H_2O below atmospheric pressure, and we assume that the same pressure exists outside the airways (although this is an oversimplification). Thus, the pressure difference expanding the airways is 5 cm H_2O. At the beginning of inspiration (B), all pressures fall and the pressure difference holding the airways open increases to 6 cm H_2O. At the end of inspiration (C), this pressure is 8 cm H_2O.

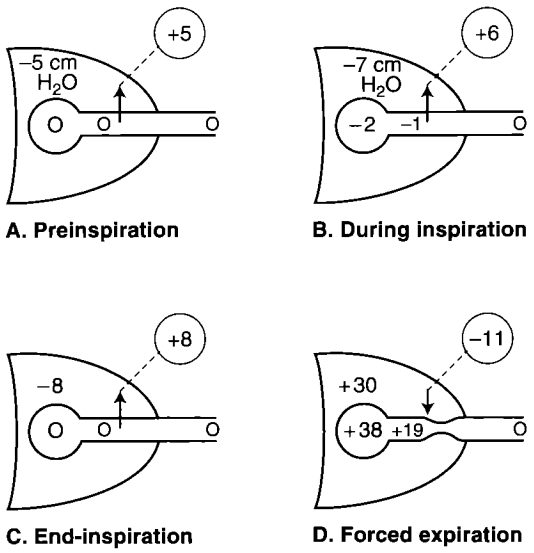
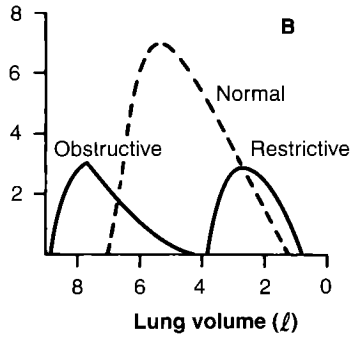


FIGURE 1-6 Diagram to Explain Dynamic Compression of the Airways During a Forced Expiration. (See text for details.)



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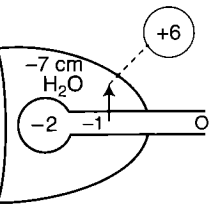
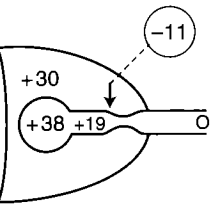


B. During inspiration



D. Forced expiration

ompression of the Airways During a

Dynamic Compression of the Airways

limits flow rate during a forced expiration.
causes flow to be independent of effort.
may limit flow during normal expiration in some patients with COPD.
is a major factor limiting exercise in COPD.

Early in a forced expiration *(D)*, both intrapleural and alveolar pressures rise greatly. The pressure at some point in the airways increases, but not as much as alveolar pressure because of the pressure drop caused by flow. Under these circumstances, we have a pressure difference of 11 cm H_2O, which tends to *close* the airways. Airway compression occurs, and now flow is determined by the difference between alveolar pressure and the pressure outside the airways at the collapse point (Starling resistor effect). Note that this pressure difference (8 cm H_2O in *D*) is the static recoil pressure of the lung and it depends only on lung volume and compliance. It is *independent* of expiratory effort.

How then can we explain the abnormal patterns in Figure 1-5*B*? In the patient with chronic bronchitis and emphysema, the low flow rate in relation to lung volume is caused by several factors. There may be thickening of the walls of the airways and excessive secretions in the lumen because of bronchitis; both increase the flow resistance. The number of small airways may be reduced because of destruction of lung tissue. Also, the patient may have a reduced static recoil pressure (even though lung volume is greatly increased) because of breakdown of elastic alveolar walls. Finally, the normal support offered to the airways by the traction of the surrounding parenchyma is probably impaired because of loss of alveolar walls, and the airways therefore collapse more easily than they should. These factors are considered in more detail in Chapter 4.

The patient with interstitial fibrosis has normal (or high) flow rates in relation to lung volume because the lung static recoil pressures are high and the caliber of the airways may be normal (or even increased) at a given lung volume. However, because of the greatly reduced compliance of the lung, volumes are very small, and absolute flow rates are therefore reduced. These changes are further discussed in Chapter 5.

This analysis shows that Figure 1-4 is a considerable oversimplification and that the forced expiratory volume, which seems so straightforward at first, is affected both by the airways and by the lung parenchyma. Thus, the terms "obstructive" and "restrictive" conceal a good deal of pathophysiology.

Partitioning of Flow Resistance from the Flow-Volume Curve

When the airways collapse during a forced expiration, the flow rate is determined by the resistance of the airways up to the point of collapse (Fig. 1-7). Beyond this point, the resistance of the airways is immaterial. Collapse occurs at (or near) the point where the pressure inside the airways is equal to the intrapleural pressure

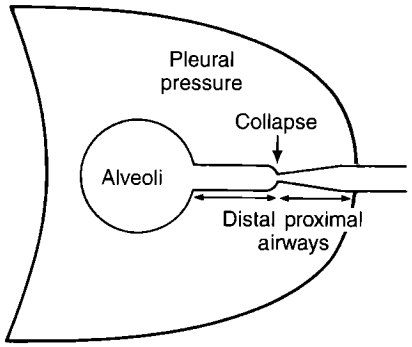


FIGURE 1-7 Dynamic Compression of the Airways. When this occurs during a forced expiration, only the resistance of the airways distal to the point of collapse (upstream segment) determines the flow rate. In the last stages of a forced vital capacity test, only the peripheral small airways are distal to the collapsed point and therefore determine the flow.

(*equal pressure point*). This is believed to be in the vicinity of the lobar bronchi early in a forced expiration. However, as lung volume reduces and the airways narrow, their resistance increases. As a result, pressure is lost more rapidly and the collapse point moves into more distal airways. Thus, late in forced expiration, flow is increasingly determined by the properties of the small distal peripheral airways.

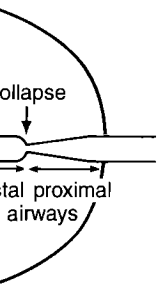
These peripheral airways (say, less than 2 mm in diameter) normally contribute less than 20% of the total airway resistance. Therefore, changes in them are difficult to detect and they constitute a "silent zone." However, it is likely that some of the earliest changes in chronic obstructive pulmonary disease occur in these small airways, and therefore maximum flow rate late in a forced expiration is often taken to reflect peripheral airway resistance.

Maximum Flows from the Flow-Volume Curve

Maximum flow ($\dot{V}max$) is frequently measured after 50% ($\dot{V}max_{50\%}$) or 75% ($\dot{V}max_{75\%}$) of the vital capacity has been exhaled. Figure 1-8 shows the abnormal flow pattern typically seen in tests of patients with chronic obstructive pulmonary disease. The later in expiration that the flow is measured, the more the measurement reflects the resistance of the very small airways. Some studies have shown abnormalities in the $\dot{V}max_{75\%}$ when other indices of a forced expiration, such as the FEV_1 or $FEF_{25-75\%}$, were normal.

Peak Expiratory Flow Rate

Peak expiratory flow rate (PEFR) is the maximum flow rate during a forced expiration starting from total lung capacity. It can be conveniently estimated with an inexpensive, portable peak flow meter. The measurement is not precise, and it depends on the patient's effort. Nevertheless, it is a valuable tool for following disease, especially asthma, and the patient can easily make repeated measurements in the home or workplace and keep a log to show to the physician.



rways. When this occurs during a forced the point of collapse (upstream segment) ced vital capacity test, only the peripheral herefore determine the flow.

in the vicinity of the lobar bronchi ng volume reduces and the airways pressure is lost more rapidly and the Thus, late in forced expiration, flow f the small distal peripheral airways. 2 mm in diameter) normally con- stance. Therefore, changes in them "silent zone." However, it is likely obstructive pulmonary disease occur um flow rate late in a forced expira- ay resistance.

Volume Curve

ured after 50% ($\dot{V}max_{50\%}$) or 75% aled. Figure 1-8 shows the abnormal ents with chronic obstructive pul- the flow is measured, the more the ry small airways. Some studies have other indices of a forced expiration,

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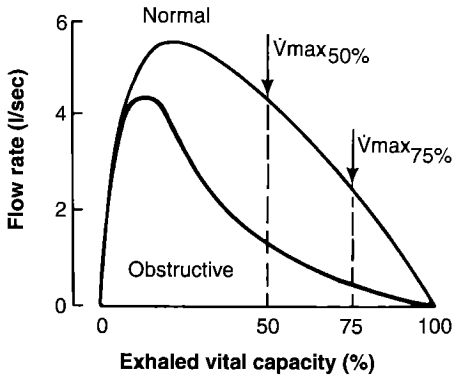

FIGURE 1-8 Example of an Expiratory Flow-Volume Curve in Chronic Obstructive Pulmonary Disease. Note the scooped-out appearance. The arrows show the maximum expiratory flow after 50% and 75% of the vital capacity have been exhaled.

Inspiratory Flow-Volume Curve

The flow-volume curve is also often measured during inspiration. This curve is not affected by the dynamic compression of the airways because the pressures during inspiration always expand the bronchi (Fig. 1-6). However, the curve is useful in detecting upper airway obstruction, which flattens the curve because maximum flow is limited (Fig. 1-9). Causes include glottic and tracheal stenosis and tracheal narrowing as a result of a compressing neoplasm. The expiratory flow-volume curve is also flattened by fixed (nonvariable) upper airway obstruction.

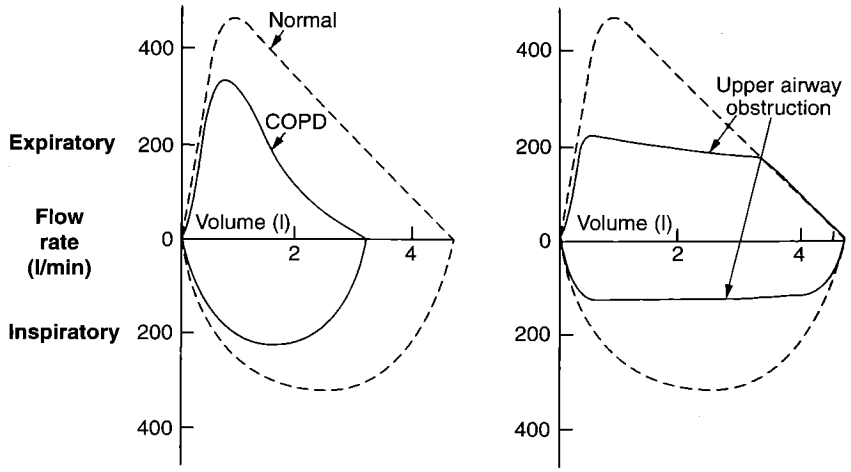

FIGURE 1-9 Expiratory and Inspiratory Flow-Volume Curves. In normal subjects and patients with chronic obstructive pulmonary disease, inspiratory flow rates are normal (or nearly so). In fixed upper airway obstruction, both inspiratory and expiratory flow rates are reduced.

■ TESTS OF UNEVEN VENTILATION

Single-Breath Nitrogen Test

The tests described so far measure ventilatory capacity. The single-breath nitrogen test measures inequality of ventilation. This topic is somewhat different but is conveniently described here.

Suppose a patient takes a vital capacity inspiration of oxygen, that is, to total lung capacity, and then exhales slowly as far as he can, that is, to residual volume. If we measure the nitrogen concentration at the mouthpiece with a rapid nitrogen analyzer, we record a pattern as shown in Figure 1-10. Four phases can be recognized. In the first, which is very short, pure oxygen is exhaled from the upper airways and the nitrogen concentration is zero. In the second phase, the nitrogen concentration rises rapidly as the anatomic dead space is washed out by alveolar gas. This phase is also short.

The third phase consists of alveolar gas, and the tracing is nearly flat with a small upward slope in normal subjects. This portion is often known as the alveolar plateau. In patients with uneven ventilation, the third phase is steeper, and the slope is a measure of the inequality of ventilation. It is expressed as the percentage increase in nitrogen concentration per liter of expired volume. In carrying out this test, the expiratory flow rate should be no more than 0.5 liters/sec in order to reduce the variability of the results.

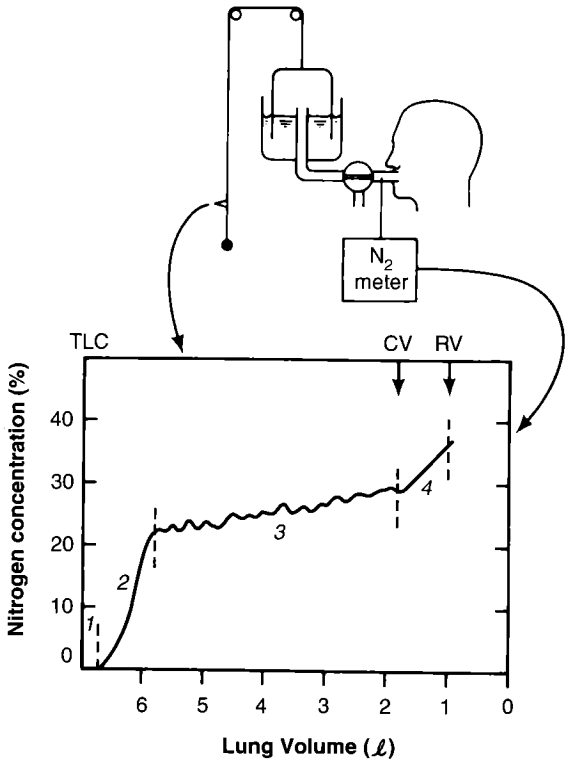

FIGURE 1-10 Single-Breath Nitrogen Test of Uneven Ventilation. Note the four phases of the expired tracing. *TLC*, total lung capacity; *CV*, closing volume; *RV*, residual volume.

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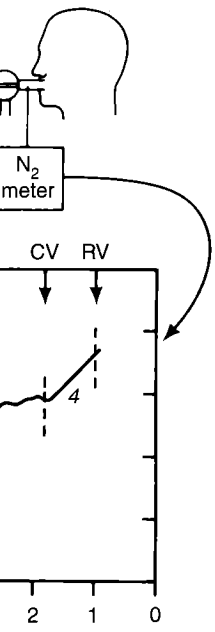

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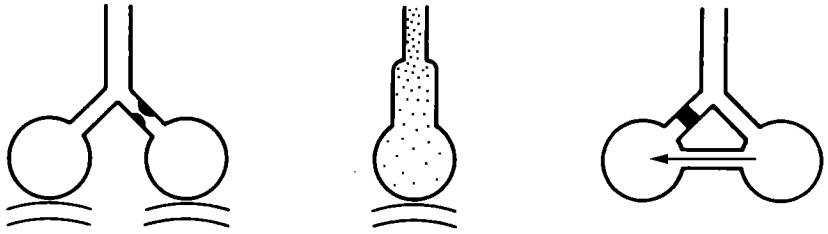

FIGURE 1-11 Three Mechanisms of Uneven Ventilation. In parallel inequality *(A)*, flow to regions with long time constants is reduced. In series inequality *(B)*, dilation of a small airway may result in incomplete diffusion along a terminal lung unit. Collateral ventilation *(C)* may also cause series inequality.

The reasons for the rise in nitrogen concentration in phase 4 are not fully understood. Apparently, some regions of lung are poorly ventilated and therefore receive relatively little of the breath of oxygen. These areas therefore have a relatively high concentration of nitrogen because there is less oxygen to dilute this gas. Also, these poorly ventilated regions tend to empty last.

Three possible mechanisms of uneven ventilation are shown in Figure 1-11. In A, the region is poorly ventilated because of partial obstruction of its airway and because of this high resistance, the region empties late. In fact, the rate of emptying of such a region is determined by its time constant, which is given by the product of its airway resistance (R) and compliance (C). The larger the time constant (RC), the longer it takes to empty. This mechanism is known as *parallel* inequality of ventilation.

Figure 1-11*B* shows the mechanism known as *series* inequality. Here there is a dilation of peripheral airspaces, which causes differences of ventilation *along* the air passages of a lung unit. In this context, we should recall that inspired gas reaches the terminal bronchioles by convective flow, that is, like water running through a hose, but its subsequent movement to the alveoli is chiefly accomplished by diffusion within the airways. Normally, the distances are so short that nearly complete equilibration of gas concentrations is established quickly. However, if the small airways enlarge, as occurs, for example, in centriacinar emphysema (see Fig. 4-4), the concentration of inspired gas in the most distal airways may remain low. Again, these poorly ventilated regions empty last.

Figure 1-11C shows another form of series inequality that occurs when some lung units receive their inspired gas from neighboring units rather than from the large airways. This is known as collateral ventilation and appears to be an important process in chronic obstructive pulmonary disease and asthma.

Uneven Ventilation

occurs in many patients with lung disease.
is an important factor contributing to impaired gas exchange.
is conveniently measured with the single-breath N_2 test.

There is still uncertainty about the relative importance of parallel and series inequality. It is likely that both operate to a small extent in people with normal ventilation and to a much greater degree in patients with obstructive pulmonary disease. Whatever the mechanism, the single-breath nitrogen test is a simple, rapid, and reliable way of measuring the degree of uneven ventilation in the lung. This is increased in most obstructive and many restrictive types of lung disease (see Chapters 4 and 5).

Closing Volume

Toward the end of the vital capacity expiration shown in Figure 1-10, the nitrogen concentration rises abruptly, signaling the onset of airway closure, or phase 4. The lung volume at which phase 4 begins is called the *closing volume*, and the closing volume plus the residual volume is known as the *closing capacity*. In practice, the onset of phase 4 is obtained by drawing a straight line through the alveolar plateau (phase 3) and noting the last point of departure of the nitrogen tracing from this line.

Unfortunately, the junction between phases 3 and 4 is seldom as clear-cut as in Figure 1-10, and there is considerable variation of this volume when the test is repeated by a patient. The test is most useful in the presence of small amounts of disease because severe disease distorts the tracing so much that the closing volume cannot be identified.

The mechanism of the onset of phase 4 is still uncertain, but many people believe that it is caused by closure of small airways in the lowest part of the lung. At residual volume just before the single breath of oxygen is inhaled, the nitrogen concentration is virtually uniform throughout the lung, but the basal alveoli are much smaller than the apical alveoli in the upright subject because of distortion of the lung by its weight. Indeed, the lowest portions are compressed so much that the small airways in the region of the respiratory bronchioles are closed. However, at the end of a vital capacity inspiration, all the alveoli are approximately the same size. Thus, the nitrogen at the base is diluted much more than that of the apex by the breath of oxygen.

During the subsequent expiration, the upper and lower zones empty together and the expired nitrogen concentration is nearly constant (Fig. 1-10). As soon as dependent airways begin to close, however, the higher nitrogen concentration in the upper zones preferentially affects the expired concentration, causing an abrupt rise. Moreover, as airway closure proceeds up the lung, the expired nitrogen progressively increases.

Recent studies show that in some subjects the closing volume is the same in the weightlessness of space as in normal gravity. (2) This finding suggests that compression of a dependent lung is not always the mechanism, and it emphasizes how uncertain we are about this topic.

The volume at which airways close is age-dependent, being as low as 10% of the vital capacity in young normal subjects but increasing to 40%, (i.e., approximately the FRC) at about the age of 65 years. There is some evidence that the test is sensitive to small amounts of disease. For example, apparently healthy cigarette smokers sometimes have increased closing volumes when their ventilatory capacity is normal.

Other Tests of Uneven Ventilation

Uneven ventilation can also be measured by a multibreath nitrogen washout during oxygen breathing. Topographic inequality of ventilation can be determined using radioactive xenon. The present chapter is confined to single-breath tests; other measurements are referred to in Chapter 3.

Tests of Early Airway Disease

There has been great interest in the possible use of some tests described in this chapter to identify patients with early airway disease. Once a patient develops the full picture of chronic obstructive pulmonary disease, the results of treatment are generally disappointing. The hope is that by identifying disease at an early stage, its progression can be slowed, for example, by the patient stopping cigarette smoking.

Among the tests that have been examined in this context are the FEV_1, $FEF_{25-75\%}$, $\dot{V}max_{50\%}$ and $\dot{V}max_{75\%}$, and the closing volume. Assessment of these tests is difficult because it depends on prospective studies and large control groups. Although work continues, it is clear that the original test of FEV_1 remains one of the most reliable and valuable tests. While more sophisticated tests should be investigated, measuring the FEV_1 and FVC remains mandatory.

KEY CONCEPTS

1. The one-second forced expiratory volume and the forced vital capacity are easy tests to do, require little equipment, and are often very informative.
2. Dynamic compression of the airways is common in COPD and is a major case of disability.
3. The small airways (less than 2 mm wide) are often the site of early airway disease, but the changes are difficult to detect.
4. Uneven ventilation is common in airway diseases and can be measured with a single-breath N_2 test.
5. The closing volume is often increased in mild airway disease and it increases with age.

QUESTIONS

For each question, choose the best answer.

1. The one-second forced expiratory volume test:
   - A. Is difficult to perform.
   - B. Can be used to assess the efficacy of bronchodilators.
   - C. Is unaffected by dynamic compression of the airways.
   - D. Is reduced in patients with fibrosis but not COPD.
   - E. Increases with age.
2. Maximum flow rate during most of a forced expiration is limited by:
   - A. Turbulence in the trachea.
   - B. Action of the diaphragm.

C. Contraction of the intercostal muscles.
D. Power of the abdominal muscles.
E. Compression of the airways.

3. The FEV_1 in a patient with COPD is reduced by:
A. Increased lung compliance.
B. Increase in the number of small airways.
C. Increased radial traction on the airways.
D. Increased elastic recoil of the lung.
E. Hypertrophy of the diaphragm.

4. The FEV_1 and FVC are measured in a patient with interstitial fibrosis of the lung. We expect:
A. Increased FEV_1.
B. Increased FVC.
C. Increased FEV_1/FVC.
D. Decreased expiratory flow rate when related to lung volume.
E. Abnormally high flow rate early in expiration.

5. The inspiratory flow-volume curve is most valuable for:
A. Detecting fixed upper airway obstruction.
B. Measuring the response to bronchodilator drugs.
C. Differentiating between chronic bronchitis and emphysema.
D. Detecting resistance in small peripheral airways.
E. Detecting fatigue of the diaphragm.

6. Concerning the single-breath nitrogen test:
A. It is usually normal in mild COPD.
B. The slope of phase 3 is increased in chronic bronchitis.
C. In phase 3, well-ventilated units empty last.
D. In normal subjects the last expired gas comes from the base of the lung.
E. The expiratory flow rate should be as fast as possible.

7. The closing volume as measured from the single-breath N_2 test:
A. Decreases with age.
B. Is highly reproducible.
C. Is affected by the small, peripheral airways.
D. Is most informative in patients with severe lung disease.
E. Is normal in mild COPD.

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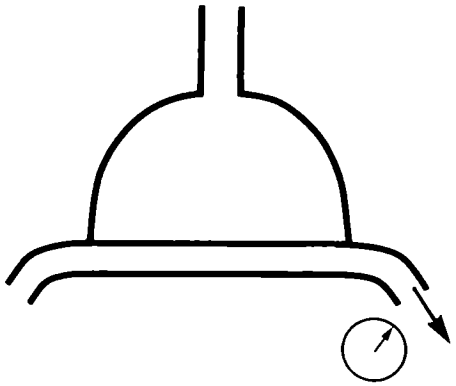

2 Gas Exchange

Chapter 1 dealt with the simplest test of lung function: the forced expiration. In addition, we looked briefly at other single-breath tests of uneven ventilation. In this chapter, we turn to the most important measurement in the management of respiratory failure: arterial blood gases. Another test of gas exchange, the diffusing capacity, is also discussed.

■ BLOOD GASES

Arterial P_{O_2}

Measurement

It is often essential to know the partial pressure of oxygen in the arterial blood of acutely ill patients. With modern blood gas electrodes, the measurement of arterial P_{O_2} is relatively simple, and the test is mandatory in the management of patients with respiratory failure.

Arterial blood is usually taken by puncture of the radial artery or from an indwelling radial artery catheter. The P_{O_2} is measured by the polarographic principle, that is, the test measures the current that flows when a small voltage is applied to electrodes. (3)

Normal Values

The normal value for P_{O_2} in young adults averages approximately 95 mm Hg, with a range of approximately 85 to 100 mm Hg. The normal value decreases steadily with age, and the average is approximately 85 mm Hg at age 60 years. The cause of the fall in P_{O_2} with age is probably increasing ventilation–perfusion inequality (see the section later in this chapter).

Whenever we read a report of an arterial P_{O_2} test, we should have the oxygen dissociation curve at the back of our minds. Figure 2-1 reminds us of two anchor points on the normal curve. One is arterial blood (P_{O_2}, 100; O_2 saturation, 97%) and the other is mixed venous blood (P_{O_2}, 40; O_2 saturation, 75%). Also we should recall that above 60 mm Hg, the curve is fairly flat and cyanosis is probably undetectable. The curve is shifted to the right by an increase in temperature,

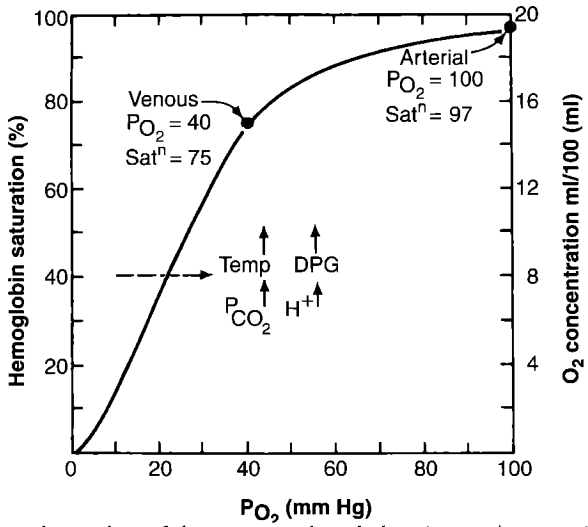

FIGURE 2-1 Anchor Points of the Oxygen Dissociation Curve. The curve is shifted to the right by an increase in temperature, P_{CO_2}, H^+, and 2,3-DPG. The oxygen concentration scale is based on a hemoglobin concentration of 14.5 g/100 ml.

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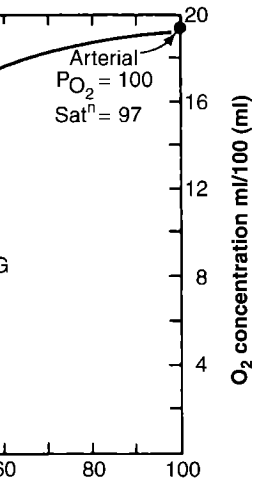

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P_{CO_2}, and H^+ concentration (these all occur in exercising muscle when enhanced unloading of O_2 is advantageous). The curve is also shifted to the right by an increase in 2,3-diphosphoglycerate (DPG) inside the red cells. 2,3-DPG is depleted in stored blood but is increased in prolonged hypoxia.

Causes of Hypoxemia

There are four primary causes of a reduced P_{O_2} in arterial blood:

1. Hypoventilation
2. Diffusion impairment
3. Shunt
4. Ventilation–perfusion inequality

A fifth cause, reduction of inspired P_{O_2}, is seen only in special circumstances such as during residence at high altitude or when breathing a gas mixture of low oxygen concentration.

Hypoventilation

This means that the volume of fresh gas going to the alveoli per unit time (alveolar ventilation) is reduced. If the resting oxygen consumption is not correspondingly reduced, hypoxemia inevitably results. Hypoventilation is commonly caused by diseases outside the lungs; indeed, very often the lungs are normal.

Two cardinal physiologic features of hypoventilation should be emphasized. First, it *always* causes a rise in P_{CO_2} and this is a valuable diagnostic feature. The relationship between the arterial P_{CO_2} and the level of alveolar ventilation in the normal lung is a simple one:

$$P_{CO_2} = \frac{\dot{V}_{CO_2}}{\dot{V}_A} \cdot K, \qquad \text{(Eq. 2.1)}$$

where $\dot{V}_{CO_2}$ is the CO_2 output, $\dot{V}_A$ is the alveolar ventilation, and K is a constant (see Appendix A for a list of symbols). This means that if the alveolar ventilation is halved, the P_{CO_2} is doubled. If the patient does not have a raised arterial P_{CO_2}, he or she is not hypoventilating!

Second, the hypoxemia can be abolished easily by increasing the inspired P_{O_2} by delivering oxygen via a face mask. This can be seen from the *alveolar gas equation*:

$$P_{A_{O_2}} = P_{I_{O_2}} - \frac{P_{A_{CO_2}}}{R} + F, \qquad \text{(Eq. 2.2)}$$

where *F* is a small correction factor that can be ignored. We will also assume that the alveolar and arterial P_{CO_2} values are the same. This equation states that if the arterial P_{CO_2} ($P_{A_{CO2}}$) and respiratory exchange ratio (*R*) remain constant (they will if the alveolar ventilation and metabolic rate remain unaltered), every mm Hg rise in inspired P_{O_2} ($P_{I_{O_2}}$) produces a corresponding rise in alveolar P_{O_2} ($P_{A_{O_2}}$). Because it is easily possible to increase the inspired P_{O_2} by several hundred mm Hg, the hypoxemia of pure hypoventilation can readily be abolished.

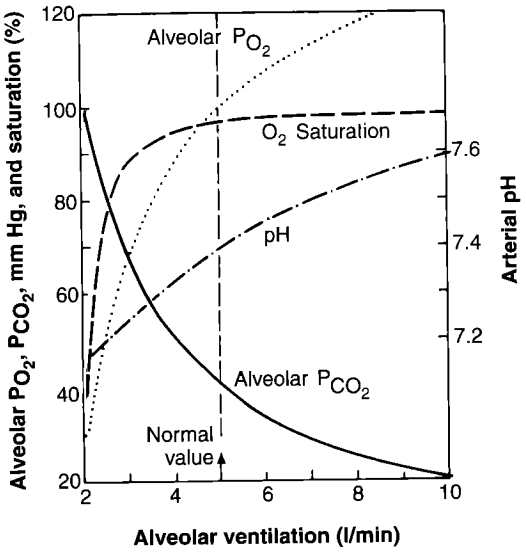


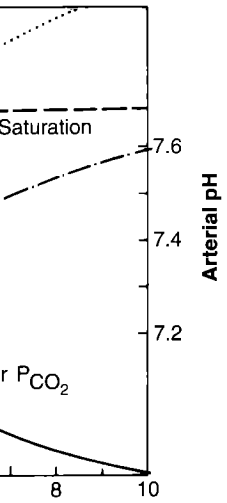
FIGURE 2-2 Gas Exchange During Hypoventilation. Values are approximate.

It is also important to appreciate that the arterial P_{O_2} cannot fall to very low levels from pure hypoventilation. Referring to Equation 2.2 again, we can see that if $R = 1$, the alveolar P_{O_2} falls 1 mm Hg for every 1 mm Hg rise in P_{CO_2}. This means that severe hypoventilation sufficient to double the P_{CO_2} from 40 to 80 mm Hg only decreases the alveolar P_{O_2} from, say, 100 to 60 mm Hg. If $R = 0.8$, the fall is somewhat greater, say, to 50 mm Hg. Also, the arterial P_{O_2} is usually a few mm Hg lower than the alveolar value. Even so, the arterial O_2 saturation will be near 80% and cyanosis will probably be just detectable (Figure 2-2). However, this is a severe degree of CO_2 retention that may result in substantial respiratory acidosis, a pH of around 7.2, and a very sick patient! Thus, hypoxemia is not the dominant feature of hypoventilation.

The causes of hypoventilation are shown in Figure 2-3 and listed Table 2-1. In addition, hypoventilation is seen in some extremely obese patients who have somnolence, polycythemia, and excessive appetite. This has been dubbed the "pickwickian syndrome" after the fat boy, Joe, in Charles Dickens's *Pickwick Papers*. The cause of the hypoventilation is uncertain, but the increased work of breathing associated with obesity is probably a factor, although some patients appear to have an abnormality of the central nervous system. There is also a rare condition of idiopathic hypoventilation, that is, of unknown cause.

Sleep apnea. This can be divided into *central*, in which there are no respiratory efforts, and *obstructive*, in which, despite activity of the respiratory muscles, there is no airflow.

Central sleep apnea often occurs in patients with hypoventilation because respiratory drive is depressed during sleep. During REM sleep, breathing is often irregular and unresponsive to chemical and vagal drives. An exception is hypoxemia, which usually remains a powerful stimulus to breathe.



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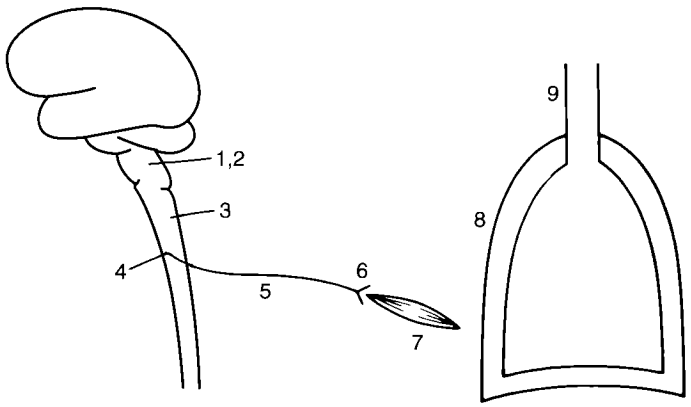

FIGURE 2-3 Causes of Hypoventilation. (See Table 2.1 for details.)

Obstructive sleep apnea is common. The first reports were in obese patients, but it is now recognized that the condition is not confined to them. Airway obstruction can be caused by backward movement of the tongue, collapse of the pharyngeal walls, greatly enlarged tonsils or adenoids, and other anatomic causes of pharyngeal narrowing. Loud snoring often occurs, and the patient may wake violently after an apneic episode. Chronic sleep deprivation sometimes occurs, and the patient may have daytime somnolence, impaired cognitive function, chronic fatigue, morning headaches, and personality disturbances such as paranoia, hostility, and agitated depression. Treatment by continuous positive airway pressure (CPAP) by means of a face mask during sleep is often effective. This reduces the daytime somnolence and can have other benefits such as reducing systemic hypertension, probably as a result of lowering the blood catecholamine levels, which are elevated by the apneic episodes.

A condition that affects infants is the *sudden infant death syndrome* (SIDS). Here the child is found dead typically in the crib with no apparent cause. The cause of this syndrome is still obscure. One hypothesis is that the nervous control of ventilation is not fully developed and the respiratory muscles are poorly coordinated.

TABLE 2-1 Some Causes of Hypoventilation (see Fig. 2-3)

1. Depression of the respiratory center by drugs (e.g., barbiturates and morphine derivatives)
2. Diseases of the medulla (e.g., encephalitis, hemorrhage, neoplasms [rare])
3. Abnormalities of the spinal cord (e.g., following high dislocation)
4. Anterior horn cell disease (e.g., poliomyelitis)
5. Diseases of the nerves to the respiratory muscles (e.g., in the Guillain-Barré syndrome or diphtheria)
6. Diseases of the myoneural junction (e.g., myasthenia gravis, anticholinesterase poisoning)
7. Diseases of the respiratory muscles (e.g., progressive muscular dystrophy)
8. Thoracic cage abnormalities (e.g., crushed chest)
9. Upper airway obstruction (e.g., tracheal compression by the thymoma)

Diffusion Impairment

This means that equilibration does not occur between the P_{O_2} in the pulmonary capillary blood and alveolar gas. Figure 2-4 reminds us of the time course for P_{O_2} along a pulmonary capillary. Under normal resting conditions, the capillary blood P_{O_2} almost reaches that of alveolar gas after about 1/3 of the total contact time of 3/4 second available in the capillary. Thus, there is plenty of time in reserve. Even with severe exercise, when the contact time may be reduced to as little as 1/4 second, equilibration almost always occurs.

However, in some diseases, the blood-gas barrier is thickened and diffusion is so slowed that equilibration may be incomplete. Figure 2-5 shows a histologic section of lung from a patient with interstitial fibrosis. (4) Note that the normally delicate alveolar walls are grossly widened. In such a lung, we expect a slower time course, as shown in Figure 2-4. Any hypoxemia that occurred at rest would be exaggerated on exercise because of the reduced contact time between blood and gas.

Diseases in which diffusion impairment may contribute to the hypoxemia, especially on exercise, include asbestosis, sarcoidosis, diffuse interstitial fibrosis including idiopathic pulmonary fibrosis (cryptogenic fibrosing alveolitis) and interstitial pneumonia, connective tissue diseases affecting the lung including scleroderma, rheumatoid lung, lupus erythematosus, Wegener's granulomatosis, Goodpasture's syndrome, and alveolar cell carcinoma. In all these conditions, the diffusion path from alveolar gas to red blood cell may be increased, at least in some regions of the lung, and the time course for oxygenation may be affected, as shown in Figure 2-4.

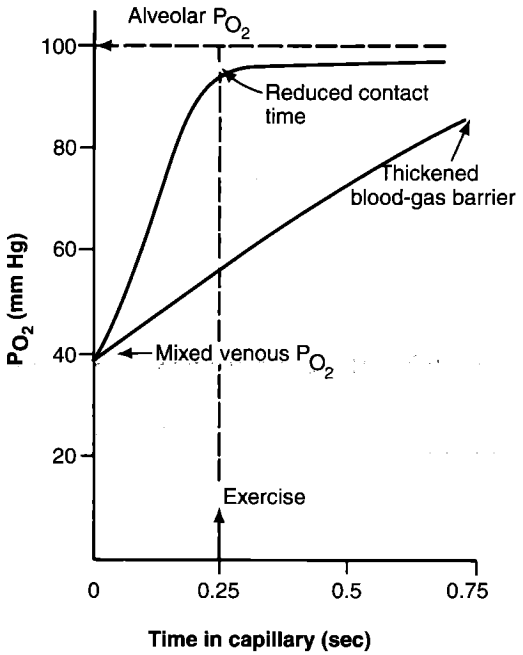

FIGURE 2-4 Changes in P_{O_2} Along the Pulmonary Capillary. During exercise, the time available for O_2 diffusion across the blood-gas barrier is reduced. A thickened alveolar wall slows the rate of diffusion.

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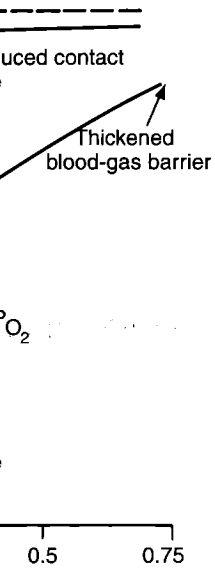

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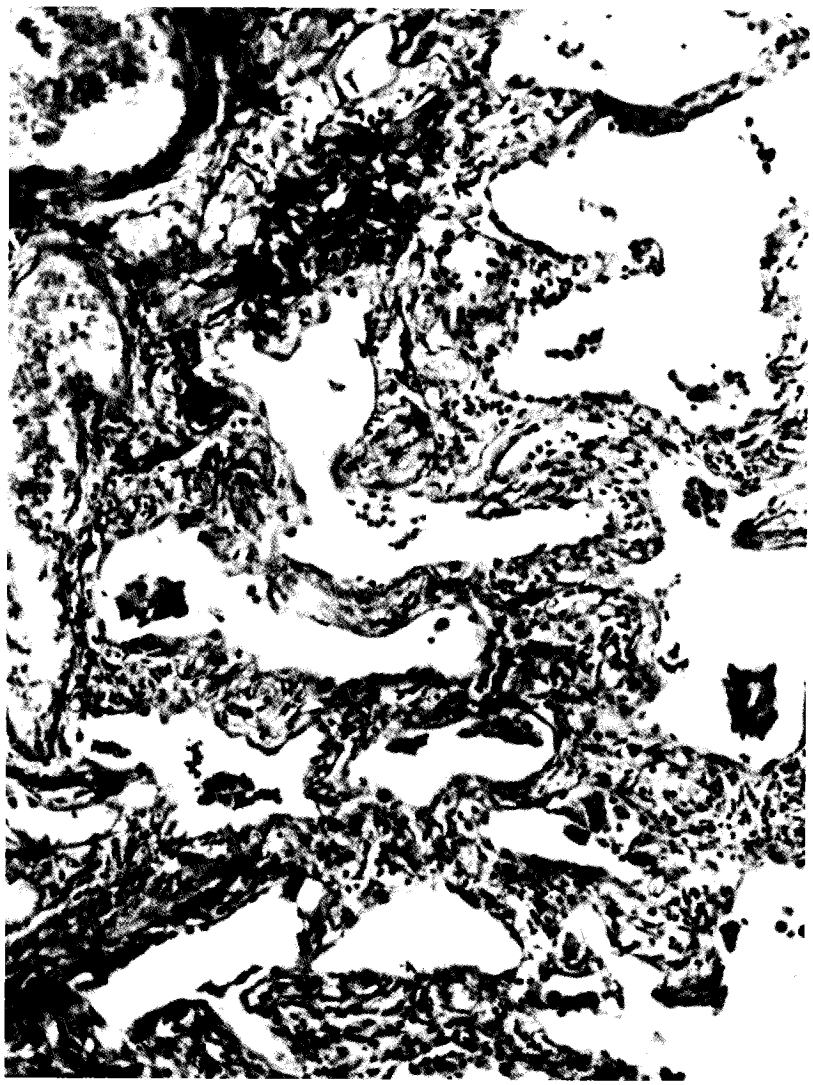

FIGURE 2-5 Section of Lung from a Patient with Diffuse Interstitial Fibrosis. Note the extreme thickening of the alveolar walls, which constitutes a barrier to diffusion (compare with Figures 5-1, 5-3, and 10-5). (From Hinson KFW. Diffuse pulmonary fibrosis. *Hum Pathol* 1970;1:275–288.)

However, the importance of diffusion impairment to the arterial hypoxemia of these patients is uncertain. As has been emphasized, the normal lung has lots of diffusion time in reserve. In addition, if we look at Figure 2-5, it is impossible to believe that the normal relationships between ventilation and blood flow can be preserved in a lung with such an abnormal architecture. We will see shortly that ventilation–perfusion inequality is a powerful cause of hypoxemia, which is undoubtedly operating in these patients. Thus, how much additional hypoxemia

should be attributed to diffusion impairment is difficult to know. It is clear that at least some of the hypoxemia on exercise is caused by this mechanism (Figure 5-6).

Hypoxemia could also result from an extreme reduction in contact time. Suppose that so much blood flow is diverted away from other regions of the lung (for example, by a large pulmonary embolus) that the time for oxygenation within the capillary is reduced to one-tenth normal. Figure 2-4 shows that hypoxemia would then be inevitable.

Hypoxemia caused by diffusion impairment can be corrected readily by administering 100% oxygen to the patient. The resultant large increase in alveolar P_{O_2} of several hundred mm Hg can easily overcome the increased diffusion resistance of the thickened blood-gas barrier. Carbon dioxide elimination is generally thought to be unaffected by diffusion abnormalities, although recent work has raised questions about this subject. Certainly, most patients with the diseases listed above do not have carbon dioxide retention. Indeed, typically the arterial P_{CO_2} is slightly lower than normal because ventilation is overstimulated, either by the hypoxemia or by intrapulmonary stretch receptors.

Shunt

A shunt allows some blood to reach the arterial system without passing through ventilated regions of the lung. Intrapulmonary shunts can be caused by arterial-venous malformations, which often have a genetic basis. In addition, an unventilated but perfused area of lung, for example, a consolidated pneumonic lobule, constitutes a shunt. It might be argued that the latter example is simply one extreme of the spectrum of ventilation–perfusion ratios and that it is therefore more reasonable to classify hypoxemia caused by this under the heading of ventilation–perfusion inequality. However, shunt causes such a characteristic pattern of gas exchange during 100% oxygen breathing that it is convenient to include unventilated alveoli under this heading. Very large shunts are often seen in adult respiratory distress syndrome (see Chapter 8). Many shunts are extrapulmonary, including those that occur in congenital heart disease through atrial or ventricular septal defects or a patent ductus arteriosus. In such patients, there must be a rise in right heart pressure; otherwise, the shunt is from left to right.

If a patient with a shunt is given pure oxygen to breathe, the arterial P_{O_2} fails to rise to the level seen in normal subjects. Figure 2-6 shows that although the end-capillary P_{O_2} may be as high as that in alveolar gas, the O_2 concentration of the shunted blood is as low as in venous blood. When a small amount of shunted blood is added to arterial blood, the O_2 concentration is depressed. This causes a large fall in arterial P_{O_2} because the O_2 dissociation curve is so flat in its upper range. As a result, it is possible to detect small shunts by measuring the arterial P_{O_2} during 100% O_2 breathing.

Only shunts behave in this way, a point of practical importance. In the other three causes of hypoxemia (hypoventilation, diffusion impairment, and ventilation–perfusion inequality) the arterial P_{O_2} nearly reaches the normal level seen in healthy subjects during 100% O_2 breathing. This may take a long time in some patients who have poorly ventilated alveoli because the nitrogen takes so long to wash out completely that the P_{O_2} is slow to reach its final level. This is probably

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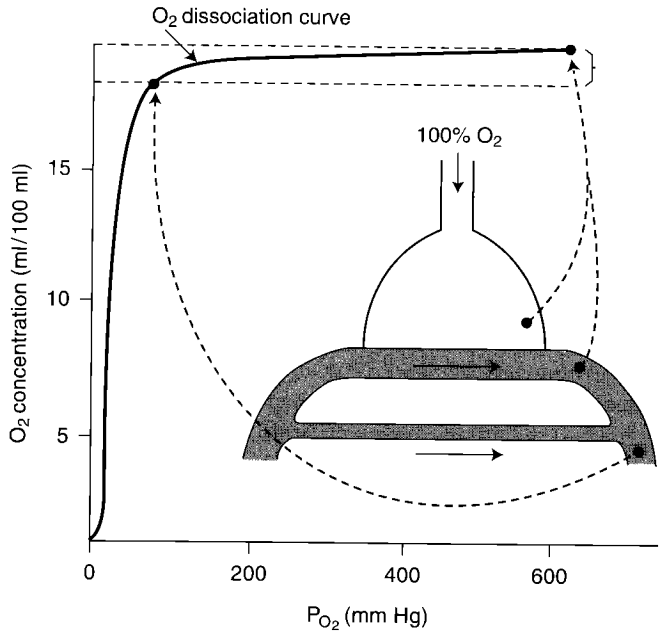

FIGURE 2-6 Depression of the Arterial P_{O_2} by a Shunt During 100% O_2 Breathing. The addition of a small amount of shunted blood with its low O_2 concentration greatly reduces the P_{O_2} of arterial blood. This is because the O_2 dissociation curve is so flat when the P_{O_2} is high.

the reason why the arterial P_{O_2} of patients with chronic obstructive pulmonary disease may only rise to 400–500 mm Hg after 15 minutes of 100% O_2 breathing.

The magnitude of the shunt during O_2 breathing can be determined from the *shunt equation:*

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{C_{c'} - C_a}{C_{c'} - C_{\bar{v}}} \qquad \text{(Eq. 2.3)}$$

where $\dot{Q}_S$ and $\dot{Q}_T$ refer to the shunt and total blood flows, and $C_{c'}$, C_a, and $C_{\bar{v}}$ refer to the O_2 concentrations of end-capillary, arterial, and mixed venous blood. The O_2 concentration of end-capillary blood is calculated from the alveolar P_{O_2}, assuming complete equilibration between the alveolar gas and the blood. Mixed venous blood is sampled with a catheter in the pulmonary artery. Alternatively, the denominator in Equation 2.3 can be calculated from the measured oxygen uptake and cardiac output.

Shunt does not usually result in a raised arterial P_{CO_2}. The tendency for this to rise is generally countered by the chemoreceptors which increase ventilation if the P_{CO_2} increases. Indeed, often the arterial P_{CO_2} is lower than normal because of the additional hypoxemic stimulus to ventilation.

Ventilation–Perfusion Inequality

In this condition, ventilation and blood flow are mismatched in various regions of the lung, with the result that all gas transfer becomes inefficient. This mechanism

Mixed Causes of Hypoxemia

These frequently occur. For example, a patient who is being mechanically ventilated because of acute respiratory failure after an automobile accident may have a large shunt through the unventilated lung in addition to severe ventilation–perfusion inequality (Figure 8-3). Again, a patient with interstitial lung disease may have some diffusion impairment, but this is certainly accompanied by ventilation–perfusion inequality and possibly by shunt as well (see Figures 5-5 and 5-6). In our present state of knowledge, it is often impossible to define accurately the mechanism of hypoxemia, especially in the acutely ill patient.

Oxygen Delivery to Tissues

Although the P_{O_2} of arterial blood is of great importance, other factors enter into the delivery of oxygen to the tissues. For example, a reduced arterial P_{O_2} is clearly more detrimental in a patient with a hemoglobin of 5 g/100 ml than it is in a patient with a normal O_2 capacity. The delivery of oxygen to the tissues depends on the oxygen capacity of the blood, the cardiac output, and the distribution of blood flow to the periphery. These factors are discussed further in Chapter 9.

Arterial P_{CO_2}

Measurement

A P_{CO_2} electrode is essentially a glass pH electrode. This is surrounded by a bicarbonate buffer, which is separated from the blood by a thin membrane through which CO_2 diffuses. The CO_2 alters the pH of the buffer, and this is measured by the electrode, which reads out the P_{CO_2} directly.

Normal Values

The normal arterial P_{CO_2} is 37–43 mm Hg and is almost unaffected by age. It tends to fall slightly during heavy exercise and to rise slightly during sleep. Sometimes a blood sample obtained by arterial puncture shows a value in the mid 30s. This can be attributed to the acute hyperventilation caused by the procedure and can be recognized by the correspondingly increased pH.

Causes of Increased Arterial P_{CO_2}

There are two major causes of CO_2 retention: hypoventilation and ventilation–perfusion inequality.

Hypoventilation

This was dealt with in some detail earlier in the chapter, where we saw that hypoventilation must cause hypoxemia and CO_2 retention, the latter being more important (Figure 2-3). The *alveolar ventilation equation*

$$P_{A_{CO_2}} = \frac{\dot{V}_{CO_2}}{\dot{V}_A} \cdot K \qquad \text{(Eq. 2.5)}$$

emphasizes the inverse relationship between the ventilation and the alveolar P_{CO_2}. In normal lungs, the arterial P_{CO_2} closely follows the alveolar value. Whereas the hypoxemia of hypoventilation can be relieved easily by increasing the inspired P_{O_2}, the CO_2 retention can only be treated by increasing the ventilation. This may require mechanical assistance, as described in Chapter 10.

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Ventilation–Perfusion Inequality

Although this condition was considered earlier, its relationship to CO_2 retention warrants further brief discussion because of confusion in this area. At one time, it was argued that ventilation–perfusion inequality does not interfere with CO_2 elimination because the overventilated regions make up for the underventilated areas. This is a fallacy, and it is important to realize that ventilation–perfusion inequality reduces the efficiency of transfer of all gases, including, for example, the anesthetic gases.

Why then do we frequently see patients with chronic pulmonary disease and undoubted ventilation–perfusion inequality who have a normal arterial P_{CO_2}? Figure 2-9 shows the usual sequence. The normal relationships between ventilation and blood flow (*A*) are disturbed by disease, and hypoxemia and CO_2 retention develop (*B*). However, the chemoreceptors respond to the increased arterial P_{CO_2} and raise the ventilation to the alveoli. The result is that the arterial P_{CO_2} is returned to its normal level (*C*). However, although the arterial P_{O_2} is somewhat raised by the increased ventilation, it does not return all the way to normal. This can be explained by the shape of the O_2 dissociation curve and, in particular, the strongly depressive action on the arterial P_{O_2} of lung units with low ventilation–perfusion ratios. Whereas units with high ventilation–perfusion ratios are effective at eliminating CO_2, they have little advantage over normal units in taking up O_2. The end result is that the arterial P_{CO_2} is effectively lowered to the normal value, but there is relatively little rise in arterial P_{O_2}.

Some patients do not make the transition from stage *B* to stage C or, having made it, revert to stage *B* and develop CO_2 retention. What is the reason for this? Generally, these patients have a high work of breathing, often because of a gross increase in airway resistance. Apparently they elect to raise their P_{CO_2} rather than to expend the extra energy to increase ventilation. It is of interest that if normal subjects are made to breathe through a narrow tube, thus increasing their work of breathing, their alveolar P_{CO_2} often rises.

We do not fully understand why some patients with ventilation–perfusion inequality increase their ventilation and some do not. As we will see in Chapter 5,

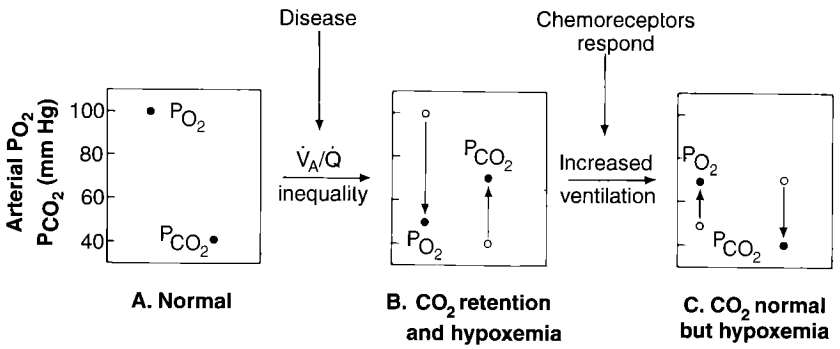

FIGURE 2-9 Arterial P_{O_2} and P_{CO_2} in Different Stages of Ventilation–Perfusion Inequality. Initially there must be both a fall in P_{O_2} and a rise in P_{CO_2}. However, when the ventilation to the alveoli is increased, the P_{CO_2} returns to normal but the P_{O_2} remains abnormally low.

many patients with emphysema hold their P_{CO_2} at the normal level even when their disease is far advanced. Patients with asthma generally do the same. This can involve a large increase in ventilation to their alveoli. However, other patients, for example, those with severe chronic bronchitis, typically allow their P_{CO_2} to rise much earlier in the course of the disease. It is possible that there is some difference in the central neurogenic control of ventilation in these two groups of patients.

Arterial pH

Measurement

Arterial pH usually is measured with a glass electrode concurrently with the arterial P_{O_2} and P_{CO_2}. It is related to the P_{CO_2} and bicarbonate concentration through the Henderson-Hasselbalch equation:

$$pH = pK + \log \frac{(HCO_3^-)}{0.03\, P_{CO_2}} \qquad \text{(Eq. 2.6)}$$

where pK = 6.1 and (HCO_3^-) is the plasma bicarbonate concentration in millimoles per liter.

Acidosis

Acidosis is a decrease in arterial pH or a process that tends to do this. Sometimes the term "acidemia" is used to refer to the actual fall in pH in the blood. Acidosis can be caused by respiratory or metabolic abnormalities or (frequently) by both.

Respiratory Acidosis

This is caused by CO_2 retention, which increases the denominator in the Henderson-Hasselbalch equation and so depresses the pH. Both mechanisms of CO_2 retention (hypoventilation and ventilation–perfusion ratio inequality) can cause respiratory acidosis.

It is important to distinguish between acute and chronic CO_2 retention. A patient with hypoventilation after an overdose of barbiturate is likely to develop acute respiratory acidosis. There is little change in bicarbonate concentration (the numerator in the Henderson-Hasselbalch equation), and the pH therefore falls rapidly as the P_{CO_2} rises. Typically, a doubling of the P_{CO_2} from 40 to 80 mm Hg in such a patient reduces the pH from 7.4 to approximately 7.2.

By contrast, a patient who develops chronic CO_2 retention over a period of many weeks as a result of increasing ventilation–perfusion inequality caused by chronic pulmonary disease typically has a smaller fall in pH. This is because the kidneys retain bicarbonate in response to the increased P_{CO_2} in the renal tubular cells, thus increasing the numerator in the Henderson-Hasselbalch equation (partially compensated respiratory acidosis).

These relationships are shown diagrammatically in Figure 2-10. (7) Contrast the steep slope of the line for acute CO_2 retention (*A*) with the shallow slope of the line for chronic hypercapnia (*B*). Note also that a patient with acute hypoventilation whose P_{CO_2} is maintained over 2 or 3 days moves toward the chronic line as his kidney conserves bicarbonate (point A to point C).

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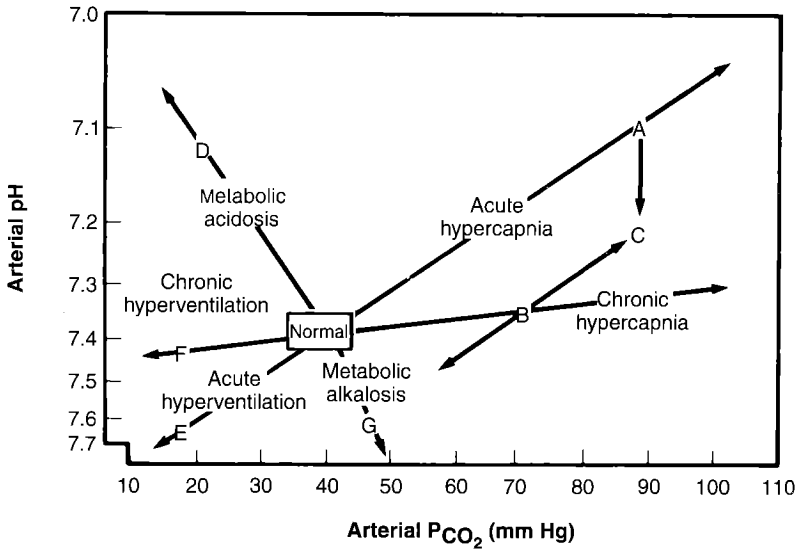

FIGURE 2-10 Arterial pH–P_{CO_2} Relationships in Various Types of Acid-Base Disturbances. (Modified from Flenley DC. Another non-logarithmic acid-base diagram? *Lancet* 1971;1: 961–965.)

Conversely, a patient with chronic obstructive pulmonary disease with long-standing CO_2 retention who develops an acute chest infection with worsening of his ventilation–perfusion relationships may move rapidly from point *B* to point C, that is, parallel to line *A*. However, if he is then mechanically ventilated, he may move back to point *B*, or even beyond.

Metabolic Acidosis

This is caused by a primary fall in the numerator (HCO_3^-) of the Henderson-Hasselbalch equation, an example being diabetic ketoacidosis. Uncompensated metabolic acidosis would be indicated by a vertical upward movement on Figure 2-10, but in practice the fall in arterial pH stimulates the peripheral chemoreceptors, increasing the ventilation and lowering the P_{CO_2}. As a result, the pH and P_{CO_2} move along line *D*.

Lactic acidosis is another form of metabolic acidosis, and this may complicate severe acute respiratory or cardiac failure as a consequence of tissue hypoxia. If such a patient is mechanically ventilated, the pH remains below 7.4 when the P_{CO_2} is returned to normal.

Alkalosis

Alkalosis (or alkalemia) results from an increase in arterial pH.

Respiratory Alkalosis

This is seen in acute hyperventilation where the pH rises, as shown by line *E* in Figure 2-10. If the hyperventilation is maintained, for example, at high altitude, compensated respiratory alkalosis is seen, with a return of the pH toward normal as the kidney excretes bicarbonate, a movement from point *E* to point *F* in Figure 2-10.

Metabolic Alkalosis

This is seen in disorders such as severe prolonged vomiting when the plasma bicarbonate concentration rises, as shown by G in Figure 2-10. Often, there is no respiratory compensation but sometimes the P_{CO_2} rises slightly. Metabolic alkalosis also occurs when a patient with long-standing lung disease and compensated respiratory acidosis is ventilated too vigorously, thus bringing the P_{CO_2} rapidly to nearly 40 mm Hg (line *B* to G).

■ DIFFUSING CAPACITY

So far, this chapter on gas exchange has been devoted to arterial blood gases and their significance. However, this is a convenient place to discuss another common test of gas exchange—the diffusing capacity of the lung for carbon monoxide.

Measurement of Diffusing Capacity

The most popular method of measuring the diffusing capacity (D_{CO}) is the single-breath method (Figure 2-11). The patient takes a vital capacity breath of 0.3% CO and 10% helium, holds his or her breath for 10 seconds, and then exhales. The first 750 ml of gas are discarded because of dead space contamination, and the next liter is collected and analyzed. The helium indicates the dilution of the inspired gas with alveolar gas and thus gives the initial alveolar P_{CO}. On the assumption that the CO is lost from alveolar gas in proportion to the P_{CO} during breathholding, the diffusing capacity is calculated as the volume of CO taken up per minute per mm Hg alveolar P_{CO}.

Causes of Reduced Diffusing Capacity

Carbon monoxide is used to measure diffusing capacity because when it is inhaled in low concentrations, the partial pressure in the pulmonary capillary blood remains extremely low in relation to the alveolar value. As a result, CO is taken up by the blood all along the capillary (contrast the time course of O_2 shown in Figure 2-4). Thus, the uptake of CO is determined by the *diffusion properties* of the blood-gas barrier and the *rate of combination* of CO with blood.

Four Types of Acid-Base Disturbance

$$pH = pK + \log \frac{(HCO_3^-)}{0.03\,P_{CO_2}}$$

	Primary	*Compensation*
Acidosis		
Respiratory	P_{CO_2} ↑	HCO_3^- ↑
Metabolic	HCO_3^- ↓	P_{CO_2} ↓
Alkalosis		
Respiratory	P_{CO_2} ↓	HCO_3^- ↓
Metabolic	HCO_3^- ↑	Often none

longed vomiting when the plasma
G in Figure 2-10. Often, there is no
P_{CO_2} rises slightly. Metabolic alkalo-
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HCO_3^-)
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	Compensation
	HCO_3^- ↑ P_{CO_2} ↓
	HCO_3^- ↓ Often none

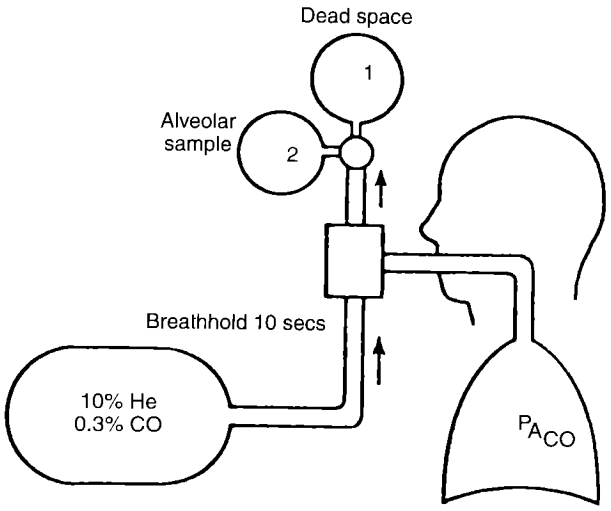

FIGURE 2-11 Measurement of the Diffusing Capacity for Carbon Monoxide by the Single-Breath Method. The subject takes a single breath of 0.3% CO with 10% helium, holds his or her breath for 10 seconds, and then exhales. The first 750 ml is discarded, then an alveolar sample is collected and analyzed.

The *diffusion properties* of the alveolar membrane depend on its thickness and area. Thus, the diffusing capacity is reduced by diseases in which the thickness is increased, including diffuse interstitial fibrosis, sarcoidosis, and asbestosis (Figure 2-5). It is also reduced when the surface area of the blood-gas barrier is reduced, for example, by pneumonectomy. The fall in diffusing capacity that occurs in emphysema is partly caused by the loss of alveolar walls and capillaries (however, see below).

The *rate of combination* of CO with blood is reduced when the number of red cells in the capillaries is reduced. This occurs in anemia and in diseases that reduce the capillary blood volume, such as pulmonary embolism. It is possible to separate the membrane and blood component of the diffusing capacity by making the measurement at a high and normal alveolar P_{O_2} (see *Respiratory Physiology: The Essentials*, 7th ed., pp. 31–33).

Interpretation of Diffusing Capacity

In many patients in whom the measured diffusing capacity is low, the interpretation is uncertain. The reason is the unevenness of ventilation, blood flow, and diffusion properties throughout the diseased lung. We know that such lungs tend to empty unevenly (Figure 1-11), so that the liter of expired gas that is analyzed for CO (Figure 2-11) is probably not representative of the whole lung.

For this reason, the diffusing capacity is sometimes referred to as the *transfer factor* (especially in Europe) to emphasize that it is more a measure of the lung's overall ability to transfer gas into the blood than a specific test of diffusion

Causes of Reduced Diffusing Capacity for Carbon Monoxide

Blood-gas barrier

Thickened in interstitial lung disease
Area is reduced in emphysema, pneumonectomy

Capillary blood

Volume reduced in pulmonary embolism
Concentration of red cells reduced in anemia

characteristics. In spite of this uncertainty of interpretation, the test has a definite place in the pulmonary function laboratory and is frequently useful in assessing the severity and type of lung disease.

KEY CONCEPTS

1. The measurement of arterial blood gases (P_{O_2}, P_{CO_2}, pH) is relatively simple with modern equipment and essential in the treatment of patients with respiratory failure.
2. The four causes of hypoxemia are hypoventilation, diffusion impairment, shunt, and ventilation–perfusion inequality. The last is by far the commonest cause.
3. Ventilation–perfusion inequality interferes with the exchange of all gases by the lung including O_2 and CO_2. All patients with this condition have a reduced arterial P_{O_2} but the P_{CO_2} may be normal if the amount of inspired gas to the alveoli is increased.
4. Acid-base abnormalities include respiratory or metabolic acidosis and respiratory or metabolic alkalosis. These cause characteristic changes in pH, P_{CO_2}, and plasma bicarbonate.
5. The diffusing capacity for carbon monoxide is a useful test of gas transfer by the lung.

QUESTIONS

1. In peripheral capillaries, more oxygen can be unloaded from the blood to the tissues at a given P_{O_2} when:
   - **A.** Blood temperature is reduced.
   - **B.** P_{CO_2} is reduced.
   - **C.** Blood pH is raised.
   - **D.** Concentration of 2,3-DPG in the red cell is raised.
   - **E.** Hydrogen ion concentration is reduced.

2. A young man with normal lungs takes an overdose of barbiturate, which causes him to hypoventilate. Which of the following will probably reach the value of 50 first (assume usual units)?
   - **A.** Arterial P_{O_2}.
   - **B.** Arterial oxygen saturation.

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C. Arterial P_{CO_2}.
D. Plasma bicarbonate concentration.
E. Base excess.

3. A previously well patient takes an overdose of a narcotic drug and is brought to the emergency room within an hour. The arterial P_{CO_2} is found to be 80 mm Hg. What is the most likely value for the arterial pH?
A. 6.8
B. 7.0
C. 7.2
D. 7.4
E. 7.6

4. A patient with chronic pulmonary disease undergoes emergency surgery. Postoperatively, the arterial P_{O_2}, P_{CO_2}, and pH are 50 mm Hg, 50 mm Hg, and 7.20, respectively. How would the acid-base status be best described?
A. Mixed respiratory and metabolic acidosis.
B. Uncompensated respiratory acidosis.
C. Fully compensated respiratory acidosis.
D. Uncompensated metabolic acidosis.
E. Fully compensated metabolic acidosis.

5. Which of the following mechanisms of hypoxemia will prevent the arterial P_{O_2} reaching the expected level if the subject is given 100% oxygen to breathe?
A. Hypoventilation.
B. Diffusion impairment.
C. Ventilation–perfusion inequality.
D. Shunt.
E. Residence at high altitude.

6. Concerning obstructive sleep apnea:
A. The condition is rare.
B. Most patients are lean.
C. Treatment by continuous positive airway pressure (CPAP) is often effective.
D. Treatment by CPAP tends to cause systemic hypertension.
E. Snoring is uncommon.

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

8. In a normal person, doubling the diffusing capacity would be expected to:

A. Increase arterial P_{O_2} during moderate exercise.
B. Increase the uptake of halothane given during anesthesia.
C. Decrease arterial P_{CO_2} during resting breathing.
D. Increase resting oxygen uptake when the subject breathes air.
E. Increase maximal oxygen uptake at extreme altitude.

9. The laboratory provides the following report on a patient's arterial blood: pH, 7.25; P_{CO_2}, 32 mm Hg; and HCO_3^- concentration, 25 mmol · l^{-1}. You conclude that there is:

A. Respiratory alkalosis with metabolic compensation.
B. Acute respiratory acidosis.
C. Metabolic acidosis with respiratory compensation.
D. Metabolic alkalosis with respiratory compensation.
E. A laboratory error.

10. An arterial blood sample is taken from a patient with acute shortness of breath breathing air at sea level. Assume the respiratory exchange ratio is 0.8. P_{O_2} = 70 torr, P_{CO_2} = 32 torr, pH = 7.30. These data indicate:

A. A primary respiratory alkalosis with metabolic compensation.
B. A normal alveolar–arterial P_{O_2} difference.
C. An arterial O_2 saturation of less than 70%.
D. The sample was mistakenly drawn from a vein.
E. A partially compensated metabolic acidosis.

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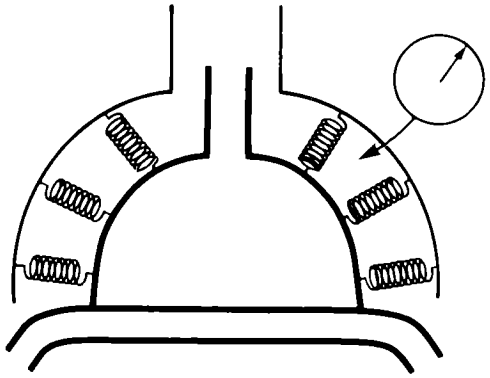

3 Other Tests

In the first two chapters, we concentrated on two simple but informative tests of pulmonary function: forced expiration and arterial blood gases. In this chapter, we briefly consider some other ways of measuring lung function. Of the large number of possible tests that have been introduced from time to time, we address only the most useful here and emphasize the principles rather than the details of their use.

■ STATIC LUNG VOLUMES

Measurement

The measurement of the vital capacity with a simple spirometer was described in Chapter 1 (Figure 1-1). This equipment can also be used to obtain the tidal volume, inspiratory capacity, and expiratory reserve volume (functional residual capacity minus the residual volume). However, the residual volume, functional residual capacity, and total lung capacity require additional measurements.

The *functional residual capacity* (FRC) can be measured with a body plethysmograph, which is essentially a large airtight box in which the patient sits. (See *Respiratory Physiology: The Essentials*, 7th ed., p. 16.) The mouthpiece is obstructed, and the patient is instructed to make a rapid inspiratory effort. As he or she expands the gas volume in the lungs, the air in the plethysmograph is compressed slightly and its pressure rises. By applying Boyle's law, the lung volume can be obtained. Another method is to use the helium dilution technique, in which a spirometer of known volume and helium concentration is connected to the patient in a closed circuit. From the degree of dilution of the helium, the unknown lung volume can be calculated. The *residual volume* (RV) can be derived from the FRC by subtracting the expiratory reserve volume.

Interpretation

The FRC and RV are typically increased in diseases in which there is an increased airway resistance, for example, emphysema, chronic bronchitis, and asthma. Indeed, at one time, an elevated RV was regarded as an essential feature of emphysema, but less emphasis is placed on this test now. The RV is raised in these conditions because airway closure occurs at an abnormally high lung volume.

A reduced FRC and RV are often seen in patients with reduced lung compliance, for example, in diffuse interstitial fibrosis. In this case, the lung is stiff and tends to recoil to a smaller resting volume.

If the FRC is measured by both the plethysmographic and gas dilution methods, a comparison of the two results is often informative. The plethysmographic method measures all the gas in the lung. However, the dilution technique "sees" only those regions of lung that communicate with the mouth. Therefore, regions behind closed airways (for example, some cysts) result in a higher value for the plethysmographic than for the dilution procedure. The same disparity is often seen in patients with chronic obstructive pulmonary disease, probably because some areas are so poorly ventilated that they do not equilibrate in the time allowed.

■ LUNG ELASTICITY

Measurement

The pressure-volume curve of the lung requires knowledge of the pressures both in the airways and around the lung (see *Respiratory Physiology: The Essentials*, 7th ed., p. 96). A good estimate of the latter can be obtained from the esophageal pressure. A small balloon on the end of a catheter is passed down through the nose or mouth, and the difference between the mouth and esophageal pressures

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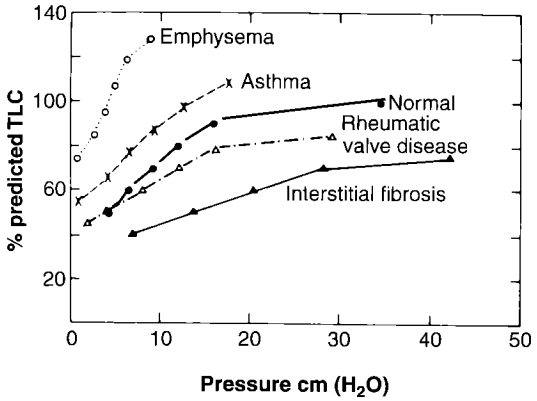

FIGURE 3-1 Pressure-Volume Curves of the Lung. Note that the curves for emphysema and asthma (during an attack) are shifted upward and to the left, whereas those for rheumatic valve disease and interstitial fibrosis are flattened. (From Bates DV, Macklem PT, Christie RV. *Respiratory Function in Disease.* 2nd ed. Philadelphia: WB Saunders, 1971.)

is recorded as the patient exhales in steps of 1 liter from total lung capacity (TLC) to RV. The resulting pressure-volume curve is not linear (Figure 3-1), so that a single value for its slope (compliance) can be misleading. However, the compliance is sometimes reported for the liter above FRC measured on the descending limb of the pressure-volume curve.

The pressure-volume curve is often reported using the percentage of predicted TLC on the vertical axis rather than using the actual lung volume in liters (Figure 3-1). (8) This procedure helps to allow for differences in body size and reduces the variability of the results.

Interpretation

Elastic recoil is *reduced* in patients with emphysema. Figure 3-1 shows that the pressure-volume curve is displaced to the left and has a steeper slope in this condition as a result of the destruction of the alveolar walls (see also Figures 4-2, 4-3, and 4-5) and the consequent disorganization of elastic tissue. The change in compliance is not reversible. The pressure-volume curve is also typically shifted to the left in patients who are having an asthma attack, but the change is reversible in some patients. The reasons for this shift are unclear. Increasing age also tends to reduce elastic recoil.

Some Conditions Affecting Lung Elasticity

Elastic recoil is *reduced* in	emphysema
	some patients with asthma
Elastic recoil is *increased* by	interstitial fibrosis
	interstitial edema

Elastic recoil is *increased* in interstitial fibrosis, which results in the deposition of fibrous tissue in the alveolar walls (see Figures 2-5 and 5-3), thus reducing the lung's distensibility. Elastic recoil also tends to increase in patients with rheumatic heart disease who have a raised pulmonary capillary pressure and some interstitial edema. However, note that measurements of the pressure-volume curve show considerable variability, and the neat results shown in Figure 3-1 are based on mean values from many patients.

■ AIRWAY RESISTANCE

Measurement

Airway resistance is measured as the pressure difference between the alveoli and the mouth divided by the flow rate. Alveolar pressure can only be measured indirectly: one way to do this is with a body plethysmograph. (See *Respiratory Physiology: The Essentials*, 7th ed., p. 163.) The subject sits in an airtight box and pants through a flow meter. The alveolar pressure can be deduced from the pressure changes in the plethysmograph because when the alveolar gas is compressed, the plethysmograph gas volume increases slightly, causing a fall in pressure. This method has the advantage that lung volume can be measured easily almost simultaneously. Figure 3-2 shows the effect of cigarette smoking on airway resistance, here expressed as its reciprocal, *conductance*. (9)

Interpretation

Airway resistance is reduced by an increase in lung volume because the expanding parenchyma exerts traction on the airway walls. Thus, any measurement of airway resistance must be related to the lung volume. Note that the small peripheral airways normally contribute little to overall resistance because there are so many

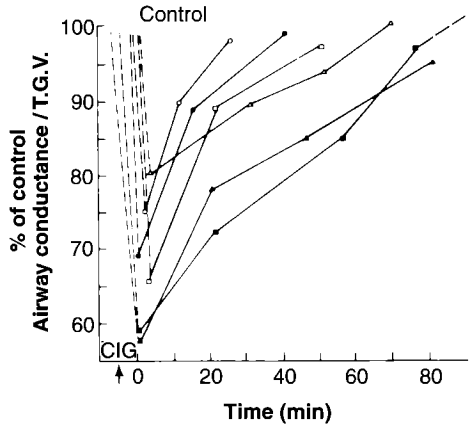

FIGURE 3-2 Effect of Cigarette Smoking on Airway Conductance as Measured in the Body Plethysmograph. The ordinate shows conductance related to thoracic gas volume (TGV). (From Nadel JA, Comroe Jr, JH. Acute effects of inhalation of cigarette smoke on airway conductance. *J Appl Physiol* 1961;16:713–716.)

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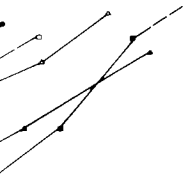

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Some Conditions Affecting Airway Resistance	
Resistance is *increased* by	chronic bronchitis
	asthma
	emphysema
	inhaled irritants (e.g., cigarette smoke)
Resistance is *decreased* by	increased lung volume

arranged in parallel. For this reason, special tests have been devised to detect early changes in small airways. These changes include the flow rate during the latter part of the flow-volume curve (see Figure 1-8) and closing volume (see Figure 1-10).

Airway resistance is *increased* in chronic bronchitis and emphysema. In chronic bronchitis, the lumen of a typical airway contains excessive secretions and the wall is thickened by mucous gland hyperplasia and edema (see Figure 4-6). In emphysema, many of the airways lose the radical traction of the tissue surrounding them because of destruction of the alveolar walls (see Figures 4-1 and 4-2). As a result, their resistance may not increase much during quiet breathing (it may be nearly normal), but with any exertion, dynamic compression (see Figure 1-6) quickly occurs on expiration, and resistance rises strikingly. Such patients often show a reasonably high flow rate early in expiration, but this abruptly drops to low values as flow limitation occurs (see the flow-volume curve in Figure 1-8). Recall that the driving pressure under these conditions is the static recoil pressure of the lung (see Figure 1-6), which is reduced in emphysema (Figure 3-1).

Airway resistance is also increased in patients with bronchial asthma. Here the factors include contraction of bronchial smooth muscle with resultant bronchoconstriction, mucous plugs occluding many of the airways, and edema of their walls (see Figure 4-13). The resistance may be high during attacks, especially in relation to lung volume, which is frequently greatly increased. The resistance is reduced by bronchodilator drugs such as β2 agonists. Even during periods of remission when the patient is asymptomatic, airway resistance is often raised.

Tracheal obstruction increases airway resistance. This may be caused by compression from outside, for example, an enlarged thyroid, or by intrinsic narrowing caused by scarring or a tumor (fixed obstruction). An important feature is that the obstruction is usually apparent during *inspiration* and it can be detected on an inspiratory flow-volume curve (see Figure 1-9). In addition, an audible stridor may be present.

■ CONTROL OF VENTILATION

Measurement

The ventilatory response to carbon dioxide can be measured with a rebreathing technique. (10) A small bag is filled with a mixture of 6–7% CO_2 in oxygen, and the patient rebreathes from this over a period of several minutes. The bag P_{CO_2} increases at the rate of 4–6 mm Hg/min because of the CO_2 being produced from

the tissues, and thus the change in ventilation per mm Hg increase in P_{CO_2} can be determined.

The ventilatory response to hypoxia can be measured in a similar way. In this instance, the bag is filled with 24% O_2, 7% CO_2, and the balance N_2. During rebreathing, the P_{CO_2} is monitored and held constant by means of a variable bypass and CO_2 absorber. (11) As the oxygen is taken up, the ventilation is related to the P_{O_2} in the bag and lungs.

Both these techniques give information about the overall ventilatory response to CO_2 or hypoxia, but they do not differentiate between patients who *will not* breathe because of central nervous system or neuromuscular inadequacy and those who *cannot* breathe because of mechanical abnormalities of the chest. To make this distinction between those who "won't" and those who "can't" breathe, the mechanical work done during inspiration can be measured. To accomplish this, the esophageal pressure is recorded with tidal volume, and the area of the pressure-volume loop is obtained. (See *Respiratory Physiology: The Essentials*, 7th ed., p. 117.) Inspiratory work recorded in this way is one useful measure of the neural output of the respiratory center.

Interpretation

The ventilatory response to CO_2 is depressed by sleep, narcotic drugs, and genetic, racial, and personality factors. An important question is why some patients with chronic pulmonary disease develop CO_2 retention and others do not. In this

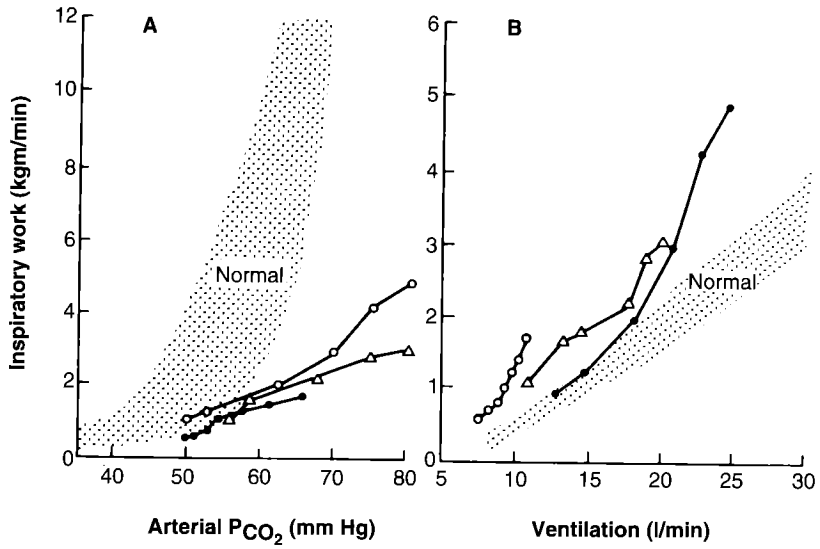

FIGURE 3-3 Ventilatory Response to CO_2 in Three Patients with Chronic Obstructive Pulmonary Disease. *(A)* Measurements show they performed an abnormally small amount of inspiratory work as the inspired P_{CO_2} was raised. *(B)* Measurements show they required an abnormally high work for a given level of ventilation. (From Lane DJ, Howell JBL. Relationship between sensitivity to carbon dioxide and clinical features in patients with chronic airways obstruction. *Thorax* 1970;25:150–159.)

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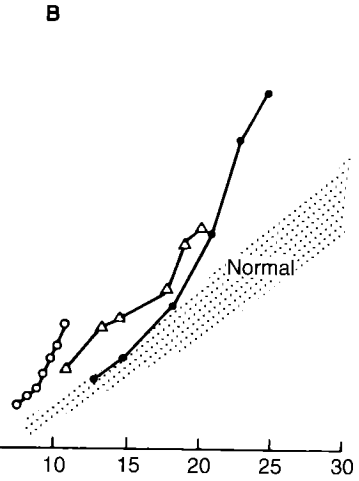

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context, considerable differences of CO_2 response exist among individuals, and it has been suggested that the course of patients with chronic respiratory disease may be related to this factor. Thus, patients who respond strongly to a rise in P_{CO_2} may be more distressed by dyspnea, whereas those who respond weakly may succumb to respiratory failure.

Figure 3-3A shows the results in three patients with chronic obstructive pulmonary disease who performed an abnormally small amount of inspiratory work in response to inspired CO_2. In addition, they required an inordinately high inspiratory work for a given amount of ventilation *(B)*. Thus, these patients had evidence of both a reduced respiratory center output and mechanical obstruction to breathing. (12)

The factors that affect the ventilatory response to hypoxia are less clearly understood. However, the response is reduced in persons who have been hypoxemic since birth, such as those born at high altitude or with cyanotic congenital heart disease. The hypoxic ventilatory response tends to be preserved during sleep. However, some patients develop sleep apnea syndromes, as discussed in Chapter 2.

■ EXERCISE TESTS

Measurement

The normal lung has enormous reserves of function at rest. For example, the O_2 uptake and CO_2 output can be increased 10-fold when a normal person exercises, and these increases occur without a fall in arterial P_{O_2} or a rise in P_{CO_2}. Therefore, to reveal minor dysfunction, the stress of exercise is often useful.

Another reason for exercise testing is to assess disability. Patients vary considerably in their own assessment of the amount of activity they can do, and an objective measurement on a treadmill, stationary bicycle, or a walk along a hallway can be revealing. Occasionally, exercise tests are diagnostic, for example, in exercise-induced asthma and in myocardial ischemia causing angina. Exercise tests can help evaluate the cause of dyspnea.

The variables that are often measured during exercise include work load, total ventilation, respiratory frequency, tidal volume, heart rate, ECG, blood pressure, O_2 uptake, CO_2 output, arterial P_{O_2}, P_{CO_2}, and pH. More specialized measurements, such as diffusing capacity, cardiac output, and blood lactate concentration, are sometimes made. Abnormal gas exchange can be characterized by the physiologic dead space and shunt as at rest.

Less formal exercise tests (so-called field exercise tests) can also be informative. One is the 6-minute walk test (6MWT), in which the patient is asked to walk as far as possible along a corridor or other flat terrain for 6 minutes. The result is expressed in meters covered and has the advantage that the test simulates real-life conditions. The results often improve with practice. Another test is the shuttle walk test, in which the patient walks around two cones placed 10 meters apart. The walking speed is controlled by an audiotape that "beeps" and the walking speed is successively increased.

Interpretation

In most instances, the interpretation of the tests during exercise is similar to that of tests done at rest except that exercise exaggerates the abnormalities. For example, a patient with interstitial lung disease who has a marginally reduced diffusing capacity at rest may show almost no increase on exercise (an abnormal result), with a marked fall in arterial P_{O_2}, a relatively small rise in cardiac output, and perhaps striking dyspnea. Figure 3-4*B* shows the exercise response of a patient with hypersensitivity pneumonitis. (13) Note the rapid increase in ventilation at relatively low work levels and the fall in arterial P_{O_2} and P_{CO_2}.

Some investigators take special note of the respiratory exchange ratio (R) as the exercise level is increased, although this requires special equipment for its continuous measurement. When the patient reaches the limit of his or her steady-state aerobic exercise (sometimes called the *anaerobic threshold*), the R rises more rapidly. This is caused by an increase in the CO_2 production secondary to the liberation of lactic acid from the hypoxic muscles. The hydrogen ions react with bicarbonate and lead to an increase in CO_2 excretion above that produced by aerobic metabolism. The fall in pH provides an additional stimulus to breathing.

Sometimes it is possible to identify the chief factor limiting exercise in a patient with mixed disease. (14) For example, patients who have both heart and lung disease present a common problem. Exercise testing may reveal that at a patient's maximum work load there is abnormal pulmonary gas exchange with a high physiologic dead space and shunt, suggesting that the patient's lung is the

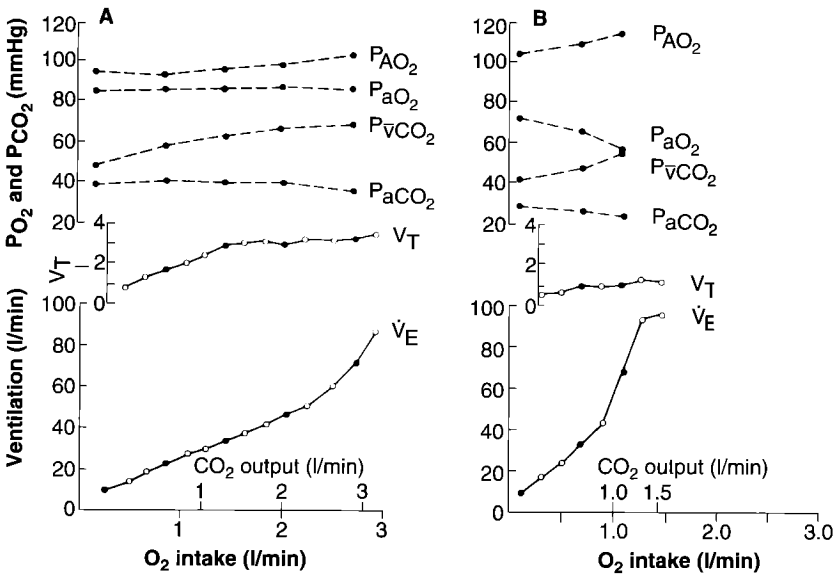

FIGURE 3-4 Results Obtained During Exercise Testing. *(A)* Normal pattern. *(B)* Results in a patient with hypersensitivity pneumonitis. Note the restricted work level evidenced by the limited O_2 intake, the excessive ventilation for the O_2 intake, and the marked fall in arterial P_{O_2}. (From Jones NL. Exercise testing in pulmonary evaluation. *N Engl J Med* 1975;293: 541–544, 647–650.)

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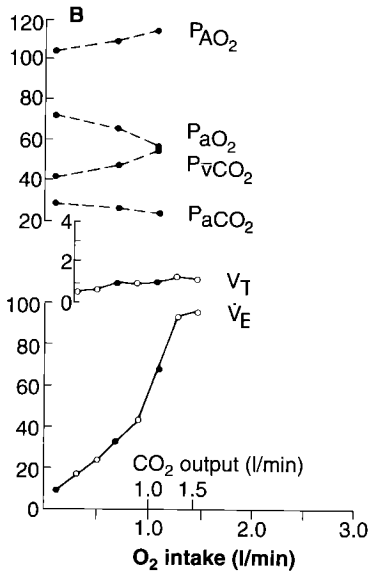

Testing. *(A)* Normal pattern. *(B)* Results the restricted work level evidenced by the O_2 intake, and the marked fall in arterial ry evaluation. *N Engl J Med* 1975;293:

weak link. Alternatively, the cardiac output may respond poorly to exercise, thus suggesting heart disease as the chief culprit. Sometimes, however, the interpretation is not clear-cut.

DYSPNEA

Dyspnea refers to the sensation of difficulty with breathing, and it should be distinguished from simple tachypnea (rapid breathing) or hyperpnea (increased ventilation). Because dyspnea is a subjective phenomenon, it is difficult to measure, and the factors responsible for it are poorly understood. Broadly speaking, dyspnea occurs when the *demand for ventilation* is out of proportion to the patient's *ability to respond* to that demand. As a result, breathing becomes difficult, uncomfortable, or labored.

An *increased demand for ventilation* is often caused by changes in the blood gases and pH level. High ventilations on exercise are common in patients with inefficient pulmonary gas exchange, especially those with large physiologic dead spaces, who tend to develop CO_2 retention and acidosis unless they achieve high ventilations. Another important factor is stimulation of intrapulmonary receptors. This factor presumably explains the high exercise ventilations in many patients with interstitial lung disease, possibly as a result of stimulation of the juxtacapillary (J) receptors (Figure 3-4*B*).

A *reduced ability to respond* to the ventilatory needs is generally caused by abnormal mechanics of the lung or chest wall. Frequently, increased airway resistance is the problem, as in asthma, but other causes include a stiff chest wall, as in kyphoscoliosis.

The assessment of dyspnea is difficult. One way is to ask the patient to indicate his perceived feeling of dyspnea on a linear scale from 1 to 10, with 1 being the lowest and 10 the highest. This type of measurement is especially useful before and after an intervention such as treatment with a bronchodilator. Exercise tolerance often is determined from a standard questionnaire that grades breathlessness according to how far the patient can walk on the level or up stairs without pausing for breath. Occasionally, in an attempt to obtain an index of dyspnea, ventilation is measured at a standard level of exercise and is then related to the patient's maximum voluntary ventilation. However, dyspnea is something that only the patient feels; as such, it cannot be measured objectively.

TOPOGRAPHIC DIFFERENCES OF LUNG FUNCTION

Measurement

The regional distribution of blood flow and ventilation in the lung can be measured with radioactive substances (see *Respiratory Physiology: The Essentials*, 7th ed., pp. 21, 43). One method of detecting areas of absent blood flow is by injection of albumin aggregates labeled with radioactive technetium. An image of the radioactivity is then made with a gamma camera, and "cold" areas containing no activity are readily apparent. A major application of this method in practice is the diagnosis of pulmonary embolism.

The distribution of blood flow can also be obtained from an intravenous injection of radioactive xenon or other gas dissolved in saline. When the gas reaches the pulmonary capillaries, it is evolved into the alveolar gas, and the radiation can be detected by a gamma camera. This method has the advantage of giving blood flow per unit volume of lung.

The distribution of ventilation can be measured in a similar way, except that the gas is inhaled into the alveoli from a spirometer. Either a single inspiration or a washin over a series of breaths can be recorded.

Interpretation

The distribution of blood flow in the upright lung is uneven, being much greater at the base than at the apex (Figure 3-5). The differences are caused by gravity and can be explained by the relationships between the pulmonary arterial, venous, and alveolar pressures. (See *Respiratory Physiology: The Essentials*, 7th ed., p. 44.) Exercise results in a more uniform distribution because of the increase in pulmonary arterial pressure; the same result is found in disease conditions such as pulmonary hypertension and left-to-right cardiac shunts. Localized lung disease, for example, a cyst, or area of fibrosis, frequently decreases regional blood flow.

The distribution of ventilation is also gravity-dependent, and normally the ventilation to the base exceeds that to the apex. The explanation is the distortion that the lung suffers because of gravity and the larger transpulmonary pressure at the apex compared with the base. (See *Respiratory Physiology: The Essentials*, 7th ed., p. 102.) Localized lung disease, for example, a bulla, usually reduces the ventilation in that area. In generalized lung disease—such as asthma, chronic bronchitis, and emphysema, and interstitial fibrosis—areas of reduced ventilation and blood flow can frequently be detected.

Healthy people show a reversal of the normal pattern of ventilation if they inhale a small amount of radioactive gas from residual volume. The reason is that the airways at the base of the lung are closed under these conditions because

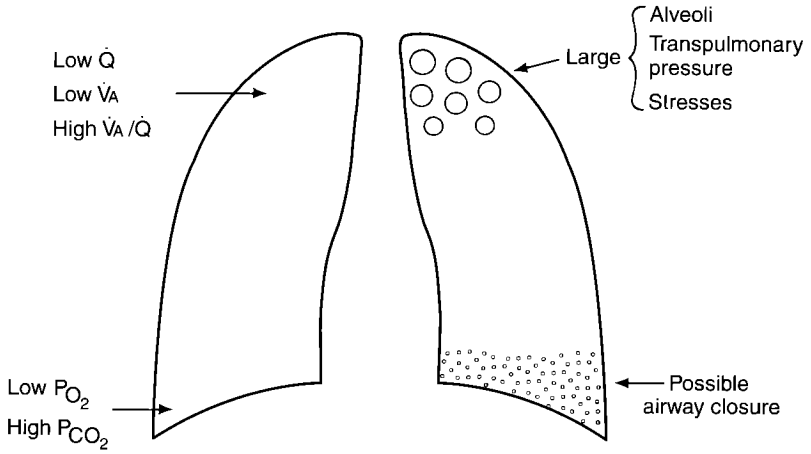

FIGURE 3-5 Regional Differences of Structure and Function in the Upright Lung.

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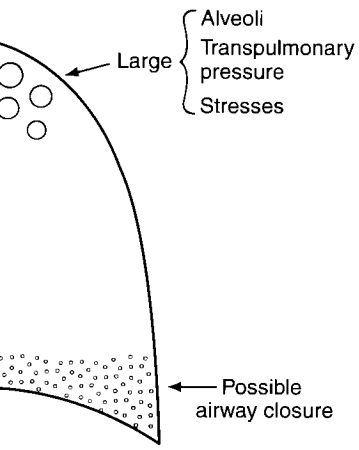

e and Function in the Upright Lung.

intrapleural pressure actually rises above airway pressure. The same pattern may occur at FRC in older subjects because the lower-zone airways close at an abnormally high lung volume. Similar findings may be seen in patients with emphysema, interstitial edema, and obesity. All these conditions exaggerate airway closure at the base of the lung.

Other regional differences of structure and function also occur. The gravity-induced distortion of the upright lung causes the alveoli at the apex to be larger than those at the base. These larger alveoli are also associated with greater mechanical stresses that may play a role in the development of some diseases, such as centriacinar emphysema (see Figure 4-5A) and spontaneous pneumothorax.

■ VALUE OF PULMONARY FUNCTION TESTS

Because this book is about the function of diseased lungs, it is natural that we should start with pulmonary function tests. However, it is important to recognize that these tests have a limited role in clinical practice. They are rarely useful in making a specific diagnosis; rather, they provide supporting information that is added to that obtained from the clinical history, physical examination, chest imaging, and laboratory tests. Lung function tests are particularly valuable in following the progress of a patient, for example, assessing the efficacy of bronchodilator therapy in a patient with asthma. They also are useful in assessing patients for surgery, determining disability for purposes of workers' compensation, and estimating the prevalence of disease in a community, for example, in a coal mine or an asbestos factory. Lung function tests are occasionally within normal limits despite obvious generalized lung disease (see Figure 7-7).

As has been emphasized, spirometry gives useful information with simple equipment. Arterial blood gases are more difficult to measure, but the data may be lifesaving for patients with respiratory failure. The value of the other tests depends largely on the clinical problem, and whether they are worth doing is related to the facilities of the pulmonary function laboratory, the expense, and the likelihood that they will give useful information.

KEY CONCEPTS

1. Lung elastic recoil is reduced in emphysema and some patients with asthma. It is increased in interstitial fibrosis and slightly in interstitial edema.
2. Airway resistance is increased in chronic bronchitis, emphysema, and asthma. It is reduced by increasing lung volume. Tracheal obstruction increases both inspiratory and expiratory resistance.
3. The control of ventilation by increased P_{CO_2} and reduced P_{O_2} varies greatly among people and may affect the clinical pattern of COPD.
4. The lung at rest has enormous reserves of function and valuable information can therefore often be obtained during exercise that stresses gas exchange.
5. Dyspnea is a common, important symptom in many lung diseases but can be truly assessed only by the patient.

QUESTIONS

1. The functional residual capacity:

- **A.** Can be measured with a single spirometer.
- **B.** Is often larger when measured by helium dilution than with a body plethysmograph.
- **C.** Is reduced during an attack of asthma.
- **D.** Is determined by a balance between the elastic recoil of the lung and chest wall.
- **E.** Falls with increasing age.

2. Airway resistance in a patient with asthma:

- **A.** Is raised by increasing lung volume.
- **B.** Is reduced by inhaling β2 agonists.
- **C.** Is increased by destruction of alveolar walls.
- **D.** Is unaffected by secretions in the airways.
- **E.** Is increased by atrophy of bronchial smooth muscle.

3. During an exercise test on a patient with mitral stenosis, it was found that the respiratory exchange ratio of expired gas rapidly rose above 1 at a low level of exercise. A likely reason is:

- **A.** Abnormally high levels of lactate in the blood.
- **B.** Abnormally low ventilation.
- **C.** Abnormally high cardiac output.
- **D.** Increased lung compliance.
- **E.** Reduced diffusing capacity of the lung.

4. In the upright human lung, which of the following is greater at the apex than the base?

- **A.** Blood flow.
- **B.** Ventilation.
- **C.** Alveolar P_{CO_2}.
- **D.** Alveolar size.
- **E.** Capillary blood volume.

5. Which of the following increases *by the largest percentage* at maximal exercise compared with rest?

- **A.** P_{CO_2} of mixed venous blood.
- **B.** Alveolar ventilation.
- **C.** Tidal volume.
- **D.** Heart rate.
- **E.** Cardiac output.