The branch of mechanics that deals with motion, the forces or pressures, that produce it, and the resistances that must be overcome is called dynamics. This chapter deals with the dynamics of the lung during breathing, but it is beyond our scope to consider the dynamics of the chest wall and respiratory muscles. This is addressed in part elsewhere in this book (see Chapter 7, “Act of Breathing: The Ventilatory Pump”). A superb, timeless review of the dynamics of breathing is contained in Mead’s Physiological Review article.1

To analyze breathing dynamics, one needs to know the volume of gas inspired and expired at the mouth, the flow rates, and the pressures required to move the lungs. With this information, one can calculate the resistances to motion of the lungs. In health, under most circumstances, there are three types of resistance: (1) the resistance to the flow of air along the upper airway and the tracheobronchial tree between the mouth and the alveoli, determined by the physical properties of the gas, how fast the gas is flowing, and the geometry of the airways; (2) the elastic resistance of the alveoli, which is determined by the size of the breath, the elastic properties of the alveolar walls, and the surface tension of the alveolar lining liquid; and (3) the resistance due to tissue viscance. The last is also a property of the alveolar walls and results from the fact that the lung exhibits hysteresis, so that the pressures required to inflate the lung are greater than those at the same volume on deflation. When breathing is very rapid, the lung’s inertial properties may lead to additional resistance to motion. Inertance depends primarily on the mass of gas in the airways and how quickly the gas is accelerated and decelerated, given by the rate of change of airflow at the mouth. Finally, in certain disease states, the respiratory muscles, which produce the pressures required to inflate the lung, must overcome a “threshold” load that is similar in effect to the inertial loads that skeletal muscles must overcome when lifting an object. These muscles initially contract isometrically and develop a force equal to the weight of the object being lifted before any motion of the object takes place. Similarly, when the respiratory muscles have to overcome a threshold load, they must develop a finite pressure before any inspiratory flow starts.

**THEORY**

**Equation of Motion of the Lung**

The pressure difference across the lung between the mouth or airway opening and the pleural space, or transpulmonary pressure ($P_L$), is the agency that moves the lung:

$$P_L = P_{ao} - P_{pl}$$

where $P_{pl}$ is pleural pressure and $P_{ao}$ is the pressure at the airway opening. The alveoli lie between the airway opening and the pleural space, and they have a pressure inside them ($P_A$) that may be different from either $P_{ao}$ or $P_{pl}$. Thus:

$$P_L = P_{ao} - P_A + P_A - P_{pl}$$

$P_{ao} - P_A$ is the pressure drop across the airways and thus is the pressure producing flow of air in and out of the lung. This is the pressure that overcomes the flow resistance of the upper airway and tracheobronchial tree ($P_{fr}$):

$$P_{fr} = P_{ao} - P_A$$

$P_A - P_{pl}$ is the pressure difference between the alveoli and the pleural space, which contains tissue viscance and the elastic recoil pressure of the lung ($P_{el}$). Ignoring tissue viscance for the time being:

$$P_{el} = P_A - P_{pl}$$

Substituting in Equation 4-2:

$$P_L = P_{fr} + P_{el}$$

This is illustrated in Figure 4-1.

$P_{fr}$ is in phase with flow, whereas, when tidal volumes are small and hysteresis can be neglected, $P_{el}$ is in phase with volume. The relationships between flow, volume, $P_{fr}$, $P_{el}$, and $P_L$ are shown in Figure 4-2.

If one considers that one complete respiratory cycle constitutes 360° (like a circle), then one observes that flow is one-quarter of a cycle or 90° ahead of volume. Similarly, $P_{fr}$, which is in phase with flow, is 90° ahead of $P_{el}$, which is

---

*During spontaneous inspiration, this pressure is positive and alveolar pressure is negative, whereas during expiration, it is negative and alveolar pressure is positive.*
in phase with volume. The bottom panel of Figure 4-2 shows how \( P_L \) can be calculated as the sum of \( P_{el} \) and \( P_{fr} \), where \( P_{fr} \) is the hatched area between \( P_t \) and \( P_{el} \).

Each of the variables flow (\( V' \)), volume (\( V \)), \( P_{fr} \), \( P_{el} \), and \( P_L \) has both a magnitude (its size) and a phase (when it occurs). It can be seen that the phase of \( P_L \) lags behind that of \( V' \) and \( P_{fr} \) but leads \( V \) and \( P_{el} \). I will show that the phase and magnitude of \( P_L \) in relation to the other variables depend, upon the lungs’ elastic, flow-resistive, and inertial properties, tidal volume (\( V_T \)), \( V' \), and respiratory rate (\( f_B \)). To have the phase and magnitude of a single variable depend on so many other variables may sound complicated. In reality, as will be seen, it is quite straightforward with the use of vector analysis.

By definition, the resistance to flow of air into and out of the lung, airway resistance (\( R_{aw} \)), is given by \( P_{fr}/V' \) and:

\[
P_{fr} = R_{aw} V'
\]  (4-6)

The elastic properties of the lung are characterized in part by lung compliance (\( C_L \)):

\[
C_L = V_T/\Delta P_{el}^±
\]  (4-7)

and

\[
\Delta P_{el} = V_T/C_L
\]

Equation 4-5 can be rewritten:

\[
\Delta P_L = P_{fr}^± + \Delta P_{el}
\]  (4-8)

Substituting for \( P_{fr} \) and \( \Delta P_{el} \):

\[
\Delta P_L = V_T/C_L + R_{aw} V'
\]  (4-9)

If breathing is quasisinusoidal, \( V_T \) and \( f_B \) must obviously determine \( V' \). This is given by the formula \( V' = 2\pi f_B \cdot j \cdot V_T \), where \( j = \sqrt{-1} \) and is used to indicate \( V \) and \( V' \) are 90° out of phase. The quantity \( 2\pi f_B \) is denoted by the Greek letter omega. Thus:

\[
\Delta P_L = V_T/C_L + R_{aw} \cdot \omega \cdot j \cdot V_T
\]  (4-10)

For most purposes, Equations 4-9 and 4-10 can be used as equations of motion of the lung. Equation 4-10 can be used when breathing is nearly sinusoidal, and Equation 4-9 when it is not. However, at \( f_B > 1.5 \) Hz, the lung’s inertial properties come into play. Lung inerterance (\( I_L \)) depends upon the rate of change of flow or acceleration (\( V'' \)). Again, if breathing is quasisinusoidal:

\[
V'' = j \cdot \omega \cdot V' = j^2 \cdot \omega^2 \cdot V_T = -\omega^2 \cdot V_T
\]

because \( (\sqrt{-1})^2 = -1 \)

This is illustrated in Figure 4-3. As \( V' \) passes through zero, \( V'' \) is maximal; when \( V' \) is maximal and for a brief instant it is not changing, \( V'' \) is zero. It can be seen that \( V_T \) and \( V'' \) are 180° out of phase. The inertial pressure (\( P_{in} \)) is in phase with
FIGURE 4-3 Phase relationships between flow, volume, and acceleration for a sinusoidal breathing pattern.

\[ V'' \text{, and therefore } P_{el} \text{ and } P_{in} \text{ are } 180^\circ \text{ out of phase. Thus, at } \]
\[ \text{breathing frequencies } > 1.5 \text{ Hz, } P_{in} \text{ subtracts from } P_{el} \text{ in the determination of } P_L \text{, and the equation of motion becomes:} \]
\[ \Delta P_L = V_T/C_L + \omega \cdot \dot{V}_aw \cdot V_T - \omega^2 I_L V_T \]
\[ \text{or} \]
\[ \Delta P_L = V_T(1/C_L + \omega \cdot \dot{V}_aw - \omega^2 I_L) \quad (4-11) \]

VECTOR ANALYSIS OF THE EQUATION OF MOTION

Circular Motion Imagine a frictionless pendulum with a pen at the bottom producing a tracing of its motion on a strip of paper moving at right angles to the pendular motion. The tracing would be a sine wave. If the paper speed were just right, the amplitude of the pendulum could be precisely equal to the period of one complete cycle, as shown in Figure 4-4A. If the time axis or direction of the paper changed every time the pendulum reached the midpoint of its motion, so that the tracing returned to its point of origin (Figure 4-4B), the pendular motion would be described as a trajectory traveling in a counterclockwise circle. The pendulum's amplitude would be given by the circle's diameter and its phase at any instant by its position on the 360° of the circle's circumference. It was from this sort of analysis that we concluded that \( V_T \) and \( \Delta P_{el} \) lag \( V' \) and \( P_{fr} \) by 90° and that \( \Delta P_{el} \) and \( P_{in} \) are 180° out of phase.

The representation of a variable undergoing sinusoidal motion by a circle in which both amplitude and phase of the variable can be determined is called vector analysis. Vectors have both amplitude and phase. If, at any instant in time, \( V' \) were to be aligned with the x-axis, then \( P_{fr} \) in phase with it, would also be aligned on the x-axis. Both \( V_L \) and \( P_{el} \), which lag \( V' \) and \( P_{fr} \) by 90°, would be aligned along the y-axis at positive values of y, whereas \( V'' \) and \( P_{in} \) would also be aligned along the y-axis at negative values of y. This is illustrated in Figure 4-5.

FIGURE 4-5 Determination of the phase relationships between lung volume \( (V_L) \), \( P_{el} \), flow \( (V') \), \( P_{fr} \), acceleration \( (V'') \), and inertial pressure \( (P_{in}) \). See text for further explanation.

Determination of Phase and Amplitude of Respiratory Variables Knowing \( V_T, f_b, R_{aw}, C_L, \text{ and } I_L \), how does one measure the phase and amplitude of \( \Delta P_{el} \), \( P_{fr} \), and \( P_{in} \) by vector analysis?

Assume a \( V_T \) of 0.5 L and an \( f_b \) of 15/min = 0.25/s, an \( R_{aw} \) of 1.5 cm H₂O/L/s, and a \( C_L \) of 0.2 L/cm H₂O. Then, \( \omega V_T = 0.785 \text{ L/s, } P_{fr} = 1.178 \text{ cm H}_2\text{O, and } \Delta P_{el} = 2.5 \text{ cm H}_2\text{O. When these values are plotted on the vector graph with } V' \text{ (closed square) and } P_{fr} \text{ (open square) on the x-axis and } V_T \text{ (closed circle) and } \Delta P_{el} \text{ (open circle) on the y-axis, the results shown in Figure 4-6 are obtained. Remember that the amplitude is the diameter of the circle, not the radius. Thus, the } V_T \text{ intersects the ordinate at a value of 0.25 not 0.5. Study this graph carefully until it is understood. It is the key to all the vector analysis that follows. The vector sum of } \Delta P_{el} \text{ and } P_{fr} \text{ provides the solution for the phase and magnitude of } \Delta P_{in} \text{ (outermost circle). } \Delta P_{in} \text{ is given by the intersection of the horizontal projection of } \Delta P_{el} \text{ with the vertical projection of } P_{fr} \text{ (point X on the graph). Its length from the origin to point X is half of its amplitude, and its phase is...} \]
the number of degrees by which it lags \( V \) and \( P_{fr} \). Note that
the magnitude of \( P_L \) is greater than that of either \( P_{el} \) or \( P_{fr} \), and for the values of \( V_T \), \( f_B \), \( C_L \) and \( R_{aw} \) chosen, the phase of \( P_L \) is closer to that of \( P_{el} \) than of \( P_{fr} \).

If breathing had been extremely slow, so that \( f_B \to 0 \), then 
\( \omega V_T \) would also be small, and \( \Delta P_L \) would be almost in phase with volume and would have a magnitude almost equal to 
\( \Delta P_{el} \), as shown in Figure 4-7A (we do not need the circles any more). On the other hand, if breathing had been very rapid, say 1 Hz, and \( V_T \) small, then \( \Delta P_L \) would be nearly in phase with \( V' \) and almost equal in magnitude to \( P_{fr} \) (Figure 4-7B). The phase and magnitude of \( \Delta P_L \) depend importantly on the pattern of breathing.

Because the amplitude of \( \Delta P_{el} \) is determined in part by 
\( C_L \) (Equation 4-7) and the amplitude of \( P_{fr} \) by \( R_{aw} \) (Equation 4-6), which are independent of the pattern of breathing, the mechanical properties of the lung are also important determinants of the phase and amplitude of \( \Delta P_L \). This is illustrated in Figure 4-8. When the lungs are stiff with pulmonary fibrosis or pulmonary edema, \( C_L \) is small and \( \Delta P_{el} \) is large. The effect on \( \Delta P_L \) is similar to the effect of a large \( V_T \) and small \( f_B \) (Figure 4-8A). On the other hand, with airways obstruction, as in asthma or chronic obstructive pulmonary disease (COPD), \( P_{fr} \) is large, and the result is similar to a rapid shallow breathing pattern (Figure 4-8B).

If one knows the breathing pattern, lung compliance, and airways resistance, one can calculate the phase and amplitude of transpulmonary pressure, the pressure that is moving the lung, and partition it into its two components, \( P_{fr} \) and \( P_{el} \), due to flow resistance and lung elastic recoil, respectively.

Conversely, if one measures \( V_T \), \( f_B \), and \( P_L \) (the usual measurements made when assessing lung mechanics), one can calculate \( C_L \) and \( R_{aw} \) as illustrated in Figure 4-9. The measured variables, \( V_T \) and \( f_B \), from which \( V' \) is calculated, and the measured values of phase and amplitude of \( \Delta P_L \) are plotted on the graph, from which \( P_{el} \) (open circle) and \( P_{fr} \) (closed circle) are obtained by dropping perpendiculars from \( P_L \) to the \( y- \) and \( x- \) axes, respectively. Knowledge of \( P_{el} \), 
\( P_{fr} \), \( V_T \), and \( \omega V_T \) then allows calculation of lung compliance and airways resistance.

In practice, this approach has been used infrequently to measure the mechanical properties of lungs, probably

---

**FIGURE 4-6** Vector analysis of the dynamics of breathing. For explanation, see text.

**FIGURE 4-7** Influence of (A) slow, deep breathing and (B) rapid, shallow breathing on the phase and magnitude of \( P_L \).

**FIGURE 4-8** Vector analysis showing the effect of stiff lungs (A) and airways obstruction (B) on \( P_{el} \), \( P_{fr} \), and \( P_L \). When the lungs are stiff, \( C_L \) is low and \( P_{el} \) is large. The effect on \( P_L \) is similar to that of slow, deep breathing (see Figure 4-7A). Conversely, when the airways are obstructed, \( R_{aw} \) is large and the effect on \( P_{fr} \) is similar to that of rapid, shallow breathing (see Figure 4-7B).
since breathing is not really sinusoidal. Determination of how accurately $\omega V_T$ predicts measured flow would show how applicable vector analysis might be in the measurement of the mechanics of breathing. Certainly, the assumption that breathing is sinusoidal has been very useful in modeling the dynamics of breathing.

At breathing frequencies $>1.5$ Hz, inertia cannot be ignored. Consider that $P_{in}$ is given by $\omega^2 V_T$, whereas $P_{el}$ is independent of $\omega$. For a given $V_T$, $P_{in}$ increases rapidly with breathing frequency, but $\Delta P_{el}$ remains constant. Because $P_{in}$ is $180^\circ$ out of phase with $P_{el}$, the vector sum of $\Delta P_{el}$ and $P_{in}$ affects the phase and magnitude of $\Delta P_L$. This is illustrated in Figure 4-10A. As $P_{in}$ increases at constant $\Delta P_{el}$, $P_L$ moves closer and closer to the phase of $P_{fr}$.

It is evident that, at a particular value of $\omega$, $\Delta P_{el}$ and $P_{in}$ will be equal and opposite. The resulting vector sum of the two will be zero. Under these circumstances, $P_L$ is the only determinant of $\Delta P_L$, which becomes in phase with and of equal magnitude to $P_L$ (Figure 4-10B), and the equation of motion reduces to $\Delta P_L = R_{aw} \omega V_T = P_{fr}$. When this occurs, $P_{fr}$ becomes $90^\circ$ out of phase with volume and $\Delta P_L$ is no longer flow dependent. The phenomenon is called hysteresis, and it quantifies the difference between the energy that is transferred between the lung and the airway during inspiration and that recovered during expiration. This difference is the area contained between the two pressure–volume curves or, in other words, the energy dissipated in a respiratory cycle. Although the dissipated energy is greatest for small capacity breaths, it is still finite during quiet breathing. The hysteretic pressure is well described by the expression:

$$ P = j\eta V_T / C_L $$

where $j$ is the mathematical device indicating that $P$ is $90^\circ$ out of phase with volume and $\eta$ is hysteresivity defined as the dimensionless ratio of the hysteretic pressure difference at mid–tidal volume to the change in elastic recoil pressure for that particular breath, as shown in Figure 4-11.\(^2\) Equation 4-12 shows that the pressure is dependent on both tidal volume and $1/C_L$ or lung elastance, and thus it specifically couples the energy dissipated by hysteresis to the lung's elastic properties, which reflect the stress-bearing elements. How can this be? Fredberg and Stamenovic give several examples.\(^2\) Attached crossbridges in smooth muscle make the muscle stiffer. However, if the muscle is stretched during inspiration, some crossbridges may break, thereby dissipating stored energy and leading to hysteresis, but with the breakage, the muscle becomes more compliant. When atelectatic alveoli inflate, it takes a substantial pressure to overcome the surface tension and viscosity of the liquid lining the airspaces and allow them to open. When opened, they tend to remain open, so the energy required to open them is dissipated, but once the airspaces are open, the lung becomes more compliant. A third example of dissipative and elastic coupling is via the surface-lining layer of surfactant at the alveolar air–liquid interface. On inflation, the number of surface-active molecules lining the surface film may be inadequate to cover the film over the whole increase in surface area that occurs. As a result, the surface film breaks, and molecules with a higher surface tension form a new lining layer until new surface-active molecules are
adsorbed onto the surface from the hypophase. Thus, elastic recoil pressures are greater on lung expansion, and it takes greater force to expand the surface. On deflation, there is an excess of surface molecules, so that, as surface area decreases, the surface film may actually resist compression, so that it buckles and the surface-active molecules are forced into the hypophase, from whence they must be subsequently recruited during the following inspiration. In these ways, one obtains insight into how elastic and dissipative properties become linked in the lung.²

In order to take hysteresivity into account, the equation of motion of the lung must be modified to:

\[ \Delta P_L = V_T/C_L + j\eta V_T/C_L + \omega j R_{aw} V_T - \omega^2 L_j V_T \]

or

\[ \Delta P_L = V_T [1/C_L + j(\eta/C_L + \omega R_{aw}) - \omega^2 L_j] \] (4-13)

To express Equation 4-12 in terms of absolute \( P_L \), one writes:

\[ P_L = P_{Lo} + V_T [1/C_L + j(\eta/C_L + \omega R_{aw}) - \omega^2 L_j] \] (4-14)

where \( P_{Lo} \) is the absolute transpulmonary pressure at end-expiratory volume.

From Equations 4-13 and 4-14, it can be seen that tidal volume, which, along with breathing frequency, determines flow and acceleration, affects every term in the equation of motion except \( P_{Lo} \), which, during quiet breathing, is transpulmonary pressure at functional residual capacity (FRC).

There are two terms in the equation of motion that are 90° out of phase with volume. When one uses the difference between mouth and esophageal pressure to measure transpulmonary pressure, the ratio of pressure in phase with flow and flow is called pulmonary resistance. This includes \( \eta V_T/C_L \), which has nothing to do with the resistance to flow along the airways. The error induced in estimating airways resistance from pulmonary resistance can be substantial, particularly if tidal volumes are large and compliance low.³,⁴

The error can become very large if one is attempting to measure the resistance of only the peripheral airways because \( \eta V_T/C_L \) is large relative to \( \omega R_{aw} V_T \).³ The error can be minimized by using small tidal volumes, which is an attractive feature of the forced oscillation technique, in which the lungs are oscillated by a loudspeaker.⁵,⁶ Furthermore, if one wishes to measure flow-resistive pressure only during inspiration or expiration, then one can avoid pressures due to hysteresis by measuring the difference between the static inflation or deflation pressures and the dynamic pressures at the same volume.⁵

Nevertheless, the dependence of hysteretic pressures on \( \eta V_T/C_L \) means that there are substantial errors in the older literature where pulmonary resistance was used to estimate the effects on the airways of interventions such as drugs, changes in lung volume, and disease. The situation becomes further complicated in that \( \eta \) is not assumed to be constant but could vary with tidal volume and elastance, the reciprocal of compliance.⁴,⁷

Hysteretic and flow-resistive effects have been experimentally separated in tissue strips and by the direct measurement of alveolar pressure with the use of alveolar capsules. These two methods provided results that were in agreement with each other, and the roles of tidal stretching of alveolar walls, lung volume history,⁸ elastance,⁴ and hysteresivity³ have been measured. However, care should be taken in comparing the behavior of tissue strips with lung volume changes in the former. The forces required for stretching are determined by the shear modulus, whereas the pressures required for volume change are determined by the bulk modulus. The two moduli are not the same.

The results of pharmacologic experiments proved surprising. Almost every intervention that influenced airway resistance also increased hysteresis.³,⁸⁻¹² In some instances, the major effects of the drug appeared to be on the lung parenchyma rather than on the airways, so that interpreting pulmonary resistance in terms of bronchoconstriction can be misleading. In tissue strips, pharmacologic agents induced changes of stiffness and also changed \( \eta \). However, the relationship between the two was different for different agents.⁴ The authors pointed out that their experiments “demonstrated the existence of distinct mechanical states that differed according to the specific agonist by which the tissues were stimulated.” In whole lungs, elastance and hysteresis were changed by changing lung volume history and by pharmacologic interventions. These alterations were separated into two distinct components, changes in \( \eta \) and changes in elastance. Again, changes in \( \eta \) and elastance were dissociated. With changes in volume history, elastance changed but \( \eta \) did not, whereas with smooth muscle agonists, both changed.¹³ When lungs were saline filled, to eliminate the surface effects, and elastance was altered by changing lung volume, hysteresis was still tightly coupled to elastance, but \( \eta \) remained constant.¹¹

![Figure 4-11](image-url) Static \( P_{EL} - V_L \) pressure–volume loop illustrating hysteresis. Hysteresivity (\( \eta \)) is the ratio of the difference in \( P_{EL} \) at mid-V_T (\( P_h \)) and the difference in \( P_{EL} \) at zero flow points: \( \eta = P_h/\Delta P_{EL} \).
These experiments reveal a fundamental property of lung tissue and the parenchymal air–liquid interface, namely the coupling of dissipative properties to the stress-bearing elements of the lung responsible for their elastic properties. They also point out the importance of separating airway from lung tissue properties in disease states and in pharmacologic interventions. Too often, changes in the properties of one could mask or appear to indicate artifactual changes in the other.

Unfortunately, very few attempts have been made to separate airway from parenchymal dissipative properties in living human lungs. The technology exists to do such experiments: whole body plethysmography can be used to measure alveolar pressure and airways resistance, and the difference between alveolar and esophageal pressure can be used to obtain the elastic pressure–volume curve. Thus, it should be possible to investigate the coupling of dissipative and elastic properties of the parenchyma, as well as to separate airway from parenchymal effects. This needs to be done particularly when the actions of pharmacologic agents and disease states on the human lung are being evaluated.

MEASUREMENT OF LUNG MECHANICS

The measurement of the mechanical properties of lungs entails the measurement of flow, volume, and pressure. Flow is measured with a pneumotachygraph, and frequently this is integrated to obtain volume. The measurement of flow is accurate and reasonably straightforward, although care must be taken when gas physical properties, particularly viscosity change, and when very rapid flow transients need to be accurately measured. This usually requires a mouthpiece and noseclip, and thus the measurement of flow poses a problem when a mouthpiece and noseclip are either undesirable or impossible. The same problems apply to the measurement of volume, as discussed below.

LUNG VOLUME MEASUREMENTS

As mentioned above, lung volume change is frequently measured by integrating a tracing of flow at the mouth. Volumes can also be measured with a spirometer or a bag-in-box system connected to the mouth. None of these is entirely satisfactory. All integrators suffer from integrator drift, so absolute changes in lung volume, such as those that occur with exercise, cannot be measured accurately. Rebreathing from a spirometer requires scrubbing of carbon dioxide and, for a stable tracing, addition of oxygen at exactly the rate at which oxygen is taken up by the pulmonary capillaries. This is not usually possible. A bag-in-box system allows one to breathe in from a bag enclosed in a box with a spirometer attached to it, and then out into the box, because the inspiratory and expiratory lines are separated by valves. This provides a stable tracing without the need to scrub carbon dioxide or add oxygen. However, the time over which volume can be measured is determined by the volume of gas contained within the bag. When this is exhausted, the measurement of volume stops.

Volume displacement or variable-flow whole body plethysmographs provide accurate measurements of changes in body volume that, during normal quiet breathing, closely reflect the volumes of gas breathed in and out of the mouth. However, under circumstances when there are large swings in alveolar pressure, there may be significant compression and decompression of alveolar gas. When this occurs, changes in body volume (measured by plethysmography) are greater than the volumes exchanged at the mouth. During a forced expiration there is substantial gas compression, so the absolute lung volume is less than the volume of gas expired at the mouth. Thus, whenever the latter is used to measure flow–volume curves, maximal expiratory flow at the measured volume is underestimated. This can lead to substantial errors in the measurement of flow–volume curves if there is marked hyperinflation and the expiratory alveolar pressures are high. This is usually the case in COPD, when the errors can be very large indeed. Although these errors are avoided when volumes are measured by whole body plethysmography, the stability of the tracings is affected by heating and humidification. Furthermore, it is obvious that whole body plethysmography cannot yet be used during exercise or easily during sleep.

Surprisingly in this era of high technology, the requirement for a mouthpiece and noseclip makes it remarkably difficult to measure ventilation in such conditions as sleep, phonation, and infancy and in critically ill patients. The same considerations apply to changes in absolute lung volume during exercise, for example. This problem has resulted in attempts to measure breathing based on body surface measurements. Two of these methods, magnetometry and inductance plethysmography, depend upon the abdomen and the rib cage, each acting as compartments with a single degree of freedom. This is an approximation leading to significant errors (generally ignored in the literature) when breathing exceeds the rather strict limits established by Konno and Mead. Furthermore, calibration changes with posture. This can be dealt with in part by measuring xiphipubic distance. However, the control of posture and respiratory effort necessary for reasonably accurate measurements renders these methods of limited value.

A new technology, optoelectronic plethysmography, involves placing of reflective markers over the surface of the chest wall, tracking each one in three dimensions, and then reconstructing the whole chest wall, and its compartments, to measure volume changes dynamically without mouthpiece and noseclip. It has undergone extensive evaluation and appears to be highly accurate. It can be used to measure ventilation in all the problem situations listed above (not yet tried in infants). It requires no assumptions with regard to the number of degrees of freedom of the rib cage and abdomen. Because it measures chest wall volume, in contrast to whole body plethysmography, which measures body volume, it is sensitive not only to gas compression and decompression but also to blood shifts from the trunk to the extremities. This new feature has been used to demonstrate substantial blood shifts during exercise with
expiratory flow–limitation, when expiratory pressures can be markedly positive.\textsuperscript{21} Although this technology has great promise, it is expensive and requires advanced electronic computations that need to be made user-friendly before the method will gain widespread use.

Another new noninvasive method, phonospirometry, estimates tracheal flow from tracheal breath sounds, obtained simply with a microphone placed on the neck.\textsuperscript{22} It appears to be at least as accurate as magnetometry and inductance plethysmography but less sensitive to chest wall distortions and changes in posture. Considerably more research will be necessary to determine its applicability to clinical situations such as sleep-disordered breathing and investigation of the sudden infant death syndrome.

**Pressure Measurements**

Esophageal pressure is an accurate measure of pleural pressure ($P_{pl}$). Esophageal pressure is equal to the pressure outside the esophagus, or $P_{pl}$ if there is no pressure difference across the esophageal wall. This is generally true if the esophagus is not distended by the pressure-measuring probe. For details concerning esophageal pressure measurements, see Baydur and colleagues\textsuperscript{23} (see also Chapter 55, “Esophageal Pressure Measurement”).

From the measurement of the static pressure–volume curve of the lung, which defines $P_A$ as a function of lung volume, and the dynamic pressure–volume curve, which encircles the static curve over the tidal volume range, one can obtain an approximate measure of $P_A$ as the difference between the static and the dynamic pressures at the same lung volume as shown in Figure 4-12.

An accurate measurement of $P_A$ in intact humans requires the use of whole body plethysmography. In excised lungs or open-chested experimental animals, it can be measured directly with capsules glued on the surface of the visceral pleura; the pleura contain holes, so that the capsule connects directly with the subpleural alveoli.

The principle of measuring $P_A$ from whole body plethysmography is most easily understood when one considers what happens when one rebreathes while sitting inside a constant-volume box. Assuming isothermal conditions and negligible humidification of inspired air (conditions that are satisfactorily met during panting), box pressure can only change to the extent that there is compression and expansion of alveolar gas. In a constant-volume plethysmograph, compression of alveolar gas requires expansion of gas within the box and thus a fall in box pressure. In order to find how much expansion is required to explain a given change in box pressure, a calibration procedure is performed in which a known volume of gas is introduced into and removed from the box with a syringe, and the resulting pressure changes are measured. Then box pressure and pressure at the mouth are measured while the subject pants against a closed airway. From Boyle’s law, the product of box pressure and box volume change (calculated from the calibration procedure) equals the product of mouth pressure (equal to alveolar pressure because no air is flowing) and lung gas volume. The last is the only unknown. This is the basis of measurement of absolute thoracic gas volume by whole body plethysmography. However, this measurement also serves to calibrate the relationship between box pressure, $P_A$, and the degree of alveolar gas compression and expansion. Subsequently, the subject rebreathes to and from the box by panting through a pneumotachygraph while box pressure is measured, the magnitude of alveolar gas compression and expansion is calculated, and, because absolute thoracic gas volume is known, $P_A$ is derived. The ratio between $P_A$ and the measured flow then provides $R_{aw}$.

**Relationship between Lung Mechanics and Ventilation Distribution**

**Time Constants**

Up to this point, I have considered the lung as a single tube representing the conducting airways and a single alveolus representing the millions of gas-exchanging airspaces making up the lung parenchyma. This model cannot be applied to the distribution of ventilation to multiple airspaces arranged in parallel. Let us pose the question: what determines how fast such a lung will fill when transpulmonary pressure is increased? Imagine a step square wave increase in transpulmonary pressure $\Delta P_L$. Neglecting inertia, at the instant this pressure is applied to the lung, $P_{fr}$ will equal $\Delta P_L$, so that:

$$\Delta P_L = P_{fr} = R_{aw} V'$$

Once the lung has completely filled, flow will cease, $P_{fr}$ will equal zero, and $\Delta P_L$ will equal $\Delta P_{el}$, so that:

$$\Delta P_L = \Delta P_{el} = \Delta V/C_L$$

and

$$R_{aw} V' = \Delta V/C_L$$
Cross-multiplying:

\[ R_{aw} C_L = \text{time} \]

The product of airway resistance and lung compliance has the units of time, and its value is the lung's time constant. The time constant is the parameter that determines how rapidly a lung will fill when \( P_L \) increases.\(^{24}\) What it states is actually rather obvious. As airway resistance increases and flow decreases at a given \( P_L \), it takes longer and longer to fill the lungs, and as compliance increases at a given flow, it takes longer to inflate the lung because it requires more volume to do so for a given \( \Delta P_{el} \). When both increase, the effects are more than additive; they are multiplicative.

However, the lungs have many parallel airspaces, each with its own compliance and flow resistance. Therefore, each parallel airspace, whether or not one is considering a single acinus, lobule, segment, or lobe, has its own time constant. If these are markedly different one from another, as occurs in some diseases, then some units will lag behind their neighbors. The fast units will fill and start to empty before the slow units have finished filling.\(^{24}\) Thus, part of the latter's inspired volume will be alveolar gas that their neighbors are expiring. Furthermore, because slow units will not have the time to fill completely before they start emptying, their tidal volume will fall, so that the fast units receive a larger fraction of the total tidal volume. This situation becomes progressively worse as breathing frequency increases and the respiratory cycle time progressively decreases relative to the time constants.\(^{24}\) This would be an unfortunate way to breathe, and it does not normally occur. What, then, is the condition for each of the parallel airspaces to fill and empty in synchrony with all its neighbors?

For this to occur at all breathing frequencies, it is necessary for all the time constants of all similar-sized parallel airspaces, large or small, to be equal.\(^{24}\) Such a constraint is difficult to achieve. The pathways to perihilar airspaces are much shorter than those to the base of the lung posteriorly. Owing to the gravity-determined gradient in pleural pressure, both the resistance to the flow of air and the compliance of airspaces are less in superior lung regions than in dependent ones. Presumably, the time constants of parallel airspaces are not all equal, and they do not have to be for the airspaces in the lung to fill and empty synchronously at physiologic breathing frequencies. As long as the time constants are short relative to the respiratory cycle time, there can be inequality of time constants.\(^{5}\)

Direct measurements of intrabronchial pressure have shown that in normal lungs most of the resistance to airflow is in the large central airways, and very little resistance is offered by the peripheral airways.\(^{3,25}\) The resistance common to parallel airspaces, namely the central airways for airspaces distal to the peripheral airways, plays no role in generating asynchrony among these peripheral units. Thus, the pertinent resistances that make up the time constants are the resistances of the peripheral airways. Because these are small, the time constants are small, on the order of 0.02 to 0.04 seconds. These are about two orders of magnitude less than the respiratory cycle times of 2 to 4 seconds at physiologic breathing frequencies, which normally range from 15/min at rest to 30/min at maximal exercise. This allows for considerable inequality among the time constants of peripheral lung units with very little asynchrony or reduction in tidal volume of the slower units. However, even if time constant inequality were sufficient to lead to asynchrony, there are two powerful influences promoting synchrony in both normal and diseased lungs: interdependence among parallel lung units\(^{26}\) and collateral ventilation.\(^{27}\)

**Collateral Ventilation**

When airways become occluded, gas can enter into the subtended airspaces via collateral channels. In excised dog lungs, collateral ventilation is extremely rapid, providing normal tidal volumes to airspaces beyond completely obstructed airways at breathing frequencies as high as 1 Hz.\(^{28}\) A model of this situation is shown in Figure 4-13. The time taken for gas to flow from unobstructed airspaces into obstructed ones via collateral channels is given by the time constant for collateral ventilation \( (T_{col}) \), or the product of the flow resistance of the collateral channels \( (R_{col}) \) and the compliance of the collaterally ventilated space \( (C_{col}) \). The fact that collateral channels deliver a normal tidal volume to airspaces beyond completely obstructed airspaces at a breathing frequency of 1 Hz indicates that \( T_{col} \) in excised dog lungs must be considerably less than 1 second. This has been experimentally verified.\(^{27}\)

![FIGURE 4-13 Two-compartment lung model illustrating collateral ventilation in the presence of complete airway obstruction to one compartment. Inspired air follows the route shown by the arrow and exchanges gas in the unobstructed airspace before entering the collaterally ventilated airspace, which receives alveolar gas. The time required to ventilate the obstructed airspace is determined by the time constant for collateral ventilation, which is the product of the resistance of the channels connecting the two compartments and the effective compliance of the collaterally ventilated space. For further explanation see text.](image-url)
One can measure $R_{\text{col}}$ by wedging a catheter in a bronchus, passing air through it at a known constant rate ($V_{\text{col}}$), and measuring the pressure at the catheter tip. If the flow is suddenly turned off, the pressure decays in a quasiexponential way. In most studies there is no sudden pressure drop, indicating that the resistance between the catheter tip and the alveoli beyond is negligible at the flow rate used. Thus, the pressure producing collateral flow ($P_{\text{col}}$) is given by the pressure difference between the catheter tip and alveolar pressure in the rest of the lung: $R_{\text{col}} = P_{\text{col}}/V_{\text{col}}$. The quasiexponential fall in pressure at the catheter tip when flow is suddenly switched off allows the measurement of $T_{\text{col}}$ as the time needed for the pressure to fall by 63% of its initial value. Dividing $T_{\text{col}}$ by $R_{\text{col}}$ gives $C_{\text{col}}$. $C_{\text{col}}$ measured in this way is considerably less than predicted by the estimated amount of lung tissue beyond the obstructed airways. The explanation for this is given below. For the present, the essential message is that the low value of $C_{\text{col}}$ is one of the major reasons why $T_{\text{col}}$ is surprisingly short.

The time constant for collateral ventilation depends on a variety of variables, including species, lung volume, the size of the airway obstructed, oxygen and carbon dioxide concentrations in the airways, and airway smooth muscle tone in the collateral channels. The lungs of large animals such as horses, cattle, and swine are completely lobulated. Because each lobule is completely separated from its neighbors by connective tissue, there is no collateral ventilation between lobules. The lungs of smaller animals such as dogs, cats, and rabbits are nonlobulated and have extensive collateral ventilation. Human lungs lie between these extremes. They are partially lobulated, so that collateral ventilation occurs between lobules but is considerably slower than in nonlobulated lungs. Although, so far as I am aware, no direct comparisons of $T_{\text{col}}$ have been made in lungs in living animals and excised lungs, the literature strongly suggests that $T_{\text{col}}$ is substantially longer in living lungs in situ than after they are excised. The reasons for this are not known.

$T_{\text{col}}$ is highly dependent on lung distending pressure and volume, more so even than airflow resistance. Furthermore, the greater the volume of lung beyond the obstructed airway, the longer is $T_{\text{col}}$. Thus, it takes longer to collaterally ventilate a part of the lung beyond an obstructed large airway than an obstructed small airway. Presumably, this reflects the external surface area/volume ratio of the collaterally ventilated space. The surface area available for collateral ventilation should be a major determinant of $R_{\text{col}}$ because it should determine the number of parallel collateral channels entering the obstructed units. As the surface area/volume ratio increases as the volume of the space decreases, it is to be expected that $T_{\text{col}}$ will be less with small airway occlusion than with large airway occlusion. However, with increases in lung volume, the surface area/volume ratio decreases. Thus, it seems likely that the caliber of collateral channels increases considerably more than is necessary to offset the decrease in surface area/volume ratio.

The collateral channels are probably not the pores of Kohn but are more likely to be the canals of Lambert and alveolar ducts that extend between lobules and acini. Evidently, they are lined with smooth muscle because $R_{\text{col}}$ is sensitive to both smooth muscle agonists and antagonists as well as oxygen and carbon dioxide concentrations.

**INTERDEPENDENCE**

Transpulmonary pressure or the pressure difference between the mouth and pleural space is somehow transmitted to all the airspaces and airways completely surrounded by lung tissue because in healthy lungs all alveoli expand and contract in synchrony with changes in transpulmonary pressure. This pressure is transmitted deep within lung tissue by tension transmitted by stretched alveolar walls to neighboring alveoli. At the pleural surface, the pressure applied to the visceral pleura by the attached alveolar walls is the sum of the forces transmitted by each alveolar wall divided by the surface area of the pleura over which they act, that is, $\Sigma F/A$. The same ratio defines the pressure applied to the external surface of any structure or group of structures completely surrounded by lung tissue. To the extent that the lung is isotropic, this ratio should be the same throughout the lung. The pressure applied at the pleural surface is counterbalanced by $P_{\text{pl}}$, which keeps the lung applied to the chest wall and diaphragm, so that $\Sigma F/A = -P_{\text{pl}}$. Thus, if $\Sigma F/A$ equals $-P_{\text{pl}}$ and is the same throughout the lung, $P_{\text{pl}}$ is applied to the outer surface of all intrapulmonary structures, whether they are blood vessels, airways, acini, or lobules. This appears to be very nearly true.

However, as discussed elsewhere in this book (see Chapter 14, “Ventilation Distribution”), there is a gravity-determined gradient in $P_{\text{pl}}$. Thus, within any given horizontal slice of healthy lung tissue, all airspaces, bronchi, bronchioles, and blood vessels are distended by very nearly the same transpulmonary pressure. Any normal variation in transpulmonary pressure is essentially in the vertical direction from top to bottom.

As the lung expands, both $\Sigma F$ and $A$ increase. But because $P_{\text{pl}}$ becomes more negative, $\Sigma F$ must increase more than $A$. Now imagine what happens if one group of airspaces becomes smaller relative to its neighbors. Under these circumstances, its surface area decreases while the alveolar walls attached to its surface are stretched: $\Sigma F/A$ increases owing both to an increase in the numerator and a decrease in the denominator. Conversely, if the airspaces expand relative to their neighbors, $\Sigma F$ decreases while $A$ increases. The interdependence of lung parenchyma tends to conserve the size of all structures within the parenchyma by increasing or decreasing the local distending pressure to maintain the homogeneity of lung parenchyma.

**SYNCHRONY OF HEALTHY LUNGS**

In healthy lungs, all alveoli expand and contract in near synchrony at physiologic breathing frequencies. This is known because, as discussed above, dynamic lung compliance is the same as static lung compliance and does not change with breathing frequency even in the presence of moderate time constant inequalities.

In the presence of more substantial time constant inequalities, the filling and emptying of units with long time
constants will be delayed. However, any delay will make these units smaller than their neighbors on inflation and larger on deflation, immediately bringing into play forces of interdependence. These forces will make the alveolar pressures in the delayed airspaces more negative on inflation and more positive on deflation than in the rest of the lung. This, in turn, will increase the flow through the airways serving the delayed spaces and create a flow across the collateral channels. The collateral flow will be determined by the difference in alveolar pressure between the normal and the delayed airspaces and the resistance to collateral flow. The increased negativity of alveolar pressure in the collaterally ventilated space due to interdependence decreases the time needed for collateral ventilation to take place and explains the decrease in measured $C_{\text{col}}$. Interdependence acts to make the compliance of the collaterally ventilated space seem less than it really is. Thus, the low value of $C_{\text{col}}$ is really an “effective” compliance resulting from interdependence of lung tissue. When time constant inequalities are such that delays occur, interdependence and collateral ventilation combine to act in concert to minimize phase lags in an attempt to maintain nearly synchronous filling and emptying of all alveoli.

**Effects of Airways Obstruction on Ventilation Distribution**

The conservative mechanisms that maintain the normal synchrony fail in disease. If the peripheral airways only comprise 10% of airways resistance or ~0.1 cm H2O/L/s, compared to central airways with a resistance of ~0.9 cm H2O/L/s, and half of them become blocked, peripheral airway resistance will double to 0.2 cm H2O/L/s. The resistance of central airways, where no structural changes have occurred, will remain the same at 0.9 cm H2O/L/s. Total resistance, which is the sum of the two, will increase from 1.0 to 1.1 cm H2O/L/s, as illustrated in Figure 4-14. This change is within the error of measurement. The obstruction is therefore difficult to detect by measuring either maximal expiratory flows or airway resistance. Nevertheless, the pathophysiologic process is severe because the airways to half of the gas-exchanging region of the lung are completely blocked. For this reason, the peripheral airways are called the lung's quiet zone because considerable disease may be present within them with only minimal effects on the usual tests of lung function. How can these structural alterations be detected by tests of lung function?

Figure 4-13 illustrates this problem. It can be seen that the airspaces beyond the obstruction can receive gas only from the unobstructed airspace where gas exchange has already occurred. In the case of the excised dog lobes discussed above, the measured pulmonary resistance was only minimally increased as a result of small beads obstructing about half of the peripheral airways. There was no change in vital capacity or the static pressure–volume curves, and dynamic compliance did not change with frequency. Yet all fresh air breathed in had to enter the unobstructed airspaces before traversing the collateral channels and entering into obstructed ones. It is unlikely that the obstructed airspace will receive any fresh gas. It will be ventilated by gas that has already exchanged oxygen and carbon dioxide. The distribution of inspired gas should be markedly abnormal.

When one considers the possibility that there could be a phase lag between the two airspaces shown in Figure 4-13, it is evident that if $T_{\text{col}}$ is finite the obstructed airspace must lag behind the unobstructed one because it takes time for gas to cross the collateral channels and fill the obstructed space. However, if respiratory cycle time is long compared to $T_{\text{col}}$, the phase lag will be small; the obstructed units could have a normal tidal volume, but an alveolar ventilation that approaches zero. The tidal volume, and alveolar ventilation of the unobstructed alveoli will be twice normal, but a volume of gas equal to half the tidal volume will escape across the collateral channels, and the alveoli will not be overdistended. The ventilation/perfusion ratio of the unobstructed units should be abnormally high and the obstructed units abnormally low, resulting in a broad and abnormal distribution of these ratios. Thus, one would predict that airways obstruction in the lung's quiet zone should lead to measurable abnormalities of gas exchange and ventilation distribution.

Finally, if $T_{\text{col}}$ is higher than in dogs, as it is in humans, one would predict that the obstructed airspaces would lag behind the unobstructed ones and that the lag would become progressively worse as $T_{\text{col}}$ became a progressively greater fraction of respiratory cycle time as breathing frequency increased. Accompanying the phase lag, there would be insufficient time for a normal tidal volume to cross the collateral channels. Whereas the total tidal volume might remain unchanged, the unobstructed units would become progressively overdistended, and the obstructed units progressively underdistended, as breathing frequency increased. An increased tidal volume of some airspaces requires an increased swing in $P_{\text{al}}$. However, the increase in the elastic recoil pressure swings would not be accompanied by an increased total tidal volume, so dynamic compliance would decrease, and this decrease should be progressive with increased breathing frequency.

All of these predictions have been confirmed. Dogs with blocked airways have abnormalities in the distribution of inspired gas and gas exchange. Among smokers whose routine lung function tests are normal, a substantial percentage have abnormal gas mixing in the lung, abnormalities of gas exchange, and frequency dependence of compliance. The combination of a normal static
pressure–volume curve and pulmonary resistance with abnormal ventilation distribution, gas exchange and frequency dependence of compliance indicates peripheral airway obstruction. There are claims in the literature that abnormally low maximal expiratory flows at low lung volumes are also diagnostic of small airway obstruction, but there is no evidence that this is so, and there are cogent reasons to believe that changes in the lung's elastic properties could account for this abnormality.

In more advanced disease, when the forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) become abnormal, all these abnormalities become more pronounced. In addition, the alveolar destruction caused by COPD increases lung compliance where alveolar destruction is present, leaving other more normal regions relatively unaffected. During a slow inspiration, inspired gas should be preferentially distributed to the most compliant (i.e., the most diseased) regions. However, as illustrated in Figure 4-15, because these regions have a high compliance as well as obstructed small airways serving them, they will be the units with the longest time constants. As a result, at rapid breathing frequencies they will become less well ventilated compared to their less diseased neighbors. This leads to major problems in the interpretation of ventilation and ventilation–perfusion scanning with the use of technetium or other contrast agents. Breathing frequency is rarely controlled in these tests. The situation is further complicated because a significant percentage of smokers have subclinical emphysema that is not suspected during life.

The alveolar destruction of COPD also decreases the resistance to collateral ventilation, so that it can become less than airways resistance. In this manner, collateral channels can become major ventilatory pathways in emphysema. This has led to the suggestion that the mechanics of breathing in patients with emphysema might be improved if they breathed through spiracles or tubes entering the lungs directly through the rib cage. Preliminary results in excised human emphysematous lungs removed during transplant surgery show that substantial volumes of trapped gas that cannot be removed through the airways can be removed via spiracles (unpublished data). This increases the vital capacity while decreasing the RV/TLC ratio. In addition, these preliminary studies indicate that the distribution of inspired gas through the spiracles is as good as, and sometimes better than, the distribution through the airways. Cooper has tried this procedure in a few patients with end-stage COPD, although he brilliantly inserted the spiracle by making a hole in an airway wall directly into the lung parenchyma instead of through the rib cage (J. Cooper, personal communication). This converts a major surgical operation into a relatively minor therapeutic bronchoscopic procedure. To date, the results are encouraging, but it must be stressed that this experimental therapy is very much in the earliest stages of development. It will be several years, if ever, before it becomes an established therapy for emphysema.

REFERENCES
