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Physiological Basis and Interpretation of Indices of Pulmonary Mechanics

by Jeffrey M. Drazen*

Tests of pulmonary mechanical function provide information about the state of the lungs, both airways and parenchyma. This information can be extracted from measurements made in experimental animals, especially the combined determination of pulmonary resistance and dynamic compliance. This report discusses the rationale upon which effects of an intervention on the lung periphery can be distinguished from those on more central airways. Further, practical considerations involved in making these measurements are discussed.

Pulmonary toxicology involves the study of how certain substances may alter the structure or function of the lung. Altered function may occur at the cellular level, tissue level, organ level or some combination of levels. The utility of pulmonary function testing is that one can, to some extent, infer the type and site of change induced by a certain stimulus, through evaluation of one or more tests. This paper reviews certain aspects of the normal physiology of pulmonary function and discusses selected aspects of performing certain tests of pulmonary function and the interpretation of mechanical function testing with appropriate selected examples.

Pulmonary Function Testing

The function of the respiratory system is to provide for adequate oxygenation of arterial blood and carbon dioxide elimination from venous blood. This functional goal is achieved by matching the ventilatory action of the lungs with the right ventricular cardiac output in an appropriate fashion. The mechanisms which account for this ventilation–perfusion matching in health and how they may be altered in disease have been the subject of extensive reviews (*1*) and are beyond the scope of this paper.

The main concern of this paper is the mechanical aspects of the ventilatory function of the lung. Briefly stated, the lung is ventilated to provide for expulsion of alveolar carbon dioxide and replenishment of alveolar oxygen. This process requires both the bulk flow of gas to and from the respiratory zone and the diffusive mixing of inspired and respired gases at an appropriate level within the airway. Tests of pulmonary ventilatory function have been devised to examine almost every aspect of this process (*2*). The main concern will be the pressures and flows that result in the bulk flow of gas within the lung. These tests are thus subclassified as tests of pulmonary mechanical function, in the sense that each examines certain aspects of the relationships between pressure, airflow, and air volume within the lung. Each of these tests can be performed on both animals and man; however, some tests are more easily performed in one setting than another. For example, tests involving forced expiratory maneuvers are more easily performed by a cooperative volunteer human subject than in animals, while other tests such as the measurement of pulmonary resistance and compliance are easily and repeatedly performed in animals. Since the evaluation of the toxic effects of inhaled substances are most commonly performed in experimental animals, the measurement of resistance and compliance will be considered in detail.

Normal Pulmonary Mechanical Function

Spontaneous ventilation is the combination of an active inspiratory phase resulting from muscular tension of the diaphragm and a predominantly passive expiratory phase. During inspiration muscular tension in the diaphragm creates a pleural pressure which is substantially subatmospheric (Fig. 1). This, in turn, results in a subatmospheric alveolar pressure and the creation of an appropriate pressure gradient for inspiratory airflow to occur. Inspiratory flow continues until enough air has entered the lungs to return the alveolar pressure to atmospheric; this point is end inspiration.

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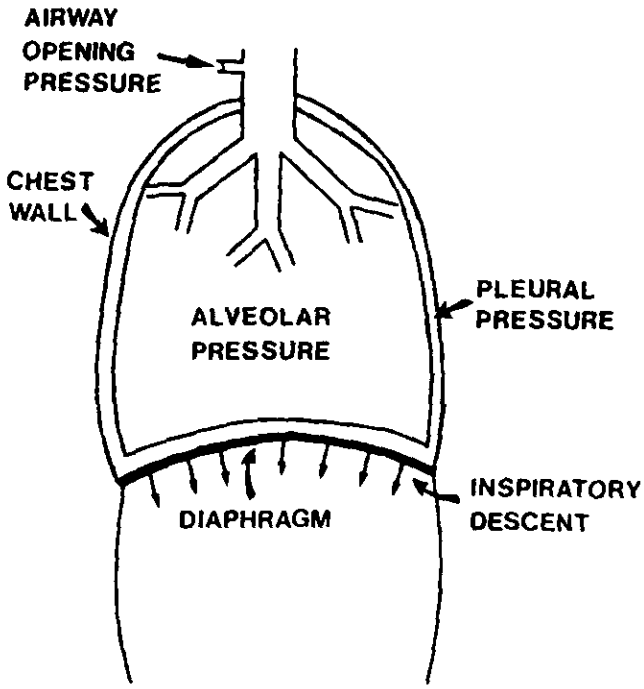

FIGURE 1. Schematic drawing of respiratory system showing the locations at which various pressures can be measured.

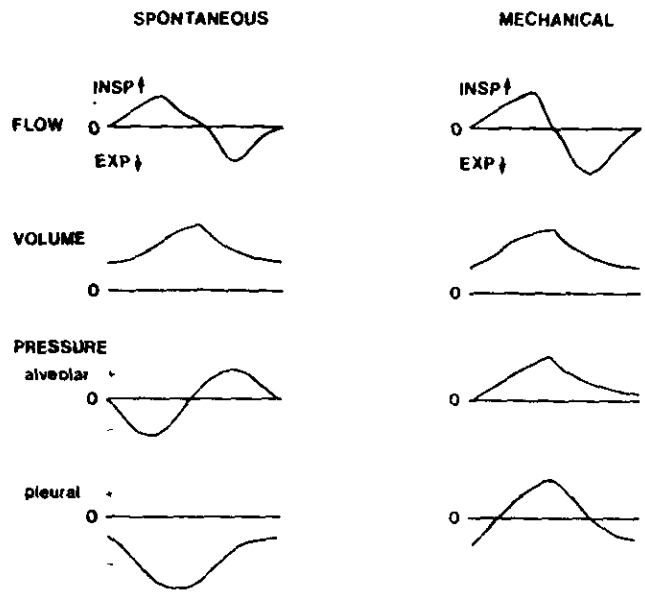

FIGURE 2. Schematic drawings of the volume, flow and pressure events during spontaneous or mechanical ventilation.

At this time (during spontaneous nonmaximal ventilation), inspiratory muscle activity ceases, a positive alveolar pressure is created by the elastic recoil of the lungs and expiratory flow ensues. Expiratory flow will continue until the inward recoil of the lung is balanced by the outward recoil of the chest wall, at which time alveolar pressure will return to atmospheric and a respiratory cycle will be completed. The relationships between the various pressures, volumes and flows are shown in Figure 2. Note specifically that alveolar pressure is subatmospheric during inspiration and supra-atmospheric during expiration, while pleural pressure remains subatmospheric throughout the respiratory cycle. In addition, note that the difference between alveolar and atmospheric pressure represents the pressure difference required to overcome the resistance to airflow of the airways, while the difference between atmospheric and pleural pressure reflects the combination of the pressure required to overcome resistance to airflow in the lung and the pressure required to inflate the lung.

Stated mathematically, we have:

$$P_{TP} = \dot{V}R_1 + V/C_1 \quad (1)$$

and

$$P_{alv} = \dot{V}R_{aw} \quad (2)$$

where P_{TP} is the difference between airway opening pressure and pleural pressure; P_{alv} is the difference between alveolar and airway opening pressure; $\dot{V}$ = airway airflow (volume/time); V = lung volume; R_1 = pulmonary resistance (pressure/volume/time); R_{aw} = airway resistance (pressure/volume/time); and C_1 = pulmonary compliance.

Equation (1) applies only at sufficiently slow respiratory frequencies that accelerative losses can be considered negligible. Equations (1) and (2) contain two terms, resistance R and compliance C, which describe the relationships between pressure and flow or pressure and volume and, as such, are constants that describe the mechanical behavior of the system. As will be outlined below, the utility of these constants is that they reflect in part the physiological state of the respiratory system. It is important to point out that airway resistance and pulmonary resistance are not equivalent. Pulmonary resistance includes both the airway resistance and any additional resistive pressure loss in phase with flow across the lung.

Note that P_{TP}, the pressure difference between the airway opening and pleural pressure, is always positive (during spontaneous respiration). This value can be derived by the subtraction of the substantially negative pleural pressure from airway opening pressure which is usually close to atmospheric. The constant negativity of pleural pressure can be easily demonstrated by violating the integrity of the chest wall which results in the flow of air into the pleural space, down the appropriate pressure gradient, and the creation of a pneumothorax.

During mechanical ventilation, via an endotracheal tube or tracheal cannula, in contrast to spontaneous ventilation, the pressure to overcome the resistive and elastic load of the lung is supplied by an external source—the mechanical ventilator. During inspiration, airway opening pressure is greater than alveolar pressure, resulting in airflow into the lung. During expiration a valve is opened which allows the lung to

empty passively into the atmosphere. Thus alveolar pressure is always supra-atmospheric and pleural pressure alternates between sub- and supra-atmospheric, as shown in Figure 2.

As mentioned above, the pulmonary mechanical indices of resistance and compliance are mechanical constants which are derived to describe the relationships between pressure and flow in the respiratory system (*2*). They can be measured during spontaneous or mechanical ventilation in a given experimental setting. We will now consider how they are determined experimentally based on the above analysis of pressure–volume–flow events within the respiratory system.

Pulmonary Compliance

Experimental Determination

Compliance is the mechanical constant which relates pressure and volume. As such, its experimental determination involves the simultaneous measurement of both pressure and volume. If one performs an experiment whereby small increments of volume are injected into or withdrawn from the lung and the pressure and volume measured at each point, a pressure–volume diagram can then be recorded. In practice this is usually done by the slow inflation and deflation of the lungs such that flow ($\dot{V}$) in Equation (1) can be considered to be zero. An idealized pressure volume diagram for the lung is shown in Figure 3. Note that the pressure at a given volume is usually greater during inflation than deflation. Although the mechanisms thought to be responsible for this behavior (known as pressure–volume hysteresis) are beyond the scope of this discussion (*3*), it is important to recognize and appreciate that the measured slope of this line (i.e., compliance) will depend on lung inflation history.

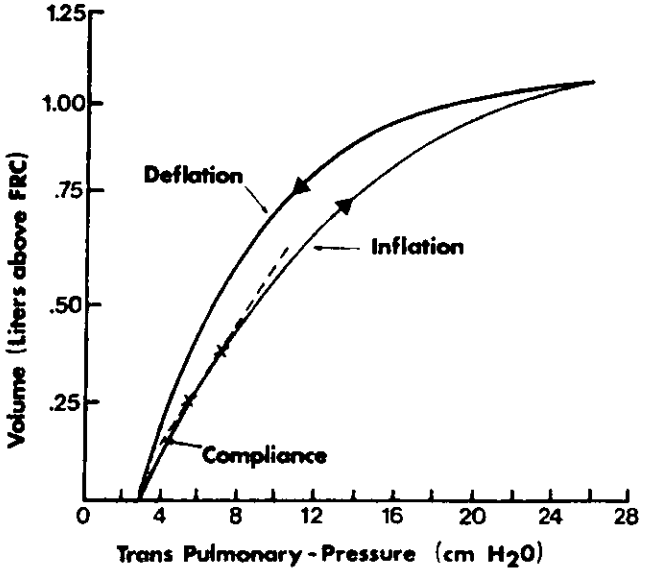

FIGURE 3. Idealized pressure–volume curve for a dog lung inflated from and deflated to functional residual capacity (FRC). Compliance is the slope as indicated. Reproduced from Drazen (*15*) with permission of author and publisher.

Specifically, compliance is defined as the ratio between the volume and pressure differences at two distinct points on the pressure–volume diagram. As such, the computed compliance will differ depending upon the volume (or pressure) range over which it is computed, the flow direction (inspiratory or expiratory) and the volume history immediately before the determination. Note in the example diagram that the relationship between pressure and volume is nearly linear in the mid-volume range during deflation after full inflation. Because this nearly linear relationship is seen in many species it is a common practice to report a static (or quasi-static) compliance during deflation in the mid-lung volume range. In this range, where the pressure–volume relationship is approximately linear, compliance will depend less on the exact pressure and volume at which it is measured and thus be subject to considerably less experimental error.

Compliance may be measured during tidal breathing. In this case the compliance is determined at the two brief instances in the respiratory cycle where flow is zero: full inspiration and full expiration. Specifically, volume and pressure are measured during a tidal cycle and the ratio of volume change to the pressure difference between full inspiration and inspiration determined. This ratio is the dynamic compliance or C_{dyn} and may differ from the static or quasi-static compliance for the reasons outlined below.

Physiologic Determinants of Compliance

Compliance is an index of the functional stiffness of the lung; compliance will decrease if the lung parenchyma becomes stiffer through such mechanisms as constriction of alveolar duct smooth muscle, acute cellular infiltration, alveolar capillary leak, or chronic fibrotic processes. In addition, airway closure, which is thought to occur predominantly in small airways, will also make the lung functionally stiffer by reducing the amount of parenchyma available to accept inspired gas. These alterations all represent changes in the small airways or parenchyma, thus making compliance a useful test to indicate changes in the periphery of the lung. However, measured compliance may also change without significant alterations in the small airways or parenchyma. This can happen if the lung volume at which compliance is measured is altered (Fig. 3). The effect of changes in small airway or parenchymal behavior on compliance is also influenced by the volume history prior to the measurements. For example, a decrease in compliance resulting from aerosol histamine may be substantially diminished by a single maximal inflation. However, as a group, these mechanisms (constriction of alveolar duct smooth muscle, alveolar

cellular infiltration or edema, airway closure, changes in lung volume, and volume history) affect both dynamic and static compliance.

Dynamic compliance can also decrease as a result of nonuniform constriction of distributing airways or by an increase in respiratory frequency in the presence of nonuniformities in the distributing airways. The mechanism which was originally proposed by Otis et al. (*4*) to explain this phenomenon is the inequality of time constants among various parallel pathways in the lung. The precise rationale has been detailed elsewhere (*4*) and will be only briefly reviewed here.

Consider the lung as a structure with two parallel pathways leading to two similar elastic structures. If the airways which lead to these structures are identical and if positive pressure is applied at the common pathway, then both structures will inflate synchronously

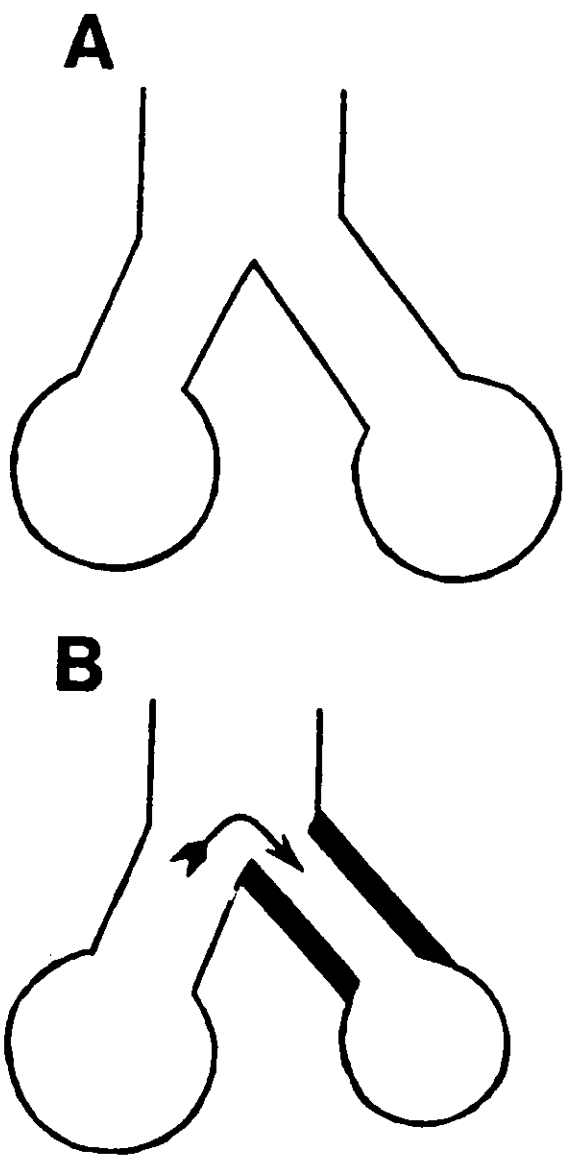

FIGURE 4. Unequal distribution of ventilation due to nonuniform narrowing of airways. See text for details.

(Fig. 4*A*). If, however, the pathway leading to one elastic element has a resistance much greater than the resistance in the pathway leading to the other element, then when airflow ceases at the common pathway; the elastic element served by the low resistance pathway will be overdistended compared to the elastic element served by the high resistance pathway (Fig. 4*B*). This will lead to a greater pressure drop across the entire system at end inspiration due to overdistention of the unit served by the low resistance pathway. In fact, at the instant of zero common pathway flow there would be some airflow from the overdistended unit to the underdistended unit. However, if the compliance of the entire system were to be calculated during dynamic cycling at a frequency such that this type of maldistribution occurred, the computed compliance would be low. This low compliance is simply due to the overdistention of some units and the underdistention of others and not to a change in the elastic properties of the parenchyma. Thus, a decrease in calculated C_{dyn} could result simply from an unequal distribution of resistances in pathways to normal alveoli. Such a mechanism can only be of importance during dynamic cycling, however, since during static maneuvers airway resistance does not effect airflow distribution.

On the basis of this analysis, it can be stated that if the lung volume over which compliance is measured, and the volume history and respiratory frequency are unchanged, alterations in compliance (whether static or dynamic) reflect changes in the distributing airways or the parenchyma. In contrast, static compliance alterations reflect changes in the parenchyma or airway closure exclusively.

Resistance

Measurement

The measurement of pulmonary resistance requires simultaneous determination of transpulmonary pressure, volume, and flow. There are two commonly employed techniques used to determine pulmonary resistance: one is the isovolume technique originally introduced by Neergard and Wirz (*5*) and applied by Amdur and Mead (*6*) for measurements in spontaneously breathing guinea pigs; the second technique is the technique of electrical subtraction, originally introduced by Mead and Whittenberger (*7*). The rationale behind each technique along with their relative advantages will now be reviewed.

In the isovolume technique, pulmonary resistance is determined as a mean of inspiratory and expiratory resistance. For example, from Equation (1) it is possible to compute C_1 by measuring P and V when $\dot{V}$ was zero. An analogous situation does not exist for R_1, as total lung volume is never zero under the usual circumstances *in vivo*. In the isovolume calculation, P and $\dot{V}$ are measured once during inspiration and at the same lung

volume during expiration in order to compute R_1. C_1 is assumed to be the same during inspiration (subscript "i") and expiration (subscript "e"). This is a reasonable assumption for tidal cycling. Thus:

$$P_i = V_i/C + \dot{V}_i R \quad (3)$$

and

$$P_e = V_e/C + \dot{V}_e R \quad (4)$$

if

$$V_i/C = V_e/C \quad (5)$$

then

$$R = (P_i - P_e)/\dot{V}_i - \dot{V}_e) \quad (6)$$

Simply stated, the effects of compliance on transpulmonary pressure are cancelled out by determining pressure and flow at points of equal lung volume. The resistance computed is an average inspiratory and expiratory resistance. In practical terms, computations of isovolume pulmonary resistance can be easily performed from strip chart recordings of pressure, volume, and flow, by dividing the pressure difference between inspiration and expiration by the flow difference (both are determined at mid tidal volume). The advantage of the technique is that it requires minimal equipment, and is rapidly and easily performed. The disadvantage of this approach is that differences in inspiratory or expiratory resistance cannot be determined with ease.

The second commonly used method for measuring pulmonary resistance is illustrated in Figure 5. It is based on Equation (1), which can be rearranged to yield Equation (7).

$$R_1 = (P - V/C_1)/\dot{V} \quad (7)$$

One can see, by inspection, that a plot of P–V/C_1 versus $\dot{V}$ will be a straight line, the slope of which is numerically equivalent to pulmonary resistance. Practically speaking, this method is easy to apply since electrical signals proportional to transpulmonary pressure and flow can be displayed on the X and Y axes of a cathode-ray oscilloscope. A signal proportional to volume change is then electrically subtracted from the total pressure signal until a closed "loop" is obtained. This occurs when the elastic component of P_{TP} is subtracted, leaving only the resistive component. The chord slope of this characteristic (between the point and the origin) is the pulmonary resistance (Fig. 5).

The advantage of this technique is that it allows separation of inspiratory and expiratory resistance and allows determination of resistance at a specific flow rate and lung volume. The disadvantage of this technique is that rapidly changing pulmonary resistance values may be hard to follow and record without special equipment (*8*).

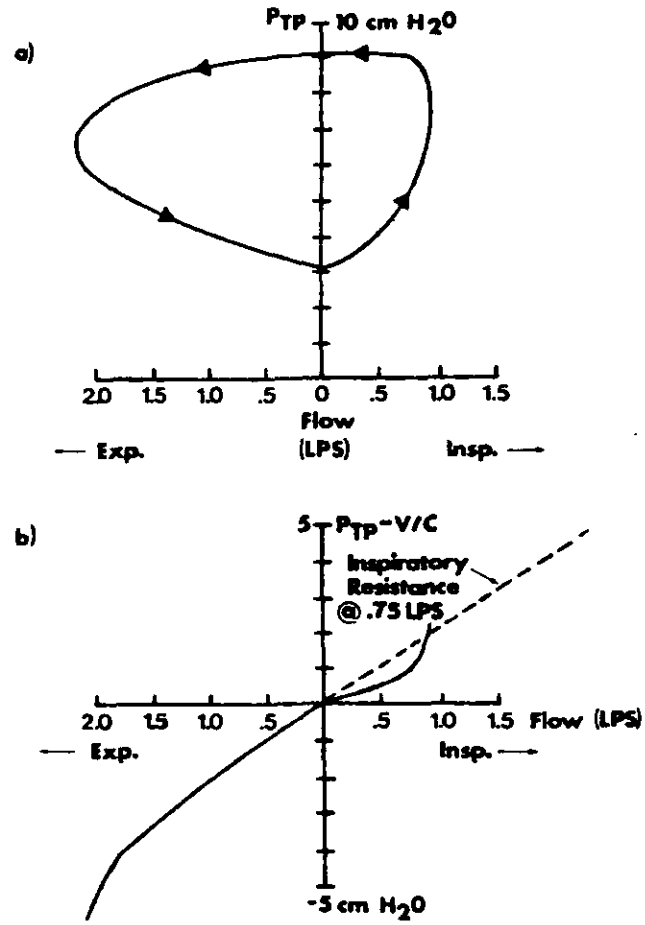

FIGURE 5. Plot of (*a*) idealized transpulmonary pressure–flow characteristic for a dog; (*b*) pressure–flow "loop" after flattening by using the technique of electrical subtraction. Interrupted line indicates inspiratory lung resistance at 0.75 L/sec. Reproduced from Drazen (*15*) with permission of author and publisher.

Physiologic Determinants of Resistance

Resistance to airflow is determined by airway size, flow direction and flow regime (*9*). Although all patent airways always have an influence on pulmonary resistance, the large airways (airways with a cross-sectional area greater than 1% of the tracheal cross section) account for the majority of the resistance to air flow. This results from the geometry of the lung, which is such that the aggregate cross section of more peripheral airways is much greater than that of the large airways. As air proceeds mouthward from the alveolus during expiration, the total cross-sectional area through which air must flow decreases over about four orders of magnitude (*10*). In the upper airway, trachea, and first few generations of major airways the cross-sectional area is smallest, and thus these structures represent over 90% of the resistance to airflow under normal circumstances. For this reason resistance is determined mostly by the central airways and is relatively insensitive to more peripheral changes in the lung. The caliber of the upper and central airways can be altered by primary airway events such as changing bronchomotor tone, by bronchial edema, or by the presence of increased amounts of mucous. Airway size is also influenced by degree of lung inflation. As lung volume increases the central airways are stretched both longitu-

dinally and radially, but the increase in diameter has more of an effect on resistance than the increase in length. As a result, lung resistance falls with an increase in lung volume (*11*). Other factors, such as airflow regime and flow direction, also play a role in determining pulmonary resistance, but the nature of these interactions is such that they are usually minor and can be easily controlled, as outlined below. Flow regime may be controlled by measuring resistance at some selected flow rate. The effects of flow direction on lung resistance may be controlled by exclusive use of inspiratory or expiratory flow resistance. If measurements of lung resistance are performed at the same lung volume and flow rate during inspiration or expiration, changes in pulmonary resistance mostly reflect alterations in the upper and central airways as detailed below.

Localization of Apparent Site of Airway Response by Determination of Resistance and Compliance

The utility of these measurements of pulmonary mechanics in toxicology is that one may be able to infer the predominant site of the airway response to an intervention through their use. Thus, one could localize the anatomic site of pulmonary response without the need for pathologic study. The rationale upon which this apparent localization is based and an example of its utility now follows:

As stated above, most of the resistance to airflow in the lung is in the upper and central airways. Therefore, an intervention which predominantly alters these airways will substantially alter pulmonary resistance. Suppose, for example, that 90% of the resistance to airflow is in the large airways, as defined above, and that in the control (pre-intervention) state that pulmonary resistance had a value of 1 unit. Thus, the large airways would contain 0.9 units of resistance and the peripheral airways 0.1 units of resistance. Now suppose that an intervention causes peripheral resistance to increase fourfold, from 0.1 to 0.4 units. In this case total resistance would increase from 1.0 to 1.3, or a 30% increase—an increase of modest magnitude that would be barely detectable above the variations in baseline resistance. In contrast, if the large airway resistance increased fourfold, total resistance would increase to 3.7 units, a total response of over a 300% increase, and a substantial response which could be easily detectable. If such a change in pulmonary resistance occurs without a change in pulmonary compliance, it is overwhelmingly likely that the predominant site of airway response was in the large airways.

If one applies this reasoning to that outlined above, one can easily see that a change in pulmonary compliance, if it occurs in the absence of a change in pulmonary resistance, represents a predominant site of action in more peripheral airways. If an isolated compliance response occurs, then one is able to interpret in this fashion changes in both static or dynamic compliance. If, however, one observes an alteration in both pulmonary resistance and dynamic pulmonary compliance, then one must make an additional determination, specifically static pulmonary compliance. If it is found that an increase in pulmonary resistance and decrease in dynamic compliance is accompanied by no change in static compliance, then one can infer that the large airways were involved in a process that was patchy or non-uniform in nature, thus altering dynamic but not static compliance. If both static and dynamic compliance are altered, along with pulmonary resistance, this suggests that the process resulting from the intervention was widespread and precise localization is difficult. The direction of changes resulting from these interventions is shown in Table 1.

Table 1. Uses of resistance and compliance to determine site of airway response.[a]

Site of response	R_1	C_{dyn}	C_{static}
Central-diffuse	Increased	No change	No change
Central-patchy	Increased	Decreased	No change
Widespread	Increased	Decreased	Decreased
Peripheral	No change	Decreased	Decreased

[a] Utilization of differential changes in pulmonary resistance and pulmonary compliance to localize sites of pulmonary response.

This analysis is not a new one, but rather was suggested in part by the work of Macklem and Mead (*12*) based on morphometric observations, most specifically those of Weibel (*10*). It has been applied to toxicological investigations previously, as illustrated below.

For example, Frank et al. (*13*) found that inhalation of SO_2 gas under controlled conditions in human subjects resulted in an increase in pulmonary resistance without a change in dynamic pulmonary compliance. This data could be interpreted to mean that the effects of SO_2 gas are predominantly on the more central airways. This supposition, based on pulmonary mechanical analysis, has been confirmed by histologic examination of the lungs of experimental animals exposed to SO_2 gas. For example, central airway lesions predominate over peripheral airway and parenchymal lesions in rats exposed to SO_2 gas (*14*).

In this review we have examined the factors that determine the pulmonary mechanical response to intervention as measured by changes in pulmonary resistance and dynamic lung compliance. These measurements, when made simultaneously, can yield useful information concerning the site and nature of pulmonary response to various interventions.

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