Effect of Lung Volume on Lung Resistance and Elasticance in Awake Subjects Measured during Sinusoidal Forcing

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Background: Although lung volume may be changed by certain procedures during anesthesia and mechanical ventilation, dependence of the dynamic mechanical properties of the lungs on lung volume are not clear. Based on studies in dogs, the authors hypothesized that changes in lung mechanics caused by anesthesia in healthy humans could be accounted for by immediate changes in lung volume and that lung resistance will not be decreased by positive end-expiratory airway pressure if tidal volume and respiratory frequency are in the normal range.

Methods: Lung resistance and dynamic lung elasticance were measured in six healthy, relaxed, seated subjects during sinusoidal volume oscillations at the mouth (5 mL/kg; 0.4 Hz) delivered at mean airway pressure from 9 to +25 cmH2O. Changes in lung volume from functional residual capacity were measured with inductance plethysmographic belts.

Results: Decreases in mean mean airway pressure that caused decreases in lung volume from functional residual capacity comparable to those typically observed during anesthesia were associated with significant increases in both dynamic lung elasticance and lung resistance. Increases in mean mean airway pressure that caused increases in lung volume from functional residual capacity did not increase lung resistance and increased dynamic lung elasticance only above about 15 cmH2O.

Conclusions: Increases in dynamic lung elasticance and lung resistance with anesthesia can be explained by the accompanying, acute decreases in lung volume, although other factors may be involved. Increasing lung volume by decreasing mean airway pressure with positive end-expiratory pressure will decrease lung resistance only if the original lung volume is low compared to awake, seated functional residual capacity. (Key words: Airway pressure. Compliance. Mechanics of breathing.)

It is important to understand the precise effects of varying mean lung volume on lung mechanical properties, i.e., elasticance and resistance. Decreases in functional residual capacity (FRC) commonly occur during the induction of anesthesia1 and as a consequence of changes in patient positioning.2 On the other hand, increases in FRC occur with application of positive end-expiratory pressure (PEEP). Although static elastic curves of the lung over the entire range of lung volume have been well described,3 these curves may not be applicable to dynamic situations such as during spontaneous or artificial ventilation. For example, the static curves indicate that the elasticance of the lung is constant as lung volume decreases below FRC. However, it has long been a common assumption† that lung elasticance (Ee) increases in patients if lung volume decreases to less than FRC, as may occur during anesthesia. Also, how PEEP affects lung mechanical properties is not well characterized.

Studies of dynamically determined Ee in humans4−7 found that elasticance is increased at low or high lung volumes. However, the lung volumes at which Ee begins to increase from minimal as volume is increased or decreased from FRC are not well defined. Our previous study in humans using physiologic frequencies and tidal volumes indicated that slight (about 200 mL) decreases in lung volume around FRC can increase Ee significantly.8 Other studies in humans have not controlled tidal volume and respiratory frequency as lung volume was changed. Because it has been shown that both of these factors affect Ee in excised lungs and that the effects depend on mean lung volume,9,10 the relationship between Ee and lung volume is not clear.

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Airway flow resistance decreases with increasing lung volume.11 However, the lung volume dependency of total lung resistance (Rt) is complex because it includes both airway flow and tissue contributions, and lung tissue resistance appears to increase at higher lung volume.9,12 Moreover, the relative contributions of the tissues and airway flow in determining Rt depend on the type of forcing used for measurement: airway flow resistance increases with increasing flow,13 whereas tissue resistance decreases with increasing frequency9,14,15 and, to a lesser extent, with increasing tidal volume.9,10 Although Rt, measured in different ways at various frequencies, has been shown to increase as lung volume decreases below FRC in humans,5,6,16,17 Rt has been reported to increase,6 decrease,5,16 or not change17 as lung volume increases above from FRC. None of these studies have kept frequency and tidal volume constant above FRC, and this could bias results if frequency and/or tidal volume change with lung volume. Thus, the behavior of Rt above FRC, e.g., when PEEP is applied, needs to be resolved.

Based on recent measurements we made in anesthetized, paralyzed dogs,18 we hypothesized that, in humans: (1) the changes in lung mechanics that accompany anesthesia could be due largely to the well known, acute, accompanying decreases in FRC; and (2) PEEP will not affect Rt if respiratory frequency and tidal volume are in the range of normal breathing. We systematically measured resistance and elastance of the lungs in awake human subjects during sinusoidal forcing (0.4 Hz) at a constant, physiologic tidal volume (about 500 mL) as mean airway pressure (Paw) was changed to as low or as high a level as could be tolerated comfortably. Unlike most studies, breathing pattern was constant as lung volume was changed. Results show the extent to which dynamically determined mechanics depend on lung volume in awake subjects, which has implications for anesthetized patients.

Methods

We studied six healthy, nonsmoking adult subjects after obtaining their informed consent and approval for the study from the University of Maryland Human Volunteers Committee. Table 1 lists the physical characteristics and pulmonary functions of each subject. Sinusoidal volume changes were delivered to the mouth from a piston pump driven by a linear motor. Airway flow was measured with a pneumotachograph (Fleisch #2) and a differential pressure transducer (Gelasto LCVR). Similar differential pressure transducers, with one port open to atmosphere, were used to measure Paw, 2.0 cm from the mouth end of a rubber mouthpiece and esophageal pressure (Poe) via a polyethylene catheter attached to a latex balloon. We inserted a 2.5-cm inner diameter plastic tube inside most of the length of the mouthpiece to prevent mechanical distortion; resistance of the measuring system was too small to be measured by our methods and was considered negligible. Placement of the balloon was checked in each subject in the following way with a method described by Baydur et al.19 Esophageal pressure and Paw were displayed X-Y with equal gains on an oscilloscope during spontaneous breathing efforts with occluded airways: the balloon was positioned so that changes in Poe and Paw during the efforts were equal. This test was repeated in each subject at FRC, near total lung capacity, and near residual volume. A fourth Gelesco LCVR transducer was used in differential mode to measure transpulmonary pressure, the difference between Paw and Poe. The Poe signal was also passed through a 0.1-Hz low-pass filter (Rockland, Series 2000) to provide continuous measurement of mean Poe.

Inductance plethysmographic belts (Respirtrace, Ambulatory Monitoring) placed around the rib cage and abdomen were used to estimate changes in lung volume from FRC caused by increases and decreases in mean Poe. For these measurements, the Respirtrace amplifier was used in DC mode, and the gains of the rib cage and abdominal signals were set equal by isovolume calibration.20 We found that, in a given subject, this isovolume calibration did not change as mean lung volume was varied from lowest to highest levels achievable. Although the rib cage and abdominal signals from the belts tends to drift in DC mode, we adjusted the signals before each measurement of lung mechan-

Table 1. Physical Characteristics and Pulmonary Functions of the Subjects

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Forced Vital Capacity (L)</th>
<th>Forced Expiratory Volume-1 s (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>32</td>
<td>185</td>
<td>84</td>
<td>6.2 (109)</td>
<td>5.4 (119)</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>40</td>
<td>178</td>
<td>97</td>
<td>5.6 (112)</td>
<td>4.8 (118)</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>29</td>
<td>170</td>
<td>58</td>
<td>3.4 (85)</td>
<td>3.3 (102)</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>31</td>
<td>173</td>
<td>77</td>
<td>5.3 (109)</td>
<td>4.6 (118)</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>30</td>
<td>185</td>
<td>86</td>
<td>7.1 (124)</td>
<td>6.6 (142)</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>49</td>
<td>180</td>
<td>82</td>
<td>4.6 (91)</td>
<td>3.9 (97)</td>
</tr>
</tbody>
</table>

Percent predicted values in parenthesis.
ics, adjusting FRC to equal zero voltage. Only occasional, minor adjustments were needed to ensure that the signals were repeatedly at zero at FRC. Thus, the summed signal from the belts was a reasonable approximation for changes in mean lung volume in the relatively brief periods of respiratory mechanics measurements described below.

Each subject sat in a chair, reclined slightly from vertical to facilitate relaxation of the trunk muscles and to maintain a constant body position. After a few deep breaths, including one to total lung capacity, the subjects exhaled passively to FRC by completely relaxing their respiratory muscles. They then closed their mouths around the mouthpiece, and the pump was started. The subjects’ cheeks were tightly compressed by hand to remove the variable contribution of the tissue of the cheeks to the measurements. The pump delivered a sequence of breaths at 0.4 Hz and a constant tidal volume (5 mL/kg). A flow of oxygen was added to a “T” connection close to the pump side of the pneumotachograph, and a vacuum source was used to draw out the flow from an opening in the housing of the piston. By adjusting the flows in and out of the pump–subject system, we could adjust mean $P_{aw}$ at the mouth at desired positive and negative, steady-state levels without affecting the measured flow to the lungs caused by the imposed oscillations. This arrangement also flushed the pump–subject system to replenish the oxygen and minimize carbon dioxide rebreathing. When mean $P_{aw}$ was constant, three consecutive breaths were measured by computer; typically, the subject was connected to the pump for about 40 s. The subject was disconnected from the mouthpiece and allowed to sit quietly for a few minutes. Then, we repeated measurements at different mean $P_{aw}$ in a pseudorandom order. In one subject, we repeated the measurements on separate days to assess the reproducibility of the methods.

**Data Analysis**

The three measured breaths (sampling rate 100/cycle) at each mean $P_{aw}$ were computer-averaged and analyzed by discrete Fourier transform at the fundamental (i.e., respiratory) frequency only, to give $R_t$ and $E_t$. Elastance was calculated by multiplying the imaginary part of each impedance by $-2\pi f$, thereby containing effects contributed by inertia. These effects should be negligible at the frequency used.21,22

Each elastance and resistance measured in a subject was normalized to the corresponding value at the mean $P_{aw}$ that most likely would occur during normal spontaneous breathing, i.e., 5 cmH$_2$O. For each subject, these normalized data were averaged into 1-cmH$_2$O bins of mean $P_{aw}$. Then, data from all subjects were averaged. Using stepwise multiple regression, we found that the relationships of average elastance and average resistance to mean $P_{aw}$ closely followed the third-order polynomial form. Polynomial regression was used to characterize the effects of mean $P_{aw}$ on the average change in end-expiratory lung volume from FRC, normalized to each subject’s vital capacity (VC).

**Results**

**Lung Mechanics**

In all subjects, $E_t$ increased at low or high mean $P_{aw}$, although the range in which $E_t$ was minimum varied (fig. 1). In the average data (fig. 2, upper curve) normalized to values obtained at 5 cmH$_2$O mean $P_{aw}$ (average $E_t$ 4.94 cmH$_2$O/L $\pm$ 0.40 SE), the relationship between normalized $E_t$ ($E_t/E_{t\text{control}}$) and mean $P_{aw}$ closely followed a third-order polynomial of the form:

$$E_t/E_{t\text{control}} = 1.41 - 0.113(P_{aw}) + 0.0085(P_{aw})^2$$

$$+ 0.00016(P_{aw})^3,$$

where $r = 0.90$, $N = 36$, and the SEs of the intercept and three regression coefficients are 0.086, 0.010, 0.0013, and 0.000044, respectively.

In all subjects, $R_t$ increased as mean $P_{aw}$ decreased below about 5 cmH$_2$O (fig. 1). At the lowest mean pressures, there was occasionally a tendency for the glottis to partly close (as judged subjectively and by large, transient increases in $R_t$) during the expiratory stroke of the piston pump, which increased the measured resistance. This resulted in variability in $R_t$ at low pressures in some subjects (e.g., subjects 1 and 6). We elected to include this variability in the subsequent data analysis rather than delete it. Above 5 cmH$_2$O $P_{aw}$, there were no consistent changes in $R_t$. In the average data (fig. 2, lower curve) normalized to values obtained at 5 cmH$_2$O mean $P_{aw}$ (average $R_t$ = 2.04 cmH$_2$O$ \cdot$ L$^{-1} \cdot$ s $\pm$ 0.36 SE), the relationship between normalized $R_t$ ($R_t/R_{t\text{control}}$) and mean $P_{aw}$ closely followed a third-order polynomial of the form:

$$R_t/R_{t\text{control}} = 1.59 - 0.113(P_{aw})$$

$$+ 0.0064(P_{aw})^2 - 0.0001(P_{aw})^3,$$

where $r = 0.95$, $N = 36$, and the SEs of the intercept and three regression coefficients are 0.06, 0.007, 0.001, and 0.00003, respectively. When only values

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above 5 cmH₂O were included in the analysis, average Rₑ was not affected by mean Pₑₑ (P > 0.1).

In the subject (2) in whom measurements were repeated, values for Eₑ and for Rₑ on different days were nearly the same (figs. 1 and 3).

Relation between Pₑₑ and Lung Volume

We found that the average relationship (fig. 4) between mean Pₑₑ and the change in end-expiratory lung volume from FRC (normalized in each subject to VC during sinusoidal forcing) followed a sigmoidal curve best described by the following:

\[
\text{Lung volume} - \text{FRC} / \text{VC} = -0.0416 + 0.0200 (\text{Pₑₑ}) + 0.000348 (\text{Pₑₑ})^2 - 0.0000164 (\text{Pₑₑ})^3,
\]

where r = 0.992, N = 36, and the SEs of the intercept and three regression coefficients are 0.0073, 0.00087, 0.0011, and 0.0000038, respectively. The coefficient for Pₑₑ indicates that respiratory system compliance is 2% VC/cmH₂O for most of the range in VC, whereas the other coefficients indicate that compliance decreases at the extremes of lung volume.

Discussion

The sigmoidal shape of the compliance curve of the respiratory system (fig. 4) compiled from inductance plethysmography compared favorably with the curve measured with traditional methods. Compliance in the mid-range of lung volume was about 0.1 L/cmH₂O. At
about 5 cmH₂O mean $P_{aw}$ in our study, end-expiratory lung volume equaled FRC, i.e., the increase in mean lung volume from FRC was equal to about half the tidal volume. Thus, this $P_{aw}$ represents the situation that would be observed during resting spontaneous breathing when seated. It should be noted that average $E_L$ and $R_t$ are minimal, or near minimal, at about 5 cmH₂O mean $P_{aw}$, and both increase if mean $P_{aw}$ falls from this.

Therefore, the data predict that, on average, lung impedance (which, at 0.4 Hz, comprises $E_L$ and $R_t$) is minimal at the mean lung volume of normal, seated breathing. However, as seen in figures 1 and 3, there is individual variability among subjects in this respect.

The data show that the immediate effects of decreases in lung volume are sufficient to cause the significant changes reported to occur in lung mechanics during

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Fig. 3. Lung resistance of six healthy, awake, seated subjects during sinusoidal volume forcing at different mean airway pressures (P_{aw}). In subject 2, values from measurements repeated on different days are indicated by open and closed symbols.

anesthesia. Functional residual capacity decreases by about 16% of VC in adults changing from sitting to supine. Data from a supine subject thus would be situated in the left portion of the curve in figure 4, and lung mechanics would correspond to the low mean P_{aw} portions of the curves in figure 2. In these ranges, both R_{L} and E_{L} increase if mean P_{aw} decreases. During induction of anesthesia in supine patients, lung volume further decreases by about 10% of VC, and our data show that E_{L} and R_{L} could increase 50–100% with this decrease in lung volume. Although reports of measured changes in E_{L} and R_{L} induced by anesthesia have varied, most studies have found 50–100% increases. Therefore, although we cannot rule out other factors, the immediate effects of decreases in FRC are sufficient to explain the changes in lung mechanics occurring during anesthesia. This is consistent with the common assumption, most recently suggested in a review by Wahba, that changes in lung mechanics during anesthesia are secondary to a decrease in FRC due to changes in the chest wall. These changes are not predictable from static deflation curves of the lung, which usually indicate constant elastance below FRC. One apparent exception was the curve measured by Caro et al., showing that static E_{L} increased in humans at both high and low lung volumes, with or without rib cage strap.

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found that halothane does not affect the relationship between $R_l$ and PEEP in open-chested dogs unless bronchoconstriction induced by vagal stimulation is present.\textsuperscript{28} In summary, the present data represent the normal relationships between lung mechanical properties and fast, short-duration changes in lung volume in healthy, awake humans. It is reasonable to assume that analogous relationships exist in anesthetized humans, although this, and the effects of lung pathology, need to be studied more.

Why does $E_l$ increase immediately at low lung volume? The increase is inconsistent with the virtually constant static $E_l$ measured below FRC.\textsuperscript{3} Our results indicate that this increase in $E_l$ is immediate, already measurable after a few seconds at the low lung volume, and therefore not due to a gradual process, such as progressive atelectasis. Rather, the increase in elastance is likely due to recruitment and derecruitment of alveoli with each breath and changes in surface film kinetic behavior. In addition, at low lung volumes, airway closure probably will occur and there will be fewer open alveolar units throughout the breathing cycle. This will decrease ventilatable volume in the lungs, which will increase $E_l$ without actually changing the mechanical properties of the lung tissue \textit{per se}. Air trapping at low lung volumes also could lead to increases in $E_l$ because the compressibility of the trapped gas is low, and this would tend to increase elastance. Elastance also could increase at low lung volume if lung tissue resistance increases, because the two properties seem to be closely coupled.\textsuperscript{29} However, to our knowledge, tissue resistance below FRC has not been measured directly.

Although $R_l$ clearly increases below FRC because of increases in airway flow resistance\textsuperscript{11} and, possibly, lung tissue resistances, variable effects on $R_l$ have been reported for increases in lung volume above FRC in previous studies in humans.\textsuperscript{5,6,16,17} Lung tissue resistance, measured in excised lungs, increases at high lung volume.\textsuperscript{9,12} Thus, there are competing tendencies for airway flow resistance to decrease and for tissue resistance to increase with increasing lung volume. Adding even greater complexity is the fact that the relative contributions of the airways and tissue to $R_l$ will depend on the frequency and tidal volumes used for measurement. If low flows are used, tissue resistance is high\textsuperscript{9,14,15} but airway flow resistance (which equals $k_1 + k_2 \times \text{flow}$, where $k_1$ and $k_2$ are non-zero constants\textsuperscript{13}) is low; at high flow rates, airway flow resistance increases but tissue resistance tends to decrease.\textsuperscript{9,14,15} During me-

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mechanical ventilation, frequency and tidal volume are roughly within the normal range of spontaneous breathing. In one study in spontaneously breathing humans at relatively normal breathing pattern, there were large increases in $R_t$ as lung volume increased above FRC. However, because either frequency and/or tidal volume were not controlled in those experiments, the results are difficult to interpret. Our results, measured at constant forcing pattern, show that $R_t$ does not consistently change with increases in lung volume above FRC in seated subjects with healthy lungs. In anesthetized supine subjects, though, lung volume may be low and a small amount of PEEP may decrease $R_t$, because the subjects' lung mechanics would correspond to the left portion of the curve in figure 3. Recently, interrupter resistance measured using the flow interruption technique (which supposedly represents the airway flow part of $R_t$), was found to not significantly increase with PEEP in patients with healthy lungs or with adult respiratory distress syndrome. However, interpretation of interrupter resistance is limited because it depends on a complex model and corresponds to an undetermined combination of forcing frequencies and amplitudes. Thus, comparisons are difficult.

From our results, we can predict changes in lung mechanics in certain clinical situations. In awake, spontaneously breathing patients with healthy lungs, FRC may be low because of a number of factors, such as posture, obesity, ascites, pregnancy, or water submergence for extracorporeal shock wave lithotripsy. A combination of these factors may cause particularly low FRC. Our results show that $E_t$ and $R_t$, and therefore work of breathing, will be higher than normal in these situations, to a degree that is roughly inversely proportional to FRC. However, in each condition, other, chronically developing factors may be present that affect lung mechanics in addition to those of acute changes in lung volume.

In mechanically ventilated patients, there is evidence that optimizing respiratory system mechanical properties with PEEP may be correlated to optimum oxygen delivery. Use of PEEP may be an important consideration even in patients with normal lung mechanical properties if cardiovascular function and gas exchange are compromised. For example, in severe liver cirrhosis, there may be pronounced intrapulmonary shunt, ventilation/perfusion mismatch, and decreased affinity of oxygen to hemoglobin. The accumulation of ascitic fluid in this condition may produce low lung volumes in the absence of parenchymal or airways disease. Our results predict that, when such patients (i.e., with healthy lungs but poor oxygenation) are anesthetized and mechanically ventilated, immediate changes in $R_t$ and $E_t$ with PEEP will depend on the patient's baseline lung volume (i.e., when no PEEP is used) relative to normal, awake FRC. This baseline will vary among patients. Lung volume probably will be low because of the anesthesia, and the additional factors mentioned above may decrease FRC further. If FRC is very low, a moderate amount of PEEP will decrease both $R_t$ and $E_t$. However, additional PEEP may not produce further decreases in $R_t$ and $E_t$, because, as seen in figure 2, the relationships between these variables and mean $P_{aw}$ are relatively flat as lung volume nears the range of awake, seated FRC. If baseline FRC in a patient is only slightly decreased compared to awake, seated FRC, moderate PEEP will not greatly affect $R_t$ or $E_t$. In other words, it can be assumed from figure 2 that, if PEEP significantly decreases $E_t$ and $R_t$, the patient's baseline FRC must have been very low. We also can predict that use of high levels of PEEP to increase lung volume more than awake, seated FRC will not change $R_t$ and may increase $E_t$ only slightly. In patients with lung disease or in patients in whom anesthesia may have large, additional effects besides those due to immediate decreases in lung volume, the relationships between lung mechanical properties and PEEP may differ from those in figure 2. In fact, such differences (e.g., a large increase in $E_t$ with moderate PEEP) may indicate abnormality. It will be useful to study these relationships in more detail.

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