Respiratory impedances and acinar gas transfer in a canine model for emphysema

GEORGE M. BARNAS, PAUL A. DELANEY, ILEANA GHEORGHIU, SRINIVAS MANDAVA, ROBERT G. RUSSELL, RENÉE KAHN, AND COLIN F. MACKENZIE

Departments of Anesthesiology, Physiology, and Pathology, and Shock Trauma Center, University of Maryland, and Research Services, Baltimore Veterans Affairs Medical Center, Baltimore, Maryland 21201

Barnas, George M., Paul A. Delaney, Ileana Gheorghiu, Srinivas Mandava, Robert G. Russell, Renée Kahn, and Colin F. Mackenzie. Respiratory impedances and acinar gas transfer in a canine model for emphysema. J. Appl. Physiol. 83(1): 179–188, 1997.—We examined how the changes in the alveoli caused by emphysema affect gas transfer out of the acinus (T\textsubscript{ac}) and lung and chest wall mechanical properties. Measurements were taken from five dogs before and 3 mo after induction of severe bilateral emphysema by exposure to papain aerosol (170–350 mg/dose) for 4 consecutive wk. With the dogs anesthetized, paralyzed, and mechanically ventilated at 0.2 Hz and 20 ml/kg, we measured T\textsubscript{ac} by the rate of washout of \textsuperscript{133}Xe from an area of the lung with occluded blood flow. Measurements were repeated at positive end-expiratory pressures (PEEP) of 10, 5, 15, 0, and 20 cmH\textsubscript{2}O. We also measured dynamic elastances and resistances of the lungs (E\textsubscript{L} and R\textsubscript{L}, respectively) and chest wall at the different PEEP and during sinusoidal forcing in the normal range of breathing frequency and tidal volume. After final measurements, tissue sections from five randomly selected areas of the lung each showed indications of emphysema. T\textsubscript{ac} during emphysema was similar to that in control dogs. E\textsubscript{L} decreased by ~50% during emphysema (P < 0.05) but did not change its dependence on frequency or tidal volume. R\textsubscript{L} did not change (P > 0.05) at the lowest frequency studied (0.2 Hz), but in some dogs it increased compared with control at the higher frequencies. Chest wall properties were not changed by emphysema (P > 0.05). We suggest that although large changes in acinar structure and E\textsubscript{L} occur during unimplicated bilateral emphysema, secondary complications must be present to cause several of the characteristic dysfunctions seen in patients with emphysema.

PATIENTS WITH PULMONARY EMPHYSEMA usually have complications, including heterogeneous lesions, bronchoconstriction, mucous plugging, and/or airway inflammation (35). In addition to decreases in static lung elastance, they usually display frequency (f) dependence of dynamic elastance (E\textsubscript{L}), airflow limitation on expiration (35), and air trapping leading to intrinsic positive end-expiratory pressure (PEEP; see Ref. 34). It has also been reported that lung resistance (R\textsubscript{L}) shows a large dependence on f (35). However, it is not clear how emphysematous changes in acinar tissue alone may affect the mechanical behavior of the airways without the presence of complications. Although overall lung size is increased with emphysema, there should be less radial force distending the airways. Therefore, it is difficult to predict how airway size, and thus resistance to flow through the airways, would be changed with emphysema alone. Also unclear is how the large changes in the structure of the acinus that occur with emphysema affect resistance to flow from the acinus. It has been suggested that an increase in peripheral R\textsubscript{L} is a major factor that determines dysfunction with emphysema (35). However, overall R\textsubscript{L} may not be affected by increases in resistance in the peripheral parts of the lung, and peripheral function must be directly measured to understand emphysema.

We addressed these issues in a chronic canine model for uncomplicated, bilateral pulmonary emphysema induced by repeated exposures to papain aerosol. We measured lung and chest wall mechanical properties during sinusoidal forcing in the normal range of f and tidal volume (V\textsubscript{T}), as previously described in healthy and edematous lungs (7). Such measurements can give information concerning functionally relevant respiratory mechanical behavior that may be lacking with other techniques (3). For example, a large negative dependence of E\textsubscript{L} on V\textsubscript{T} and of R\textsubscript{L} on f occurs during pulmonary edema (7). Also as previously described (1, 5, 23), we measured \textsuperscript{133}Xe washout (XeW) in a lung region (~30% of 1 lung) during 90 s of mechanical ventilation while pulmonary blood flow to the region was occluded. With this technique, \textsuperscript{133}Xe is injected into the nonperfused lung region during apnea, and apnea is continued for 15 s before ventilation is reinstated and washout is measured. Thus there is sufficient time for the \textsuperscript{133}Xe to diffuse throughout the acini by the beginning of washout. XeW is affected by the gas transfer from the acini to the airways (T\textsubscript{ac}) caused by the ventilation (1, 5) and is a more direct index than other current methods for studying acinar gas transfer, such as measurement of exhaled gas in single or multiple breaths or monitoring of dispersion of inhaled aerosol bolus. T\textsubscript{ac} is affected by increases in resistance to flow from the acinus and has been shown to be greatly decreased during pulmonary edema unless a high level of PEEP is applied (1).

The goal of this study was to quantify the effects of uncomplicated pulmonary emphysema on the mechanical properties of the lungs and chest wall in the normal range of breathing f and V\textsubscript{T}, on the f and V\textsubscript{T} dependencies of these properties, and on the mechanical function of the most peripheral parts of the lung. We hypothesized that some of these variables may be unaffected by this model of emphysema because complications that usually occur in patients with emphysema would not be present. If so, this would suggest that the interaction of emphysema with these complications may be important in determining dysfunction. We used...
a chronic papain model that was designed to produce very extensive emphysematous changes in the acini, and we waited a relatively long time after the papain exposure to make measurements to ensure that temporary lesions caused by the papain, unrelated to emphysematous changes, were probably reversed.

METHODS

Animal preparation and measurements. Five female beagle dogs (9.5–13.5 kg, 1–2 yr old) were anesthetized with pentobarbital sodium (30 mg/kg iv). After intubating their tracheas with a 9.0-mm-ID cuffed endotracheal tube (Mallinckrodt, Hi-Lo Jet), we mechanically ventilated them (Siemens-Elema 900C servoventilator) while they were in the supine position at fractional inspired O2 (FIO2) of 0.6. Except when impedance measurements were being made, the dogs were maintained with VT at 20 ml/kg body wt; respiratory f was 0.2 Hz. The inspiratory flow was a square wave, inspiratory-to-expiratory time ratio was 1:2, and inspiratory pause was 10% of total cycle. PEEP of 5 cmH2O was routinely applied. Anesthesia and neuromuscular blockade were maintained with a continuous infusion of thiopental sodium (3 mg·kg−1·h−1) and pancuronium bromide (0.08 mg·kg−1·h−1) in normal saline at 60 ml/h. In addition, we infused each dog with 6% hetastarch in saline solution at 25 ml/kg to minimize cardiovascular changes caused by increases in PEEP. We measured airway flow with a pneumotachograph (Fleisch no. 1) attached to the end of the endotracheal tube and a differential pressure transducer (Cesco LCVR). Airway pressure (Paw) was measured (Cesco LCVR) through a sampling port in the endotracheal tube that opened at its tip. Esophageal pressure (Pes) was measured (Cesco LCVR) via a polyethylene catheter attached to a 10-cm-long thin-walled latex balloon placed in the caudal part of the esophagus. The accuracy of the esophageal balloon was verified with a method modified from Baydur et al. (8), as previously discussed (7). A fourth Cesco LCVR transducer measured transpulmonary pressure, the difference between Paw and Pes. Arterial O2 saturation (SaO2) was continuously monitored by a pulse oximeter (Nellcor, N-100) attached to the tongue, and SaO2 remained >95% at all times. Body temperature, monitored in the pulmonary artery, was controlled between 36.5 and 37.5°C with a heat lamp and blanket.

For the study of XeW in protocol 1, we inserted a triple-lumen, thermostirpated pulmonary artery catheter (Opticath P7110) percutaneously via the femoral vein and advanced it into a branch of a pulmonary artery. The catheter was used to inject 133Xe, to sample blood, and to measure cardiac output (Qt). OXimex 3 thermoluidation computer, Abbott). Arterial and mixed venous blood gases were sampled simultaneously and analyzed (Stat Profile, NOVA Biomedical), with temperature correction. SaO2, and mixed venous O2 saturations and contents were measured with a CO-oximeter (Instrumentation Labs, model 282). Mean expired CO2 concentration was continuously measured in a mixing chamber (Marquette Gas Analyzer-A).

For the measurements of lung and chest wall impedances during sinusoidal forcing in protocol 2, inductance plethysmographic belts (Respitrace, Ambulatory Monitoring) were placed around the rib cage and abdomen to measure mean lung volume above functional residual capacity (FRC). For these measurements, the Respitrace amplifier was used in DC mode, and the electrical gains of the rib cage and abdominal signals were set to equal values. The summed signal from the belts was linearly related to changes in lung volume made during the static elastance measurements. The difference between the mean volume during forcing and the volume at the end of the period of 0 cmH2O Paw immediately after forcing was taken as the volume above FRC.

Protocol 1: XeW. A few minutes before each set of measurements, the dog was hyperinflated with six breaths of >550 ml at 10 cmH2O PEEP to provide a constant volume history, and then VT was returned to control for 15 min, at the level of PEEP to be measured. Immediately before injection of 133Xe, we measured Ei and R1, and, as indicated below, cardiorespiratory variables as well as arterial and mixed venous gases. We then inflated the balloon of the pulmonary artery catheter and monitored the pressure at the tip of the catheter to ensure proper occlusion (the balloon remained inflated until the end of each scanning period). Ventilation was stopped, and 133Xe (1–2 mCi dissolved in 4 ml of saline) was injected through the cannula in the occluded pulmonary artery and flushed with 4 ml of saline. Scanning by a gamma scintillation camera (Nucleonics) positioned 1–2 cm above the sternum commenced 10 s after the injection at 1 frame/s for 90 s. Ventilation was returned 15 s after the injection. After the image acquisition was completed, we reduced PEEP to 0 for a single breath to measure the change in lung volume above FRC, from integration of airway flow, caused by the previous level of PEEP. The sequence of PEEP was 10, 5, 15, 10, 0, and 20 cmH2O.

At each level of PEEP, we also calculated Ei and R1 by using multiple regression as previously described (1) from measurements of airway flow, Paw, and Pes. During each of these measurements, inspiratory-to-expiratory time ratio was temporally changed to 1:1 with no inspiratory pause to improve accuracy (3). In two of the dogs, we also measured FRC at 0 cmH2O PEEP by nitrogen washout (20), with measurements of expiratory flow and nitrogen concentration (MedSpect mass spectrometer, Allegheny International).

Protocol 2: Respiratory impedances. In each dog, on the same day as protocol 1, static elastances of the total respiratory system, lungs, and chest wall were plotted from Paw, Pes, and VT, respectively, at the end of a 6-s inspiratory pause after inflation to different volumes. Then, lung and chest wall impedances were measured during sinusoidal forcing. About 1 min before each measurement of lung and chest wall impedances, VT was increased to 550 ml for three successive breaths. To obtain measurements, we used a three-way valve system to switch the dog from the mechanical ventilator to a piston pump driven by a linear motor. A series of sinusoidal volume oscillations at 300 ml (0.2, 0.4, 0.6, 0.8, and 1.0 Hz; five or seven cycles at each f) was delivered while a low flow of 60% O2 to the pump-dog system was adjusted to keep end-expiratory Paw at 0 cmH2O. After the volume forcing, Paw was allowed to fall to 0 cmH2O for 4 s to measure changes in mean lung volume above FRC, and then the dog was switched to the mechanical ventilator. Next, the procedure was repeated at VT of 100, 200, and 50 ml. At these lower VT values, the f sequence additionally included 2 Hz, and 60% O2 flow into the system was adjusted to keep mean Paw equal to that observed during forcing with 300 ml (7.5 ± 0.4 cmH2O). In other words, at all f and VT values, mean Paw was constant. Then measurements were made at each of the VR and f combinations at a constant mean Paw (15.0 ± 0.8 cmH2O) twice as high as that just employed. The entire protocol was then repeated two more times to give a total of three trials at each combination of mean Paw, f, and VR.

Protocol 3: Induction of emphysema and final measurement. After control measurements were made in each dog, we used a method previously described (37) to produce lung injury. While the dogs were anesthetized as described above, they were exposed to aerosolized papain (170–350 mg in 15
ml 0.05 M sodium acetate) delivered to both lungs through the endotracheal tube during mechanical ventilation, using a nebulizer (Misty-Neb, Baxter) with 4 l/min O2 flow. Dogs were exposed immediately after control measurements and once each week for the following 3 wk. They were allowed to awaken after each exposure and showed no untoward clinical signs. Protocol 1 and 2 were repeated in each dog 3 mo after the last papain exposure and again during anesthesia and paralysis as described for controls. The mean Paw used for forcing during emphysema were 5.9 ± 0.4 and 11.8 ± 0.9 cmH2O. Determinations of FRC were made at these times in the two dogs measured in the control state.

Histology. After final measurements were made, five randomly selected areas of the lung were fixed on 10% neutral-buffered Formalin. The lungs were not inflated during fixation. Tissues were embedded in paraffin, and 5-µm sections were stained with hematoxylin and eosin for examination with light microscopy.

Data analysis: Protocol 1. The XeW curves were analyzed with the use of Gamma II software, as previously described (1, 5, 23), by identifying the regions of interest within the lung by computer and performing a monoeponential regression analysis of the counts measured during the scan, beginning at the first breath. There was no difference between the two measurements of XeW made in each of the dogs at 10 cmH2O PEEP, during control and during emphysema (P > 0.05, paired t-tests), so values at 10 cmH2O PEEP in a given condition were averaged.

Physiological dead space (Vds) was calculated from the Enghoff modification of Bohr equation (equipment dead space = 40 ml) and shunt fraction (Qs/Qt) from the shunt equation (31). Also we calculated alveolar ventilation (Va) as 12 × (VT − Vds − 40 ml), where f was 12/min. FRC in the two dogs we measured was near that predicted by body weight (13), and increases in FRC after induction of emphysema were in the same range as that measured in other studies using papain in dogs (14, 16, 17, 27, 36). Therefore, we assumed that FRC values before and after induction of emphysema were the same in all of our dogs as the average of the two dogs measured. We then estimated alveolar volume at each PEEP by adding the increment in volume above FRC caused by the PEEP (measured in protocol 1) to the estimated FRC and subtracting the Vds. Tad was calculated, as previously described (1), from the product of XeW and the estimated alveolar volume. The effects of PEEP and emphysema on each variable were tested with two-way analysis of variance (ANOVA) for repeated measures with Bonferroni correction. To test whether the slopes of the relationships between lung volume and PEEP, XeW and PEEP, and Vos and mean transpulmonary pressure were affected by emphysema, we used a general linear multiple regression that accounts for repeated measures in the same dog (4). Significant interaction terms indicated changes in slope caused by emphysema. The accepted level of significance in all tests was P < 0.05.

Data analysis: Protocol 2. All pressure and flow signals were low-pass filtered at 5 Hz (series 730, Frequency Devices). The first two or three cycles at each f were discarded to avoid transients that may occur on switching. The remaining three cycles were digitized (sampling rate = 32 samples/ cycle), computer averaged, and analyzed by discrete Fourier transform (3). In the closed chest, resistances and dynamic elastances of the chest wall (Row, Ecw) and lungs (Rl, El) were calculated from the complex ratios of Pes and Paw − Pes, respectively, to flow. Note that dynamic elastances were calculated by multiplying the imaginary part of the impedance by −2πf and therefore can contain effects contributed by inertia. These effects should be small at the frequencies measured in the present study (3).

We used the stepwise multiple linear regression that accounts for repeated measurements in the same dog (4) first to test whether there was a difference among values for resistances and for elastances between control and emphysema at each mean Paw, considering the entire range of f and Vt of forcing. Then we separated the data and repeated the stepwise multiple regression in each of the groups at each mean Paw to test for the effects (i.e., regression coefficients) of f and Vt on El, Rl, Ecw, and Row. Significant regression coefficients indicated that the dependent variable increases (positive coefficient) or decreases (negative coefficient) with an increase in the independent variable. We used ANOVA with Bonferroni correction to test for differences in the regression coefficients among the groups. Multiple regression was also used to test whether mean lung volume during sinusoidal forcing was affected by mean Paw, emphysema, and Vt. Using linear regression, we calculated static elastances as the slopes of the relationships between appropriate pressures and volumes. These elastances were calculated for two ranges of volumes: 350 ml and below (the range during sinusoidal forcing at the lower mean Paw) and 350 ml and above. ANOVA with Bonferroni correction was used to compare each elastance in the different conditions. The accepted level of significance was P < 0.05 for all analyses.

RESULTS

Protocol 1. The relationship between the increase in lung volume from FRC and increments in PEEP was 27.3 ± 2.1 (SE) ml/cmH2O for control and increased (P < 0.05) to 33.1 ± 1.3 ml/cmH2O with emphysema (Fig. 1). Vos increased and Vd decreased with increasing PEEP, but neither was affected by emphysema (Fig. 1). XeW decreased with increasing PEEP in both control and emphysema (Fig. 1), but the slope of this decrease was less (P < 0.05) with emphysema (−0.06 ± 0.01 min/cmH2O) than with control (−0.11 ± 0.01 min/cmH2O). Estimated Tad (Fig. 2) was not affected by emphysema (P > 0.05).

El was decreased with emphysema compared with control (P < 0.05) and tended to increase at higher PEEP in both control and emphysema (Fig. 3), but the slope of this increase was less (P < 0.05) with emphysema (−0.15 ± 0.05 min/cmH2O) than with control (−0.21 ± 0.04 min/cmH2O). Estimated Tad (Fig. 2) was not affected by emphysema (P > 0.05).

El was decreased with emphysema compared with control (P < 0.05) and tended to increase at higher PEEP in both control and emphysema (Fig. 3), but the slope of this increase was less (P < 0.05) with emphysema (−0.15 ± 0.05 min/cmH2O) than with control (−0.21 ± 0.04 min/cmH2O). Estimated Tad (Fig. 2) was not affected by emphysema (P > 0.05).

Although PEEP affected Qt, Qs/Qt, mean arterial pressure, and pulmonary arterial pressure (Ppa) (Fig. 4), emphysema did not (P > 0.05). Similarly, emphysema did not affect (P > 0.05) heart rate or stroke volume (not shown). Arterial O2 tension was 342 ± 6.62 Torr at 0 cmH2O PEEP during control and was not changed by PEEP or emphysema (P > 0.05). Arterial CO2 tension during control decreased (P < 0.05) from 36.2 ± 1.0 Torr at 0 cmH2O PEEP during control to 41.6 ± 2.3 Torr at 20 cmH2O PEEP. With emphysema, it was not different from control at any PEEP (P > 0.05).

FRC during control measurements was 399 and 323 ml in the 2 dogs in which it was measured. FRC was 510 and 493 ml, respectively, in the same dogs after induction of emphysema.

Protocol 2. Static elastances (Fig. 5) of the respiratory system and of the lungs increased above 350 ml
Both elasticances decreased with emphysema in either volume range \((P < 0.05)\) (Table 1). Static elastance of the chest wall decreased \((P < 0.05)\) above 350 ml during both control and emphysema. Static chest wall elastance during emphysema was slightly higher than control \((P < 0.05)\) above 350 ml only.

During sinusoidal forcing, mean lung volume at the lower mean Paw was ~200 ml above FRC for both control and emphysema measurements (Table 2). At the higher mean Paw, mean volume above FRC was ~400 ml for both conditions.

\(E_L\) increased \((P < 0.05)\) as mean Paw was increased in both control and emphysema (Fig. 6). \(E_L\) decreased with emphysema \((P < 0.05)\) at either mean Paw (Fig. 6). The regression coefficient for the effect of Paw on \(E_L\) was \(2.4 \pm 1.0 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}^{-1}\) and was not changed by...
emphysema or mean Paw (P > 0.05). There was no
dependence on VT (P > 0.05) in any condition.

With control, RL was not affected (P > 0.05) by mean
Paw (Fig. 6). At low mean Paw, the regression coefficient
for the dependence of RL on 1/f was 0.34 ± 0.10
cmH₂O/land was not changed at the higher mean Paw
(P > 0.05). At 0.2 Hz, RL was not different with
emphysema (P > 0.05). However, changes in RL throughout
the entire range of f with emphysema were somewhat
variable among dogs. At the lower mean Paw, RL
increased throughout most of the range of f compared
with controls in three of the dogs; in those cases, RL was
also less dependent on f. At the higher mean Paw, RL
returned to values similar to control in two of those
dogs. With the average data including all f, RL
increased with emphysema compared with control (P <
0.05) at the low mean Paw only, and RL decreased (P <
0.05) as mean Paw was increased (Fig. 6). With the
average data during emphysema, there was no dependence
of RL on 1/f (P > 0.05). There was no evidence of
airway narrowing or inflammation.

DISCUSSION

The main findings of this study were large decreases
in E_L with emphysema that were not dependent on f
and no changes in transfer of gas from the acinus. RL
was increased at the higher f with emphysema in some
dogs. Chest wall mechanical properties were not af-
fection by the emphysema.

Comparisons with other studies. Papain has been
used in many studies as a model for emphysema, and
several different protocols have been employed. Studies
differ in the type of exposure (aerosol vs. intratracheal
or intrabronchial instillation), dose, length and number
of repetitions of exposure, and the period from last
exposure to measurements. There is evidence that the
model does not become stable until ~1 mo after the last
exposure (21, 25, 33). The most common findings in
studies using papain are increases in static or dynamic
lung compliance (14, 16, 17, 25, 27, 36) and FRC (9,
14, 17, 18, 21, 26, 27, 36), although in some studies
these were not significant (10, 25). Our protocol of four
repeated aerosol exposures was among the highest
total doses given, and we expected that almost all
acinar regions would be affected. Because we found
definite evidence of emphysematous changes in tissue
samples from throughout the lung, it is likely that the
protocol produced a uniform distribution of extensive,
although patchy, emphysema. In addition, lack of
changes in E_L with f also indicates uniform lung
mechanical behavior (32). Although this is unlike the condition expected in most patients, it enabled evaluation of the effects of emphysema without complicating factors, and it allowed for the assumption that Xe/W from the area of the lung studied would be characteristic of the lung as a whole.

Although we found that cardiovascular variables and arterial blood gases in our model for emphysema were not changed from control, increases in \( P_{pa} \) have been reported in a similar model elsewhere (28, 37). The high \( FIO_2 \) used in our study probably prevented any increases in \( P_{path} \) that might have caused hypoxic vasoconstriction in those studies. Therefore, possible indirect effects that were due to cardiovascular changes with emphysema probably did not contribute to the results in our model.

In various studies in patients with emphysema, static elastance near FRC has been reported to decrease from 32 to 60% compared with normal subjects (11, 12, 15, 22), although one early study reported no difference (38). Thus the 39% decrease in static elastance near FRC we found in the present dog model is within the range generally found in human patients. However, dynamically determined elastance (i.e., \( EL \)) decreased by 50% in the dog model, whereas \( EL \) in patients with emphysema has been reported to not change (11) or to increase (29) compared with normal patients. The discrepancy is probably due to the complications of airway abnormalities and heterogeneity of lesion that are usually found in patients. With such conditions, \( EL \) increases as respiratory \( f \) increases (11, 29) and may be less than, equal to, or higher than control values, depending on the \( f \) at which it is measured. In fact, it has been suggested that one of the primary indications of onset of emphysema is frequency dependence of \( EL \) (35). We found no increase in the frequency dependence of \( EL \) after induction of emphysema in the papain-treated dogs, indicating that emphysema was homogeneously induced throughout.

<table>
<thead>
<tr>
<th>Volume</th>
<th>Control</th>
<th>Emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 ml</td>
<td>206 ± 21</td>
<td>198 ± 27</td>
</tr>
<tr>
<td>100 ml</td>
<td>206 ± 15</td>
<td>198 ± 23</td>
</tr>
<tr>
<td>200 ml</td>
<td>201 ± 12</td>
<td>201 ± 18</td>
</tr>
<tr>
<td>300 ml</td>
<td>183 ± 10</td>
<td>194 ± 18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tidal volume, ml</th>
<th>Paw, 5.9 cmH(_2)O</th>
<th>Paw, 15.0 cmH(_2)O</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 ml</td>
<td>395 ± 17*</td>
<td>399 ± 28*</td>
</tr>
<tr>
<td>100 ml</td>
<td>372 ± 23*</td>
<td>412 ± 35*</td>
</tr>
<tr>
<td>200 ml</td>
<td>374 ± 34*</td>
<td>397 ± 27*</td>
</tr>
<tr>
<td>300 ml</td>
<td>344 ± 25*</td>
<td>402 ± 31*</td>
</tr>
</tbody>
</table>

Values are means ± SE. Paw, airway pressure. * Different from low mean Paw in corresponding condition, \( P < 0.05 \).
the lung. As mentioned above, tissue samples corroborate this. Previous studies in excised hamster lungs (30) and intact dogs (14) after exposure to papain did find f dependence of EL. However, those studies used less extensive dosing and a shorter recovery period than the present study.

Acinar gas transfer. As previously discussed, our measurements of XeW reflect transfer of gas, mostly by diffusion, from the acini to the convective gas front, which in turn will be limited by convective gas transfer from the mouth to the entrance of the acini (1). The most important factor for the decrease in XeW with increasing PEEP is probably the resulting increase in alveolar volume, because washout of a substance from a chamber is generally inversely proportional to the volume of the chamber (1). The rate of Tad (in l/min) equals the product of XeW and alveolar volume (1). Calculated Tad (Fig. 2) is nearly identical for the two conditions at all PEEP. Although papain-induced emphysema causes large structural changes in the acini
none of these changes increases resistance to gas transfer. Pushpakom et al. (36) did find increases in peripheral airway resistance in excised dog lungs after papain treatment, and this resistance could possibly be influenced by changes in the acini. However, as pointed out by Klassen et al. (21), measurements were made when some transient lesions in response to papain may have still been present.

RL. At the lowest breathing f studied (all measurements in protocol 1 and 0.2-Hz measurements in protocol 2), we found no consistent changes in RL between control and emphysematous lungs. Other studies using the papain model have also found no changes in morphology and diameter of the bronchi or small airways (10, 21, 25, 27, 30) and no changes in RL at routine ventilator f (9, 16–18, 25, 36), including studies that changed lung volume (14, 21, 30). Thus the structural changes in the papain-induced model of emphysema occur at the acinar level, and there seem to be no structural changes of the airways. However, specific morphometric studies of the peripheral airways have not yet been done, and subtle changes may occur. Furthermore, the structural changes in the acini do not interfere with Taci, because, as discussed above, acinar resistance does not appear to be increased.

At the higher f, RL was much higher than control in some conditions in some dogs. The mechanism for these increases in RL are difficult to identify because we could discern no correlation of the occurrence of these increases with any measured factor. One possibility is that flow limitation occurred during some of the higher expiratory flow rates. Maximum expiratory flows at mid-lung volume have been reported to be between 0.5 and 1.0 l/s (21) in emphysematous lungs from dogs in the same range of body weight as the dogs in the present study. Our protocols infringed on this range only at 0.6 Hz at 300 ml Vt, at 0.8 and 1.0 Hz at 200 and 300 ml Vtr, and at 2.0 Hz at 100 and 200 ml Vtr. However, changes in Paw and Pes during the sinusoidal forcing were always sinusoidal and symmetrical. That is, we did not observe any large, sudden decreases in Paw to the negative range that we have sometimes seen during the expiratory limb of the forcing at very high sinusoidal flow rates (i.e., flows at 2.0 Hz with 300 ml Vtr or higher) that indicate flow limitation. Because of the above evidence, we do not believe expiratory flow limitation occurred.

As we have discussed (7), RL is complexly determined by airway resistance and lung tissue resistance (Rti). In the normal range of breathing, each of the components of RL depends differently on f, Vt, and mean lung volume. Increases in RL, when they occurred during emphysema, may have been due to increases in Rti. In fact, Rti in excised, emphysematous human lungs, measured during low-amplitude oscillations from 2 to 32 Hz, was higher than in control lungs (42). The mechanisms governing Rti are not clear. We have previously discussed that, based on a model introduced by Wilson and Bachofen (43), Rti will be determined by the force-length relationships of the peripheral connective tissue and the axial tissue fibers surrounding the alveolar duct, the surface tension-surface area relationship of the alveolar surface film, and the interaction between the latter two relationships (39). If the hysteretic properties of each of these determinants are not closely matched, increases in Rti could occur. We found increases in Rti in rabbit lungs despite decreases in Ei caused by lavage with a silicon fluid with a constant tension-area relationship (39). Therefore, it is possible for Rti to increase in emphysema despite decreases in Ei. Why this increase was so inconsistent in the present data remains unknown. It is interesting to note, however, that we have observed similar patterns of RL in the normal range of f and Vt in anesthetized and/or paralyzed, mechanically ventilated patients with chronic obstructive pulmonary disease (2). In those studies, RL was evaluated during the inspiratory half of the ventilatory cycle only, and values were thus independent of flow limitation that occurred during expiration. Analogous to the average response of the dogs during emphysema compared with control, RL in the patients decreased less with increasing f than did the RL in patients with healthy lungs; therefore, the difference compared with healthy lungs was enhanced at the
higher f. These results contradict previous reports that
dependence of $R_L$ on $f$ increases with emphysema in
patients (35). However, measurements of $R_L$ in those
previous reports were made at $f$ much higher than the
normal range of breathing, and $V_T$ was not regulated to
be in the normal range.

Thus although we suggest that increases in $R_{ti}$ can
sometimes occur with emphysema, further studies are
needed to examine why this happens. Whether such
presumed increases in $R_{ti}$ are important in patients
with emphysema also needs to be considered.

$E_{cw}$ and $R_{cw}$. The relative constancy of static elas-
tance and dynamic properties of the chest wall with
emphysema in these dogs compared with controls
agrees with lack of changes in static $E_{cw}$ in dogs with
unilateral (26) or bilateral (14) emphysema induced by
papain and in hamsters with bilateral emphysema
induced by elastase (41). The dependencies of $E_{cw}$ and
$R_{cw}$ on $f$ and $V_T$ were also not affected by emphysema.
These dependencies seem to be a fundamental aspect of
chest wall mechanical behavior, because we have found
similar dependencies in human, chicken, and previous
dog studies (40). We have attributed these characteris-
tic dependencies to a combination of viscoelastic and
viscous behavior (40). Although FRC was increased
with papain-induced emphysema, we have also shown
that increases in lung volume have no effect on dynamic
chest wall properties (6). It is possible that configura-
tions of the rib cage and/or diaphragm-abdomen may
have been affected by emphysema, but this was not
examined in the present study. Therefore, we do not
make any inferences of how respiratory muscle func-
tion may have been compromised in this canine model
for emphysema.

Summary. The data suggest that increases in overall
lung volume and decreases in radial traction caused by
emphysematous changes in the acini have no effect on
airways function in uncomplicated, severe emphysema
at the lower end of normal range of breathing $f$ in the
dog. Complicating factors such as localized heteroge-
neous lesions, bronchoconstriction, and airway inflam-
mation may be needed for increased airways resis-
tance, flow limitation and/or air trapping (i.e., intrinsic
PEEP (34)) to occur during normal breathing. For
example, Hogg et al. (19) found that excised lungs from
patients with emphysema showed mucus plugging as
well as narrowing and obliteration of the small air-
ways, complications that do not seem to occur in the
papain animal model. Increased $f$ dependence of $E_{L}$
does not occur without the presence of complications,
but $R_L$ can greatly increase compared with healthy
lungs at higher flow rates. The mechanism for this
increase in resistance is still unknown. Finally, it
should be noted that differences in anatomy between
human and canine lungs (e.g., dogs have relatively
stiffer tracheae and larger airways) may cause func-
tional mechanical differences [e.g., maximum flow per
gram lung weight is greater in the dog and less
dependent on lung volume (24)]. It is possible, there-
fore, that species differences may also contribute to
some of the discrepancies between patients with
emphysema and the canine papain model.

This research was supported by National Heart, Lung, and Blood
Institute Grant HL-33009.

Address for reprint requests: G. M. Barnas, Anesthesiology Re-
search Laboratories, Univ. of Maryland, Rm. 534 MSTF Bldg., 10
South Pine St., Baltimore, MD 21201.

Received 1 October 1996; accepted in final form 12 March 1997.

REFERENCES

    Choi, B. H. Hoff, and C. F. Mackenzie. Effects of PEEP on
    acinar gas transfer in healthy and lung-injured dogs. Am. J.

2. Barnas, G. M., T. B. Gilbert, M. J. Krasna, M. Fiocco, B. M.
    Kattapuram, and G. Kaschorke. Dynamic lung properties in
    severe COPD in the normal range of breathing (Abstract). Am. J.

3. Barnas, G. M., P. Harinath, M. D. Green, B. Suki, D. W.
    Kaschka, and K. R. Lutchen. Influence of waveform and analysis
    technique on lung and chest wall properties. Respir. Physiol. 96:

    Sexton, P. C. Imle, and P. D. Wilson. Dependencies of respira-
tory system resistance and elastance on amplitude and fre-

    Donohue, C. S. Kong, and C. F. Mackenzie. Effect of pulmo-
    nary edema on acinar gas mixing. J. Appl. Physiol. 76: 560–564,
    1994.

    and tidal volume on lung and chest wall mechanics in the dog.

7. Barnas, G. M., D. Stanenovic, and K. R. Lutchen. Lung and
    chest wall impedances in the dog in normal range of breathing:
effects of pulmonary edema. J. Appl. Physiol. 73: 1040–1046,

    Milic-Emili. A simple method for assessing the validity of the

    function tests in rats with progressive papain-induced emphy-

10. Caldwell, E. J. Physiologic and anatomic effects of papain on

11. Cherniack, R. M. The physical properties of the lung in chronic
    obstructive pulmonary emphysema. J. Clin. Invest. 35: 394–404,
    1956.

    Pulmonary conductance and elastic recoil relationships in asthma

    Craig. Pulmonary mechanics during induced pulmonary edema in

14. D’Angelo, E. Effect of papain-induced emphysema on the distri-
    bution of pleural surface pressure. Respir. Physiol. 27: 1–20,
    1976.

15. Finucane, K. E., and H. J. H. Colebatch. Elastic behavior of the
    lung in patients with airway obstruction. J. Appl. Physiol. 26:

16. Goldring, I. P. S. S. Park, C. S. Shim, L. Greenburg, and
    J. M. Ratner. Histopathology and mechanical properties of the
    lung in experimental emphysema. Pathol. Microbiol. 35: 176–
    180, 1970.

    Hermeyer, K. M. Mueller, and P. Lawin. Single breath $N_2$
    washout in papain-induced emphysema. Intensive CareMed. 15:

    Bromberg. Forced oscillatory respiratory parameters following


