Static lung-lung interactions in unilateral emphysema

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Margulies, Susan S., Robert W. Schriner, Mark A. Schroeder, and Rolf D. Hubmayr. Static lung-lung interactions in unilateral emphysema. J. Appl. Physiol. 73(2): 545-551, 1992.—Motivated by the introduction of single-lung transplantation into clinical practice, we compared the static mechanical properties of the respiratory system in six supine dogs before (at baseline) with those after the induction of unilateral emphysema. Relaxation volume (Vrel), total lung capacity (TLC), and static compliance of the emphysematous lung increased to 214 ± 68, 186 ± 39, and 253 ± 95% (SD) of baseline, respectively. Vrel of the nonemphysematous lung fell to 81 ± 28% of baseline, with no significant change in TLC of the nonemphysematous lung or its pressure-volume relationship, indicating that unilateral hyperinflation does not cause dropout of contralateral lung units. After unilateral emphysema, the chest wall shifted to a higher unstressed or neutral volume (when pleural pressure equals atmospheric pressure) in three of six animals, minimizing the anticipated decrease in lung recoil pressure at the higher respiratory system Vrel. The pattern of relative lung emptying in the intact dog and in the excised lungs was similar during stepwise deflations from TLC, suggesting that mean pleural pressure of the hemithoraces is equal. We conclude that in the dog the static volume distribution between emphysematous and nonemphysematous lungs is determined only by differences in lung recoil and compliance.

WITH THE INTRODUCTION of single lung transplantation (SLT) into clinical practice, questions have been raised about the mechanisms of interaction between two lungs with different mechanical properties. Failure of early SLT patients with chronic obstructive pulmonary disease (COPD) was attributed to unfavorable lung-lung interaction (20), and SLT was discontinued for emphysema until 1989, when two centers reported a successful outcome from SLT in a few patients with COPD (13,23).

The aim of this study was to evaluate the effects of a unilateral loss of lung recoil on the interpulmonary volume and transpulmonary pressure distribution in dogs to gain insight into the mechanisms that govern lung-lung interdependence. With this goal in mind, we studied the static mechanical properties of lungs and chest wall in dogs before and after the induction of unilateral emphysema (UE) with papain (21). Specifically, we investigated the treatment-induced changes in the relaxation volume (Vrel) and the static compliance of each lung, the chest wall recoil and compliance, and we also determined the mean pleural pressure (Ppl) over each lung at Vrel and during quasistatic deflations from total lung capacity (TLC).

METHODS

Instillation of elastolytic enzymes, such as papain, induces emphysema in animals that histologically and functionally resembles human panacinar emphysema (19). In this study, UE was produced in dogs with a technique similar to that described by Mink (15). Eight adult mongrel dogs (≥1 yr) weighing 28-44 kg were anesthetized with pentobarbital sodium (30 mg/kg), intubated with a Y-shaped dual-lumen endotracheal tube (Kottmaier; Willy Rusch), and placed in a lateral decubitus posture. A mixture of 4 ml (25 mg/ml) of papain solution (type III; Sigma Chemical) diluted in 40 ml of sterile normal saline was injected through a PE-200 catheter into the airways of the dependent lung. After the instillation, the dogs were mechanically ventilated for 6 h (tidal volume = 15 ml/kg, fractional O2 concentration = 0.6). Penicillin and gentamicin were administered every 12 h for a total of four doses to prevent bacterial infection. The instillation procedure was repeated at approximately weekly intervals for an average of four treatments. Two dogs died because of pulmonary hemorrhage and hypoxic respiratory failure during the induction of emphysema. Of the remaining six dogs, the left lung was treated in dogs 1-3 and the right lung in dogs 4-6.

Measurements of Vrel and the static elastic properties of the intact respiratory system were made before the initial papain instillation (baseline values) and again at least 3 mo after the final treatment. On these occasions, anteroposterior projection X-rays were taken at Vrel to document respiratory system geometry. The dogs were anesthetized with pentobarbital sodium (25-30 mg/kg), placed in the supine posture, intubated with a Kottmaier dual-lumen endotracheal tube, and mechanically ventilated with a Harvard pump. Complete separation between the airways of the right and left lung was assumed if a right-to-left airway pressure difference of 10 cmH2O could be maintained during a single lung inflation. To estimate pleural pressure, a balloon catheter was placed in the mid- to lower esophagus. Its position was adjusted until the drop in esophageal pressure (Pes) during inspiratory efforts against an occluded airway fell to within 1 cmH2O and/or 10% of the change in airway pressure (Pao) (2). Right and left Pao were recorded from the oral ends of the respective endotracheal tube lumina. Gas flow to each lung was measured with a pneumotacho-

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The relaxation volume of each lung was measured in duplicate with a nitrogen equilibration technique, and the two values were averaged. With the lungs at Vrel, a calibrated supersyringe was filled with a known volume of O2 (Vsyringe) and connected to one lumen of the divided endotracheal tube. After five slow manual inflations and deflations of the lung, the resident gas in the lung was equilibrated with the gas in the supersyringe. The nitrogen concentration in the room (and therefore in the lung) and in the supersyringe before and after equilibration was measured with a mass spectrometer (200 MGA, Centronics), and Vrel was computed with the following relationship

$$V_{rel} = \frac{N_2 \text{after} - N_2 \text{before}}{N_2 \text{room} - N_2 \text{after}} \times V_{syringe}$$

In a separate preliminary study, we validated the N2 equilibration technique in three dogs. N2 equilibration between lungs and syringe was complete after three inflations. Vrel was determined simultaneously by gas dilution and body plethysmography eight times in each animal, and the volume differences between techniques were averaged. Across dogs, the gas-dilution technique measurements were within 1 ± 3% (SD) of those determined by body plethysmography.

The lungs were inflated in parallel with a calibrated supersyringe from Vrel to TLC (Pao = 30 cmH2O), and the inspiratory capacity (IC) of the right and left lung was determined from the integrated flow signals. The lungs were inflated twice with the supersyringe to TLC to establish a constant volume history and then deflated in a stepwise manner to Vrel during the baseline studies and to residual volume (RV) after induction of UE. Deflation maneuvers were performed in triplicate and averaged. The pressure-volume (PV) curve for each lung was constructed from the in vivo transpulmonary pressure (Ptp = Pao - Pes), and the volumes were determined by integrating the gas flow from each lung at each deflation step.

To determine if Ppl is equal in the hemithoraces during the quasistatic stepwise deflation maneuver, the deflation maneuvers were repeated in the lungs after excision. The animals were given a lethal dose of pentobarbital, and the chest wall was opened by a sternotomy. The lungs were inspected during mechanical ventilation to ensure patency of all lobar bronchi and then were excised and degassed, and the deflation maneuvers were repeated. TLC of the excised lungs was defined at a Ptp of 25 cmH2O. In dog 6, the lungs leaked after they were treated with papain. The sum of e and ne (b) describes the initial combined lung PV curve (thin solid line). The intersection between line b and the chest wall curve (cw, thin solid line) is represented by an open circle and defines the baseline volume and Ppl of the respiratory system at Vrel. The posttreatment pressure-volume relationships are illustrated with heavy lines identified as E, NE, B, and CW, for the emphysematous lung, nonemphysematous lung, both lungs, and chest wall, respectively. The intersection of B and CW lines (Cl) represents the new system relaxation volume and Ppl. Baseline Vrel of each lung can be obtained from the corresponding thin broken line at baseline relaxation Ppl. Posttreatment Vrel of each lung can be obtained in a similar fashion, from the appropriate heavy line at posttreatment relaxation Ppl.

The unilateral loss of lung recoil and the consequent increase in thoracic gas volume produced a parallel shift of the chest wall curve to the left in the three dogs with more severe hyperinflation (dogs 1, 3, and 6). The slope (compliance) of the chest wall curve was unaffected by treatment [7.8 ± 1.1% baseline TLC/cmH2O (before) compared with 8.6 ± 0.8% baseline TLC/cmH2O (after) treatment; P = 0.34], and the PV relationship remained linear even at volumes above baseline TLC. The reduction in recoil was attenuated by the shift in the chest wall PV curve after treatment. Recoil pressure at Vrel decreased by only 1.4 ± 1.1 cmH2O after induction of unilateral emphysema.

**Lung volumes.** The treatment-induced changes in Vrel, IC, and TLC of emphysematous and nonemphysematous lungs are shown in Fig. 2 for all six dogs. The Vrel, IC, and TLC of the emphysematous lung increased significantly to 214 ± 68, 171 ± 27, and 186 ± 39% of the baseline (pretreatment) values, respectively. Vrel of the untreated or nonemphysematous lung decreased slightly (81 ± 28% baseline Vrel; P = NS), whereas TLC did not change (97 ± 21% baseline TLC; P = NS). System TLC and Vrel increased significantly to 141 ± 21 and 150 ± 45% baseline values, respectively.

Treatment-induced changes in lung volumes were evident when baseline and posttreatment X-rays were compared. For example, films taken before (Fig. 3, left) and after (Fig. 3, right) right-sided emphysema was induced in dog 6 reveal that the mediastinum shifted to the left, and the right hemidiaphragm was displaced caudal by
the enlarged right lung. Although it is difficult to quantitate these lung and chest wall changes from these projection X-rays, N₂ washout measurements show that Vrel increased to 294% baseline in the right papain-treated lung and decreased to 62% baseline in the left untreated or normal lung.

**Lung elastic properties.** Figure 4 presents the in vivo static lung compliance for each lung before and after induction of unilateral emphysema. Compliance of each lung was computed at the corresponding system Vrel. The compliance of the nonemphysematous lung was unaffected by treatment of the contralateral lung (0.11 ± 0.05 before and 0.09 ± 0.07 l/cmH₂O after treatment; \( P = \text{NS} \)). However, the compliance of the treated lung increased significantly from 0.11 ± 0.05 to 0.24 ± 0.09 l/cmH₂O as a result of repeated papain instillations.

Figure 5 shows the individual and group mean deflation PV curves of the excised emphysematous (□) and nonemphysematous (●) lungs. Deflation volume on the ordinate is expressed as liters from TLC. Pressure on the abscissa reflects Ptp (equivalent to Pao) in cmH₂O. The curves depart significantly from each other only at transpulmonary pressures below 5 cmH₂O. Thus the compli-
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Emphysematous Lung Nonemphysematous Lung

Baseline Unilateral Emphysema Baseline Unilateral Emphysema

FIG. 4. Static compliance (Cst, L) of treated and untreated lung before and after induction of unilateral emphysema. Compliance of each lung was calculated at corresponding system Vrel. Means ± SD across dogs are shown to side with open circle and error bars.

FIG. 5. Individual and group average deflation PV curves of excised lungs. Upward arrows mark estimated transpulmonary pressure (Ptp) of lungs at Vrel in vivo. ⋄, emphysematous lung; ⋄, nonemphysematous lung.

DISCUSSION

The goal of this study was to evaluate the effects of a unilateral loss of lung recoil on the interpulmonary volume and transpulmonary pressure distribution in dogs to gain insight into the mechanisms that govern interdependence between lungs with different elastic properties. The data presented in this communication were measured during static or nearly static maneuvers. The high resistance of the divided endotracheal tube precluded any insightful dynamic measurements during spontaneous ventilation. The following sections discuss the implications of our findings for static lung-lung interactions.
Untreated or nonemphysematous lung. Alterations in the shape and volume of the chest wall or lung container that occur in response to changes in body posture, thoracoabdominal strapping, inhalational anesthesia, and high spinal cord injury have been shown to affect the pulmonary recoil PV relationship (1, 3, 7, 16, 25). Microatelectasis, lung distortion, shifts in central blood volume, and alterations in composition and properties of surfactant have been proposed as mechanisms responsible for these changes in the lung (9). In a similar manner, chronic hyperinflation of the treated lung may alter the shape of the chest wall and the volume of untreated lung. We observe a reduction in the Vrel of the untreated lung in unilateral emphysema (Figs. 1 and 2). The fall in Vrel may be caused by loss of recoil in the contralateral emphysematous lung and a shift of the mediastinum toward the untreated lung (Fig. 3). However, the deformation of the structures surrounding the normal lung is not large enough to alter its maximal volume or recoil properties significantly. Moreover, after treatment the TLC of the nonemphysematous lung and its compliance at system Vrel were unchanged (Figs. 2 and 4).

We conclude from this evidence that the untreated lung was unaffected by the induction of unilateral emphysema. Implicit in this conclusion are two assumptions: 1) that the nonemphysematous lung is expanded to near its maximal volume at Pao = 30 cmH2O even after the induction of contralateral emphysema and 2) that changes in Pes accurately reflect changes in lung surface pressure. Both assumptions seem reasonable in view of the findings shown in Fig. 6.

Interpulmonary distribution of Ppl. The side-to-side distribution of Ppl affects regional volumes predicted from regional lung elastic properties (14). The issue of Ppl distribution has not been addressed in previous reports, despite its fundamental role in defining the mechanisms of lung-lung interactions and predicting the consequences of SLT in emphysema (24).

Because the loss of elastic recoil alters the distribution of forces between the lung and its surrounding structures, both the emphysematous lung and its container (the hemithorax) assume a different volume and shape after papain treatment. The new geometry is determined by a force balance that depends on the relative resistance of mediastinum, diaphragm-abdomen, and the rib cage boundaries to displacement and deformation. For example, in the presence of unilateral hyperinflation, if the mediastinal boundary is relatively compliant compared with that of diaphragm/abdomen and rib cage, then the average Ppl will increase (become less negative) but at the same time remain equal in both hemithoraces. However, if the mediastinum behaves like a steel plate rigidly anchored at the midline, the transmission of Ppl between the hemithoraces would be incomplete and Ppl would increase in the hyperinflated hemithorax more than in the contralateral side. Because the transpulmonary PV relationships are different for a normal and an emphysematous lung (Fig. 5), the interpulmonary distribution of Ppl is a major determinant of not only the static volume distribution between the lungs but also the inspired gas distribution during breathing as well (14).

On the basis of the data shown in Fig. 6, we conclude that average Ppl remains equal in the hemithoraces during a quasistatic deflation maneuver. This finding implies that the mediastinal compliance in dogs is large relative to the compliance of the chest wall. The finding of a uniform Ppl (with respect to lung side) conflicts with observations we have made in normal dogs during unilateral lung inflation [Hubmayr and Margulies (10)]. Under those circumstances Ppl is always greater within the hemithorax that houses the bigger lung. Structural adaptations of the mediastinum and chest wall from chronic hyperinflation and differences in lung stiffness may account for the discrepancy in findings.

Changes in the elastic properties of the chest wall. In supine dogs, the unstressed or neutral volume of the chest wall (when Ppl = 0) is ~55% TLC. The neutral volume of the chest wall defines the upper limit of Vrel that can result from a loss of lung recoil without chest wall adaptation. If Vrel were above the neutral volume, transpulmonary pressure would be negative. Commonly, Vrel of patients with severe airways obstruction may increase to or even exceed baseline or predicted TLC. Such a large increase in lung volume is possible only if the chest wall PV relationship is altered to increase the neutral volume. Sharp et al. (18) measured the chest wall PV curve in 15 anesthetized paralyzed subjects with severe COPD. Although they report that the slope (compliance)
of the curves was in the normal range, reploting the data to express lung volumes as percent predicted TLC reveals a large increase in the unstressed volume of the chest wall compared with normal controls.

The chest wall data presented in Fig. 1 demonstrate that thoracic gas volume at a given Pes increased with treatment, particularly in those animals with the most severe hyperinflation. A treatment-induced change in the position of the heart away from the esophageal balloon would result in an artifactual decrease in Pes at isovolume. This event is unlikely, however, for two reasons. First, the chest wall PV curve shifted in dogs with left-sided as well as right-sided emphysema. Second, the results are similar when Ppl is estimated with the in vitro PV curve of the nonemphysematous lung, which was not altered by treatment. Furthermore, an adaptation of the chest wall to chronic hyperinflation has been reported in emphysematous hamsters (22) and in dogs after expiratory threshold loading (4). In contrast to these findings, D'Angelo (6) could not demonstrate changes in the chest wall PV curve in papain-treated dogs with bilateral emphysema. The fact that he studied his animals only 4 wk after the final treatment may account for the lack of chronic chest wall adaptation.

It is not known where or how the chest wall adapts to produce a shift of the chest wall PV curve with no change in slope. Kikuchi et al. (12) suggested that the passive length-tension properties of respiratory muscles contribute substantially to the volume dependence of chest wall recoil in dogs. Thus the leftward shift of the chest wall PV curve might be attributed to changes in the passive properties of respiratory muscles. Furthermore, there is experimental evidence that respiratory muscles can indeed adapt to altered use. For example, chronic hyperinflation induces changes in chest wall geometry that, in turn, affect the functional requirements of the respiratory muscles (17). Experimental emphysema has been shown to induce sarcocerec dropout and a consequent reduction in the optimal length of the diaphragm in hamsters (8, 11). Additional studies are necessary to establish a cause-and-effect relationship between chronic hyperinflation and alteration of the elastic properties of the chest wall muscles.

Irrespective of cause or nature of this adaptation, the increase in chest wall recoil at isovolume may be an important factor in preserving the maximal flow-generating capacity of the lungs in the tidal breathing range. In the absence of such adaptation, Ptp at Vrel would fall even more, possibly leading to airway closure, atelectasis, and an impairment in pulmonary gas exchange.

Conclusions. The three major findings of our study can be summarized as follows. 1) Although Vrel decreased in the nonemphysematous lung, TLC and elastic properties remained unchanged. This finding is consistent with an absence of adaptation processes such as unit dropout and/or microatelectasis in the untreated lung caused by chronic hyperinflation of the contralateral lung. 2) Changes in the elastic properties of the treated lung produced unilateral hyperinflation, yet the average Ppl remained equal in the two hemithoraces. This result implies that the compliance of the mediastinum and the deformability of the lungs are large relative to those of the chest wall, allowing the thorax to assume a new unFORM Ppl despite side-to-side differences in lung size and shape. 3) The chest wall PV curve tended to shift leftward to a higher relaxation volume, attenuating the fall of the predicted Ptp at the new system Vrel. This shift is evidence of a structural adaptation of the thorax to chronic hyperinflation. These findings will form the basis for the development of future investigations in both experimental models and patients with single lung transplants in emphysema.

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