Preventing mediastinal shift after pneumonectomy does not abolish physiological compensation


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The purpose of the present study was to determine whether preventing mediastinal shift and, consequently, lung strain after pneumonectomy impairs the effect of the mediastinal shift on the functional compensation after pneumonectomy.

The relative contributions to overall functional compensation from these two sources remain controversial. Data from McBride and colleagues (21, 22) in ferrets suggest that lung stretch is the more important growth stimulus. On the other hand, studies using plombage to prevent expansion of the remaining lung across the midline after pneumonectomy or lobectomy in mice and rats suggest this only delays growth without prohibiting it (2, 7). There have been no studies on the effect of the mediastinal shift on the functional compensation after pneumonectomy.

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licated the shape and resting volume of the right lung. In 5 of the 10 dogs studied, the prosthesis was kept inflated to maintain the mediastinum at the midline. In the remaining five dogs, the prostheses remained deflated as controls. Effects of the prosthesis on the size and shape of the thorax and remaining lung were determined by chest X-ray and computerized tomographic (CT) scan. Physiological studies included measurements of diffusing capacity and pulmonary blood flow at rest and exercise by a previously established rebreathing technique.

METHODS

All experimental protocols were approved by the Institutional Animal Care and Research Advisory Committee. Ten, adult male, mixed-breed foxhounds were studied beginning at about 1 yr of age.

Construction of the prosthesis. Magnetic resonance imaging was used to reconstruct a three-dimensional model of the normal right lung. A normal adult dog was anesthetized, intubated, and placed in the magnet in a 30° right anterior oblique position. A calibrated syringe was used to hyperventilate the dog, followed by passive exhalation to functional residual capacity (FRC). A volume equivalent to a transpulmonary pressure of 20 cmH2O was delivered, and the breath was held during imaging. A cardiac-gated single-spin echo, 1-cm section, multiphase sequence with an echo time of 30 ms was used. The right hemithorax was reconstructed using a computer-directed plotter to trace out each image in real dimensions on plotting paper. These plots were transferred onto sheets of lemon wood (1.0-cm thickness). The wooden sections were cut, stacked, glued, and smoothed to provide a physical model of the right lung. This model was used to generate a mold from which a seamless silastic inflatable prosthesis was made (CUI, Carpinteria, CA). Wall thickness of the prosthesis was ~0.5 mm. A silicone filling tube was attached to the dorsolateral surface of the prosthesis through a reinforced patch (Fig. 1).

Pneumonectomy and implantation of prosthesis. Each dog underwent right pneumonectomy under general anesthesia as described previously (28). After the right lung was removed, the prosthesis was placed in the empty right hemithorax. The filling tube was tunneled through the intercostal space, connected to a subcutaneous injection port, and buried at the nape of the neck. The chest wall was closed in five layers, and the residual air in the thorax was partially aspirated.

In one-half of the animals (Inf), the prosthesis was kept inflated with an equal mixture of air and sulfur hexafluoride to a volume 20% higher than the animal’s FRC measured in the supine position. This volume successfully maintained the mediastinum in the midline (Fig. 2A). Mixing air with sulfur hexafluoride retards the rate of gas absorption from the prosthesis. In the remaining five animals (Def), the prosthesis was kept deflated, containing a minimal amount (<50 ml) of gas and allowing mediastinal shift to occur (Fig. 2B). The volume of the prosthesis was checked weekly for the first month to determine the optimal filling volume and then at monthly intervals by helium dilution, via the subcutaneous injection port, using a mass spectrometer (MGA 1100, Perkin-Elmer). After each measurement, the prosthesis was refilled to the desired volume, and the mediastinal position was verified by chest X-ray. All animals tolerated the chronic presence of the prosthesis without systemic complications.

Exercise training, respiratory mask, and carotid artery loops. Animals were trained to run freely on a motorized treadmill using protocols previously described (28). Dogs exercised for 30 min daily, 5 days/wk, at 60–80% of the previously achieved maximal load. Exercise training began before pneumonectomy and resumed 3–4 wk after surgery. A leak-free mask was constructed for each animal to fit its dental configuration, as described previously (1, 4). Bilateral carotid loops were constructed to allow acute catheterization of the artery (23). Physiological measurements were taken 5–7 mo after surgery.

Physiological measurements at rest. The dog was anesthetized with pentobarbital sodium (25 mg/kg intravenously), intubated, and ventilated with a Harvard pump in the supine position at a tidal volume of 15 ml/kg. End-tidal CO2 concentration was monitored by a mass spectrometer (Perkin-Elmer MGA 1100) and maintained at 30–35 Torr to suppress spontaneous respiration. Body temperature was maintained with a circulating thermal pad, and rectal temperature was continuously monitored. A latex balloon-tipped catheter was inserted into the lower one-third of the esophagus and filled with 1 ml of air. Identical pressure transducers and carrier amplifiers monitored pressures in the esophagus and at the entrance of the endotracheal tube. Signals were digitized by computer at 50 Hz. Pulmonary capillary blood flow, lung tissue volume, DTco2, and FRC were measured by a rebreathing method using gas mixtures containing 0.3% C18O, 0.6% C3H2, and 9% He in a balance of either air or O2 (13). Tidal volumes during rebreathing were 30, 45, and 60 ml/kg, delivered by a calibrated syringe, and rebreathing was carried...
out for 16 s at 30 breaths/min. Membrane diffusing capacity for carbon monoxide (D_{mCO}) and pulmonary capillary blood volume (Vc) were calculated by the Roughton-Forster method (27).

Maximal oxygen uptake. Exercise measurements were made 3–5 mo after surgery. The breathing port of the respiratory mask was connected to a two-way low-resistance valve (Hans Rudolph 2700, Kansas City, MO). The expiratory port was connected through wide-bore tubing to a mixing chamber and a heated pneumotachometer (Hans Rudolph 3813). Pressure drop across the pneumotachometer was monitored by a transducer fed through a carrier amplifier, and output signal was digitized and integrated to obtain volume. The pneumotachometer was calibrated each day with a 3-liter syringe (31). Expired O\(_2\) and CO\(_2\) concentrations were measured with a mass spectrometer, sampling distal to the mixing chamber. O\(_2\) uptake and CO\(_2\) production were calculated by computer and averaged every 10–20 breaths. Maximal O\(_2\) uptake was determined twice a month using an incremental protocol, starting with a warm-up period at 6 mph, 0% grade for 5 min, followed by incrementing the speed and/or grade at 3-min intervals. Rectal temperature, ventilation, O\(_2\) uptake, CO\(_2\) production, and heart rate were monitored continuously until the dog either began to lag or a plateau of O\(_2\) uptake was reached. After testing, the dog cooled down by walking at 3 mph, 0% grade until rectal temperature fell below 39°C.

Rebreathing measurements during exercise. These procedures have been described previously (13, 28). The respiratory mask was attached to a three-way pneumatic balloon valve (Hans Rudolph 8200 series) that connected the dog to either the open circuit or to a 3-liter anesthetic bag containing 0.3% C\(_{18}\)O, 0.6% C\(_2\)H\(_2\), and 9% He in a balance of either 30 or 100% O\(_2\). The anesthetic bag was filled by an automated filling system to a volume 200 ml greater than the expected tidal volume at each workload. After dogs exercised for 3 min at each constant workload, the pneumatic valve was computer-activated at a selected end-expiration, allowing the dog to rebreathe from the anesthetic bag for 6–10 s while gas concentrations were measured continuously. Respiratory rate at heavy exercise reached 100–120 breaths/min, yielding at least 8–10 breaths during rebreathing. End-inspiratory system volume and end-expiratory lung volume were measured by helium dilution. Pulmonary blood flow and septal tissue volume were measured from the slope and intercept, respectively, of exponential C\(_3\)H\(_2\) disappearance with respect to time, and D_{LCO} was measured from the slope of exponential C\(^{18}\)O disappearance with respect to time. D_{mCO} and Vc were obtained from measurements of D_{LCO} at two different alveolar O\(_2\) tensions. Extravascular septal tissue volume was calculated by subtracting Vc from total septal tissue volume. All rebreathing data were corrected for mixing efficiency with a method adapted from Hook and Meyer (10). The Bunsen solubility coefficient for C\(_2\)H\(_2\) in blood and tissue was corrected to the measured body temperature and hematocrit (15).

CT scan. CT scans were performed 6–10 mo after surgery. These procedures have been described previously (29). The dog was anesthetized, intubated, and ventilated at a tidal volume of 15 ml/kg. A scout film was obtained to define anatomic landmarks. Consecutive images were obtained using a Toshiba TCT 900S scanner at 5-mm intervals between the apex and costophrenic angle, first in the supine and then in the prone position. Before each imaging sequence, the dog was hyperventilated with three large breaths followed by passive exhalation to FRC. A volume of 45 ml/kg was then delivered via a calibrated syringe, and the breath was held during imaging. The delivered volume had been previously determined to give a transpulmonary pressure of 20 cmH\(_2\)O. The contour of the lung was traced from each image by software available on the scanner. Major hilar vessels and main stem bronchi were excluded. An average density (in Hounsfield units) was determined for each lung image. During calibration, the density of water was set at zero and the density of air in the intratracheal air column at \(-1,000\). The density of lung tissue was assumed to be that of muscle in the same animal (52–59). Total lung volume (V\(_L\), i.e., air + tissue) was estimated by numerical integration of the outlined areas of all images by Simpson’s rule. Relative contribution of tissue (V\(_{ti}\)) and air (V\(_{air}\)) to V\(_L\) was estimated as

\[
V_{air} = V_L \times \frac{\text{CT density of tissue} - \text{CT density of lung}}{\text{CT density of tissue} - \text{CT density of air}}
\]
Estimates of lung tissue volume by CT scan include the blood volume + extravascular tissue volume. To compare topographical volume distribution among dogs of different sizes along the cranial to caudal axis, transverse images were referenced with respect to the corresponding thoracic and lumbar vertebral bodies. To determine the effect of pneumonectomy on the shape and volume distribution of the bony thorax, the thoracic contour of each image was traced and partitioned between the right and left hemithorax by a line drawn from the midpoint of the sternum to the midpoint of the corresponding vertebral body.

Data analysis. Results were normalized with respect to body weight and are expressed as means ± SE. Resting measurements, maximal oxygen uptake, and submaximal exercise measurements at a given pulmonary blood flow were compared among groups by factorial ANOVA (Statview, SAS Institute, Cary, NC). Topographic distribution of lung volumes was compared by repeated-measures ANOVA. \( P < 0.05 \) was considered significant.

RESULTS

Prosthesis volume. In the Inf group, volume within the prosthesis was reabsorbed at an average rate of 1.0–1.5 ml \( \cdot \) kg\(^{-1} \cdot \) wk\(^{-1} \). The average maintenance volume was 33.7 ± 2.6 ml/kg. Average inflation volumes were 28.9 ± 2.1 and 37.4 ± 2.6 ml/kg before and after refilling, respectively.

Table 1. Volume measurements from CT scans in prone and supine positions

<table>
<thead>
<tr>
<th></th>
<th>Inf</th>
<th>Def</th>
<th>Inf</th>
<th>Def</th>
<th>Inf vs. Def</th>
<th>Prone vs. Supine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air in lung + prosthesis, ml/kg</td>
<td>115.6 ± 5.1</td>
<td>78.3 ± 3.1</td>
<td>102.6 ± 6.9</td>
<td>69.8 ± 2.7</td>
<td>&lt;0.0001</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Air in lung, ml/kg</td>
<td>65.7 ± 6.0</td>
<td>78.3 ± 3.1</td>
<td>53.6 ± 6.5</td>
<td>69.8 ± 2.7</td>
<td>&lt;0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Lung tissue volume, ml/kg</td>
<td>11.7 ± 0.5</td>
<td>10.2 ± 0.4</td>
<td>8.2 ± 0.4</td>
<td>9.1 ± 0.6</td>
<td>NS</td>
<td>&lt;0.0005</td>
</tr>
</tbody>
</table>

Data are means ± SE. CT, computerized tomography; Inf, inflated prosthesis group; Def, deflated prosthesis group; NS, not significant.
The presence of ~200 ml of gas that gradually accumulated in the deflated prosthesis. Average FRC in the Inf group was significantly smaller than in all other groups. There were no other discriminating differences among the three groups of pneumonectomized dogs. Consistent with data from CT scan, rebreathing measurements showed no significant differences in average total or extravascular septal tissue volumes, although tissue volumes in all pneumonectomized groups were lower than that of Sham animals.

**Exercise measurements.** Measurements at peak exercise are summarized in Table 3. Peak O\(_2\) uptake and cardiac output were significantly lower in the Inf, Def, and RPNX groups compared with the Sham group. The average FRC measured in each dog during treadmill exercise correlated significantly with lung volume measured by CT scan in the prone position (Fig. 5), indicating the internal consistency of our results. In the Inf group, FRC, DL\(_{\text{CO}}\), and Dm\(_{\text{CO}}\) at peak exercise were all significantly lower than in the other groups. From rest to exercise, DL\(_{\text{CO}}\) increased with respect to cardiac output due to increases in both Dm\(_{\text{CO}}\) and Vc. (Fig. 6). At a given submaximal exercise intensity, DL\(_{\text{CO}}\), Dm\(_{\text{CO}}\), and FRC were significantly lower in the Inf group than in the other groups. However, the slopes of the relationships between DL\(_{\text{CO}}\) and cardiac output were not significantly different among groups. Therefore, the presence or absence of prosthesis after right pneumonectomy did not affect the slope of DL\(_{\text{CO}}\) recruitment but only its magnitude at a given cardiac output.

**Effect of delayed deflation of the prosthesis.** In one dog (dog Z) with an initially inflated prosthesis, a small leak unexpectedly developed ~9 mo after pneumonectomy; chest X-ray showed almost complete collapse of the prosthesis. Subsequently, the prosthesis was refilled at frequent intervals; however, adequate filling could not be maintained, and mediastinal shift occurred. Data from this dog Z after 9 mo were excluded from group comparisons. After deflation of the prosthesis, both FRC and DL\(_{\text{CO}}\) in dog Z progressively rose over the next 3 mo (Fig. 7). At 12 mo after pneumonectomy, DL\(_{\text{CO}}\) at a given pulmonary blood flow in dog Z was similar to that in dogs with a continually deflated prosthesis. Normally, DL\(_{\text{CO}}\) increases due to increases in both Dm\(_{\text{CO}}\) and Vc. (Fig. 6). At a given submaximal exercise intensity, DL\(_{\text{CO}}\), Dm\(_{\text{CO}}\), and FRC were significantly lower in the Inf group than in the other groups. However, the slopes of the relationships between DL\(_{\text{CO}}\) and cardiac output were not significantly different among groups. Therefore, the presence or absence of prosthesis after right pneumonectomy did not affect the slope of DL\(_{\text{CO}}\) recruitment but only its magnitude at a given cardiac output.

**Table 2. Resting measurements of gas exchange**

<table>
<thead>
<tr>
<th></th>
<th>Inf</th>
<th>Def</th>
<th>RPNX</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>23.6 ± 0.8*</td>
<td>32.3 ± 1.9†</td>
<td>24.9 ± 0.8</td>
<td>25.3 ± 0.9</td>
</tr>
<tr>
<td>FRC, ml/kg</td>
<td>24.6 ± 0.9††</td>
<td>29.1 ± 0.7††</td>
<td>41.1 ± 1.6</td>
<td>41.1 ± 1.4</td>
</tr>
<tr>
<td>Cardiac output, l·min(^{-1})·kg(^{-1})</td>
<td>0.063 ± 0.008‡</td>
<td>0.054 ± 0.005††</td>
<td>0.082 ± 0.003‡</td>
<td>0.093 ± 0.003‡</td>
</tr>
<tr>
<td>DL(_{\text{CO}}), ml·min(^{-1})·Torr(^{-1})·kg(^{-1})</td>
<td>0.42 ± 0.02‡</td>
<td>0.43 ± 0.03†</td>
<td>0.44 ± 0.02‡</td>
<td>0.42 ± 0.05‡</td>
</tr>
<tr>
<td>Dm(_{\text{CO}}), ml·min(^{-1})·Torr(^{-1})·kg(^{-1})</td>
<td>1.03 ± 0.03‡</td>
<td>0.90 ± 0.02‡</td>
<td>0.96 ± 0.11‡</td>
<td>1.22 ± 0.10‡</td>
</tr>
<tr>
<td>Capillary blood volume, ml</td>
<td>1.12 ± 0.03‡</td>
<td>1.31 ± 0.02‡</td>
<td>1.65 ± 0.13‡</td>
<td>2.35 ± 0.18‡</td>
</tr>
<tr>
<td>Total septal tissue volume, ml</td>
<td>6.5 ± 0.7‡</td>
<td>7.2 ± 0.4‡</td>
<td>8.0 ± 0.8</td>
<td>10.6 ± 1.2</td>
</tr>
<tr>
<td>Extravascular septal tissue volume, ml</td>
<td>5.9 ± 0.4‡</td>
<td>6.1 ± 0.4</td>
<td>6.4 ± 1.4</td>
<td>8.3 ± 1.0</td>
</tr>
</tbody>
</table>

Values are means ± SE. Measurements were made under anesthesia in the supine position. Data for RPNX and Sham groups are from Hsia et al. (13). RPNX, right pneumonectomy without prosthesis; Sham, right thoracotomy without pneumonectomy; DL\(_{\text{CO}}\), lung diffusion capacity for carbon monoxide; Dm\(_{\text{CO}}\), membrane diffusion capacity for carbon monoxide. *P < 0.05 vs. Def; †P < 0.05 vs. RPNX; ‡P < 0.05 vs. Sham.
acutely expands, presumably due to unfolding of alveolar septa and stretching or thinning of the alveolar-capillary barrier. The normal relationship between DLCO and acute changes in lung volume in anesthetized dogs has been previously measured (5) and is shown in Fig. 8A. The acute effect of lung volume on DLCO is compared with the chronic effect occurring over 3 mo in dog Z (Fig. 8B). The initial increase in DLCO measured in dog Z 1 mo after prosthesis collapse is consistent with that expected from the simple mechanical effects of acute lung expansion, but DLCO subsequently increased significantly more than that expected from simple lung expansion. Thus, following delayed mediastinal shift, the increase in DLCO lagged behind the increase in lung volume. Only ~30% of the final increase in DLCO in dog Z after prosthesis deflation could be explained by volume increase; the remaining 70% must be attributed to other processes, such as structural growth of new alveolar septa.

**DISCUSSION**

**Attempts to prevent mediastinal shift after pneumonectomy.** Cohn (6) first showed, in rats, that filling the empty thoracic space after pneumonectomy with wax plombage reduced or eliminated the increase in size of the remaining lung, leading to the widely accepted conclusion that postpneumonectomy lung growth was induced solely by lung expansion, i.e., if expansion of the remaining lung was prevented, growth was prevented. Fisher and Simnett (7), however, measuring kinetics of lung tissue growth in pneumonectomized rats using mitotic index, found that plombage delayed but did not eliminate the growth response of the remaining lung. Brody et al. (2) using [3H]thymidine-labeled DNA to study the kinetics of lung growth in pneumonectomized mice, also found that wax plombage only delayed the growth response. Olson and Hoffman (24) studied rabbits before and after pneumonectomy and found that wax plombage did not completely prevent expansion of the remaining lung. Instead of expanding laterally across the midline, the remaining lung changed shape and elongated in the cranial-caudal direction, depressing the diaphragm. It is difficult to reconcile the results from Olson and Hoffman (24) with those from Cohn (6); only in the former study were the shape and volume of the remaining lung defined before and after pneumonectomy. However, assuming that the shape change and expansion of the remaining lung reflects regenerative growth, the data of Olson and Hoffman (24) are consistent with those of Fisher and Simnett (7) and Brody et al. (2), all suggesting that regenerative growth is not completely prevented by plombage. It is unclear whether the shape change of the lung after pneumonectomy was caused by externally applied distending pressures (i.e., by respiratory muscles) or whether it was induced independently. It is also unclear whether the shape change was related to mechanical effects of the relatively rigid wax.

**Effect of mediastinal shift on lung volume after pneumonectomy.** By imitating the shape, size, and content of the normal right lung using a biocompatible material, we attempted to prevent mediastinal shift and lung expansion after pneumonectomy while maintaining, as much as possible, the normal mechanical cardiothoracic and pulmonary interactions. Our results show that preventing mediastinal shift significantly inhibits the recruitment of DLCO during exercise, but expansion of lung air and tissue volumes was not completely prevented, suggesting that compensatory lung growth was not eliminated. In pneumonectomized adult dogs, the remaining left lung normally doubles in volume (13). In the present study, the resting FRC in Inf animals was 60 and 84% of that in Sham and Def.

![Fig. 5](http://jap.physiology.org/). A significant correlation (r) occurred between average function residual capacity (FRC) measured during exercise and lung air volume measured in the prone position by CT scan. FRC = 0.628; CT volume = +28.3, r = 0.86.
animals, respectively. Thus the remaining lung in the Inf group still increased in size \(\sim 30\%\), despite maintaining the mediastinum in the midline. This persistent expansion, the consequence of a depressed left hemidiaphragm, was qualitatively similar to the findings of Olson and Hoffman (24) in pneumonectomized rabbits. Septal tissue volume of the remaining lung, whether measured by CT scan or by rebreathing, was not affected by the inflated prosthesis. Septal tissue volume increased \(\sim 60\%\) above that expected for a normal left lung, regardless of whether the prosthesis was inflated or not. Thus our results are consistent with those of Fisher and Simnett (7), Brody et al. (2), and Olson and Hoffman (24), although in different species. All these data support the conclusion that preventing mediastinal shift after pneumonectomy only partially prevents lung expansion and the compensatory increase in lung tissue volume, i.e., the compensatory tissue response is not completely dependent on lung strain.

**Effect of mediastinal shift on gas exchange compensation.** After pneumonectomy, changes in resting \(D_{L_{\text{CO}}}\) are not a reliable index of compensation because blood flow through the remaining lung doubles; an increased flow recruits more capillaries and can mask a true impairment in diffusive gas exchange capacity. Impairment becomes evident when \(D_{L_{\text{CO}}}\) is compared during exercise at a given pulmonary blood flow. In the present study, \(D_{L_{\text{CO}}}\) is significantly lower in the Inf group than in either Def or RPNX groups. The reduction of \(D_{L_{\text{CO}}}\) in the presence of an inflated prosthesis could result from 1) impaired recruitment of existing capillaries and capillary surface area, because stretching, unfolding, and thinning of the alveolar-capillary barrier was prevented, or 2) impaired postpneumonectomy lung growth, because mechanical strain on the remaining lung was relieved. We have observed that postpneumonectomy compensation in adult animals is slowly progressive. The time course has not been fully defined, but probably spans up to 1 yr (12, 14). In the present study, exercise measurements were taken 3–5 mo after surgery, i.e., before full compensation was complete. Therefore, it is possible that \(D_{L_{\text{CO}}}\) recruitment in animals with inflated prosthesis may continue to improve. Physiological studies cannot directly address the question of lung growth. Nevertheless, data from dog Z provide compelling indirect evidence that regenerative lung growth was in fact inhibited by an inflated prosthesis during the first 9 mo. In dog Z, lung volume continued to increase for more than 3 mo after delayed prosthesis deflation. The small increase in \(D_{L_{\text{CO}}}\) seen early after prosthesis deflation was in keeping with that expected from acute volume expansion, but the subsequent accelerated increase in \(D_{L_{\text{CO}}}\) could

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**Fig. 6.** Diffusing capacities of the lung for carbon monoxide (\(D_{L_{\text{CO}}}\); A), FRC (B), membrane diffusing capacity (\(D_{M_{\text{CO}}}\); C), and pulmonary capillary blood volume (\(V_c\); D) are plotted with respect to pulmonary blood flow for individual dogs during exercise. At a given blood flow, \(D_{L_{\text{CO}}}\) and FRC are significantly lower in the INF group (closed symbols, solid regression lines) than in the DEF group (open symbols, broken regression lines). The difference is due to a lower \(D_{M_{\text{CO}}}\) in the INF group (C). There was no significant difference in \(V_c\) between groups (D).
not be explained by volume change alone and suggested structural alveolar growth. Thus delayed mediastinal shift months after pneumonectomy can still elicit the full range of physiological compensatory responses.

Potential stimuli for lung growth. The primary stimuli for compensatory lung growth are believed to be mechanical in origin. Mechanical distortion has long been known to induce cellular growth and alter cellular function. The best concrete example of stretch- and strain-induced cellular growth is epidermal growth induced by silicone tissue expanders routinely used by plastic surgeons. The subdermal expander is progressively inflated to induce stretching of the overlying skin and to generate epidermal tissue for homologous skin grafting (18, 25, 30). In the lung, two mechanical signals are thought to be important stimuli of tissue responses after pneumonectomy: 1) alveolar septal strain induced by lung expansion into the empty hemithorax (19, 20) and 2) vascular distortion induced by a doubling of blood flow through the remaining lung, resulting in shear stress and/or capillary distension (8, 9).

We observed an enlarged thoracic volume, elongation of the left lung, and displacement of the left hemidiaphragm after right pneumonectomy when the mediastinal shift was prevented by an inflated prosthesis. The fact that the left lung expanded ~20% in the caudal direction when lateral expansion was prevented suggests that postpneumonectomy lung expansion does not occur simply to fill the empty space. Rather, there must be other forces that elongate the lung. One possibility is an increased tidal activity of the inspiratory muscles, particularly the diaphragm, causing caudal expansion of the lung. Alternatively, endothelial shear and capillary distension from diversion of the

![Figure 7](https://example.com/fig7.png)

Fig. 7. One dog (dog Z) experienced delayed mediastinal shift ~9 mo after pneumonectomy. At a given pulmonary blood flow during exercise, there was a rapid and progressive increase of FRC with corresponding increases in DLco, over the subsequent 3 mo (B). By 13-mo postpneumonectomy, DLco at a given pulmonary blood flow had risen to that seen in dogs with a perpetually deflated prosthesis (A).

![Figure 8](https://example.com/fig8.png)

Fig. 8. A: normal relationship between lung volume and DLco in dogs at rest under anesthesia in the supine position measured by a rebreathing technique. Data are from Carlin et al. (5). B: increase in DLco in dog Z after delayed prosthesis deflation compared with DLco expected from simple lung expansion, based on the relationship in A and expressed at a fixed pulmonary blood flow (0.5 L/min). Comparison assumes the fractional increase in DLco per unit increase in lung volume in A and B is the same. On the basis of this assumption, simple mechanical effect of lung expansion explains <40% of the observed increases in DLco in dog Z.
total cardiac output through the remaining lung may induce growth along the direction of least resistance, even in the absence of a high, negative pleural pressure. Both of these mechanisms might be involved. It is unlikely that the small increase (20%) in lung volume alone could independently induce tissue growth. On the basis of previous data (11), more than doubling the volume of the remaining lung after resection is required to induce alveolar growth in the absence of added lung stretch. On the other hand, increased pulmonary perfusion in isolated rat lungs can induce immediate-early gene expression (c-fos and junB) similar to that seen in vivo in rats after pneumonectomy (8). Ligating one pulmonary artery can increase perfusion and augment alveolar growth of the contralateral lung in the newborn pig (9). These studies suggest that increased blood flow through the remaining lung can potentially stimulate lung growth; however, neither the cellular response nor the physiological correlates have been characterized. McBride et al. (22) found that banding one lobar artery in pneumonectomized ferrets (i.e., restricting blood flow through one lobe of the remaining lung and further increasing blood flow through the other remaining lobes) did not significantly affect the volume of banded or unbanded lobes 3 wk after surgery. No other measurements were performed, and these findings do not rule out a much slower response to a chronically elevated pulmonary blood flow that is consistent with delayed lung growth in the absence of lung distension, as suggested by the plombage data of Fisher and Simnett (7) and Brody et al. (2).

In conclusion, our data indicate that, after right pneumonectomy in the adult dog, expansion of the remaining lung is important but is not the only source for the compensatory recruitment of alveolar-capillary gas exchange during exercise. In response to chronic expansion of the remaining lung, recruitment of diffusing capacity is enhanced, partly as a consequence of mechanical stretching, unfolding, and thinning of the alveolar-capillary membrane and partly as a consequence of compensatory alveolar growth. The importance of lung expansion in the compensatory response is highlighted by the delayed deflation of the prosthesis ~9 mo after pneumonectomy in dog Z, which resulted in progressive lung expansion and normalization of alveolar-capillary recruitment over the subsequent months. Our data also provide indirect evidence that compensatory alveolar growth was not completely prevented when expansion of the remaining lung across the midline was inhibited by the inflated prosthesis.

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