In vivo assessment of changes in air and tissue volumes after pneumonectomy

S. TAKEDA, E. Y. WU, R. H. EPSTEIN, A. S. ESTRERA, AND C. C. W. HSIA

Departments of Internal Medicine, Radiology, and Surgery, University of Texas Southwestern Medical Center, Dallas, Texas 75235-9034

Takeda, S., E. Y. Wu, R. H. Epstein, A. S. Estrera, and C. C. W. Hsia. In vivo assessment of changes in air and tissue volumes after pneumonectomy. J. Appl. Physiol. 82(4):1340–1348, 1997.—We examined the progression and topographical distribution of postpneumonectomy volume changes in immature foxhounds undergoing right pneumonectomy (R-Pnx, n = 5) or sham pneumonectomy (Sham, n = 6) at 2 mo of age and subsequently raised to maturity. Volumes of lung air (Vair) and tissue (Vti) were estimated by computerized tomography (CT) scan at 7, 22, and 52 wk after surgery at a transpulmonary pressure of 20 cmH2O. Estimates of Vti by tomography (CT) scan and by an acetylene rebreathing (Rb) technique. Lung Vti estimated by CT scan (VtiCT) includes the volume of all septal (Vti sept) and nonseptal tissues (Vti nonspt), plus the volume of blood contained in small- and medium-sized blood vessels as well as alveolar capillaries. In contrast, lung Vti estimated by the acetylene Rb technique (VtiRb) includes only the Vti sept and capillary blood (VC) that participate in gas exchange and hence equilibrates rapidly with inspired acetylene. Our objectives were to utilize these two noninvasive techniques to determine 1) the temporal progression and topographical distribution of Vair and Vti of the lung and 2) the relative changes in Vti sept and Vti nonspt during the period of somatic maturation in immature dogs after right pneumonectomy (R-Pnx).

In addition, distortion of the thorax occurs after pneumonectomy. On chest radiographs taken previously in dogs after R-Pnx, the right hemithorax appears smaller, whereas the left hemithorax appears larger than before pneumonectomy, suggesting that compensatory inflation and/or growth of the remaining left lung may exert an expanding force on the left rib cage. A second objective of this study, therefore, was to examine whether early R-Pnx in immature animals results in distortion of volume distribution between the two hemithoraxes.

MATERIALS AND METHODS

Experimental groups. All procedures were approved by the Institutional Review Board for Animal Research. Litter-matched male purebred foxhounds were obtained from commercial breeders and underwent either R-Pnx (n = 6) or right thoracotomy without pneumonectomy (Sham; n = 6) under isoflurane anesthesia at 2 mo of age. In the R-Pnx group, a right lateral thoracotomy was made in the fifth intercostal space; the right main pulmonary artery and veins were isolated and doubly ligated. The right main bronchus was then divided and closed with staples. Air leakage was checked by immersing the bronchial stump in warm saline. After hemostasis was confirmed, the thorax was closed in three layers, and residual air in the right thorax was aspirated by a syringe. Dogs in the Sham group underwent right thoracotomy in the same fashion; the pleural space was opened and closed without pneumonectomy. One animal in the R-Pnx group died in the postoperative period because of the development of pulmonary edema. All other animals survived and were studied serially until reaching adulthood.

Measurements by CT scan. CT scan was performed under pentobarbital sodium anesthesia (25 mg/kg iv) at 7, 22, and 52 wk after surgery. Animals were intubated with a cuffed endotracheal tube, ventilated with a Harvard respirator at a tidal volume of 15 ml/kg, and placed in the supine position on the CT table. Before each image, the dog was hyperventilated to prevent spontaneous breathing during the period of imaging. Then the dog was disconnected from the respirator and...
allowed to exhale to functional residual capacity (FRC). The lungs were then inflated with a calibrated syringe at a volume previously determined to yield a transpulmonary pressure (Ptp) of 20 cm H₂O. By using a rapid scanner (Toshiba TCT 900S), a scout film was obtained to determine anatomic landmarks. Consecutive transverse tomographic images were obtained at 5-mm intervals between the apex and the costophrenic angle. The contours of the right and left lung in each image were traced separately, and the areas were measured by using software provided by the manufacturer. Major hilar blood vessels and main stem bronchi were excluded from measurement. An average CT number for each lung field was established. During calibration, the CT number of water was set at 0 and of air at −1,000 (mean value of intratracheal air was −990 to −1,030). Total Vt was estimated by numerical integration of volumes from all images by using the trapezoidal rule similar to that described previously (14, 15). Assuming that lung tissue had a CT number equal to that of muscle in the same dog (i.e., 52–59), relative contributions of tissue (Vti) and air (Vair) to the Vt were computed:

\[
\text{Vti} = Vl - Vair
\]

\[
Vt = Vl - Vair
\]

CT no. of tissue − CT no. of lung
CT no. of tissue − CT no. of lung

\[
Vti = Vl \times \frac{CT \text{ no. of tissue} - CT \text{ no. of lung}}{CT \text{ no. of tissue} - CT \text{ no. of air}}
\]

\[
Vair = Vl \times \frac{CT \text{ no. of tissue} - CT \text{ no. of air}}{CT \text{ no. of tissue} - CT \text{ no. of lung}}
\]

Estimates of Vti of each CT image were compared by paired t-test. Differences were regarded as significant if P < 0.05.

RESULTS

There were no significant differences in body weight and expressed as means ± SE. Vair and Vti measured by CT scan at 7, 22, and 52 wk were compared with corresponding values estimated by the Rb technique by linear least-squares regression. At each time point, data from the R-Pnx and Sham groups were compared by one-way analysis of variance (ANOVA). Serial measurements and topographical distributions of Vl and thoracic volume were compared between groups by repeated measures ANOVA (StatView v. 4.0, Abacus Concepts). Measurements between left and right hemithoraces on each image were compared by paired t-test. Differences were regarded as significant if P < 0.05.

The C¹⁸O disappearance curve was used to adjust zero time. Vc was estimated from lung diffusing capacity (DLCO) measured at two levels of alveolar O₂ tensions, as described previously (12). Only the log linear portion of the end-tidal acetylene and C¹⁸O disappearance curves was utilized in this analysis. The first three breaths and breaths beyond 12 s of Rb were routinely discarded. Extravascular Vti of each dog was estimated by subtracting Vc from Vti measured by Rb (Vti − Vc).

Statistics. Data were normalized for body weight and expressed as means ± SE. Vair and Vti measured by CT scan at 7, 22, and 52 wk were compared with corresponding values estimated by the Rb technique by linear least-squares regression. At each time point, data from the R-Pnx and Sham groups were compared by one-way analysis of variance (ANOVA). Serial measurements and topographical distributions of Vl and thoracic volume were compared between groups by repeated measures ANOVA (StatView v. 4.0, Abacus Concepts). Measurements between left and right hemithoraces on each image were compared by paired t-test. Differences were regarded as significant if P < 0.05.

There were no significant differences in body weight between groups at all time points: 16.2 ± 2.4, 29.8 ± 2.2, and 31.2 ± 1.2 kg for R-Pnx group; 16.5 ± 1.5, 29.7 ± 2.7, and 31.9 ± 2.3 kg for Sham group at 7, 22, and 52 wk, respectively (means ± SE). On average, the Vair and Vti of the left lung estimated by CT scan constituted 42 ± 1% (SE) of total volume in Sham group animals. The typical anatomic changes are illustrated in one CT image from a dog 52 wk after pneumonectomy (Fig. 1). Figure 2 shows the linear correlations of lung Vair and Vti measured by CT scan and by the Rb technique for all dogs. Two outlier points >3 SD below the mean were omitted. There were strong correlations for both relationships. The relationship for lung Vair was slightly but significantly below unity (Fig. 2A). Vti was consistently higher than Vair (Fig. 2B).

Figure 3 shows the progression of total Vair at Ptp = 20 cm H₂O measured by CT or Rb at the three time points in each group. As measured by CT scan, Vair was significantly (P < 0.05) lower in dogs after R-Pnx than in control animals. As measured by Rb, Vair was not significantly different between groups; this is because differences in Vair became exaggerated with lung inflation. As shown by previously published data from these same dogs, FRC was similar between groups, but at a Ptp of 30 cm H₂O, Vl was significantly lower in dogs after R-Pnx than in Sham animals (21). At 20 cm H₂O, the difference is intermediate. Figure 4 compares Vti of each dog between groups; this estimate includes Vti, Vti, and Vc. In the R-Pnx group, Vti was lower than in controls and decreased further between 7 and 22 wk after surgery. Estimates of Vc at different times were similar between groups and were published previously (21). Figure 5 shows the partition of Vti into septal and nonseptal components at different times. There was no significant difference between groups in extravascular Vti (Fig. 5A). Vti was only slightly lower in controls at 7 wk but declined with time and was significantly lower in the R-Pnx group (30% of control values) at maturity (Fig. 5B). Figure 6 shows the ratios...
There were no significant differences in Vtisept/Vair between groups, but the ratio of Vtinonsept/Vair became significantly lower in the R-Pnx group with time, indicating that growth of nonseptal tissue did not keep pace with increasing VL. Table 1 summarizes the final VL measured at maturity (14 mo of age).

As measured by CT scan, the cranial-caudal distributions of VL and Vti at each thoracic vertebral level at each time point are shown in Figs. 7 and 8, respectively. Data from Sham animals are shown for both lungs and for the left lung alone. The positions of the heart and great vessels approximately correspond to vertebral levels 6 to 9. The distributions of VL were similar among the three time points. VL in the R-Pnx animal was lower than in both lungs of the Sham animal at each vertebral level. At 7 wk after R-Pnx, the distribution of total Vti was similar to that in both lungs of Sham animals. However, as the animal matured, total Vti became significantly lower than in controls, particularly at the mid- and lower lung zones. Figure 9 shows the relative increases of VL and Vti in the R-Pnx group, expressed as a percentage of corresponding values in the left lung of Sham animals. The initial accelerated increase of Vti at 7 wk after R-Pnx was particularly marked in the midlung region, being greatest just above and below the heart. Subsequently, Vti increased proportionally to Vair, and the distributions of these were similar between groups. There were significant regional variations in the extent of Vair compensation.

The greatest relative volume expansion occurred in the regions immediately cephalad and caudal to the level of the heart.

Volumes of the left and right hemithorax measured at 52 wk after surgery are shown in Table 2. Volume of each hemithorax and total thoracic volume were significantly smaller in the R-Pnx group compared with the corresponding hemithorax in the Sham group. In addition, the right hemithorax was smaller than the left in both groups; the difference was statistically significant in the R-Pnx group but not in the Sham group. The distribution of thoracic volume is shown in Fig. 10. In both groups, the left hemithorax was significantly larger than the right in most images, regardless of anatomic level. Compared with the corresponding thorax in Sham animals, thoracic volume in animals after R-Pnx was lower at all anatomic levels.

**DISCUSSION**

Critique of methods. We found a strong correlation in lung gas volume estimated by CT scan and a Rb method. On average, Vair\textsubscript{CT} was lower than Vair\textsubscript{Rb} by \(~9\%\). These results differ from the reports of Hyde et al. (13) and Wandtke et al. (23), who found that gas volume at FRC calculated by CT scan underestimated FRC measured by Rb helium by 18 to 34% in dogs. This underestimation was attributed to a large extent to inaccuracies in CT measurement, e.g., boundary delineation, partial volume effect, beaming hardening, and
sampling limitations, all of which can be expected to become exaggerated by a lower \( V_L \). On the other hand, our CT measurements were obtained at an inflating pressure of 20 cmH\( _2 \)O, which corresponds to a lung gas volume more than twice that measured at FRC. At the higher \( V_L \), contrast between lung and the surrounding tissue is enhanced; technical errors associated with CT measurement should be minimized. This methodological difference probably explains the closer agreement between CT and Rb measurements of lung gas volume in the present study. Estimates of total lung \( V\\text{ti}_{\text{CT}} \) in our Sham animals at maturity were 14.6 ml/kg, slightly smaller than the 17 ml/kg reported by Hyde et al. (13) and 18 ml/kg by Johnson et al. (14).

There is a strong correlation between lung \( V\\text{ti}_{\text{sept}} \) measured by the acetylene Rb technique and \( V\\text{ti}_{\text{sept}} \) measured at postmortem by morphometric techniques (14). The average \( V\\text{ti}_{\text{Rb}} \) in our Sham animals at maturity was 8.6 ml/kg, slightly lower than the values obtained by Peterson et al. (12 ml/kg; Ref. 20) and Crapo et al. (~11.5 ml/kg; Ref. 4) but similar to that of Hyde et al. (9.0 ml/kg; Ref. 13). Lung \( V_L \) measured by CT scan is consistently higher than that by Rb acetylene by ~50%. This discrepancy is because of the inclusion of lung \( V\\text{ti}_{\text{nonsept}} \) in the CT estimates and has also been reported previously in both normal and pneumonectomized beagles (14, 15).

Fig. 3. By CT scan, total lung \( V_L \) at 20 cmH\( _2 \)O transpulmonary pressure (Ptp) was significantly lower (\( P < 0.05 \)) in dogs after R-Pnx than in sham-operated animals. By Rb technique, total lung \( V_L \) at same Ptp was not significantly different between groups.
Compensatory lung growth: septal vs. nonseptal tissue. In immature dogs after left pneumonectomy (L-Pnx), the remaining lung was shown to undergo an early compensatory increase in the rate of alveolar growth, resulting in an increased alveolar number and VL (22). However, that study was terminated before maturity was reached. The only previous long-term study in immature dogs, by Davies et al. (5), questioned whether the acceleration of alveolar growth seen early after pneumonectomy would persist until maturity. In the present group of dogs, separate studies show that this increased rate of alveolar growth persists (21); DLCO increased nearly twofold within 4–8 wk after R-Pnx and continued to increase at a normal developmental rate until maturity. This enhanced growth of the remaining lung yielded a DLCO equivalent to that measured in two lungs of control dogs at maturity. On the other hand, VL at a given distending pressure and lung compliance remained persistently lower and resis-
tance to air flow remained higher than normal. These mechanical abnormalities suggest either that growth of the airway lags behind that of lung parenchyma (dysan-
axis) or that there had been compositional change in the connective tissue matrix to cause both an increase in viscous tissue resistance and restriction of lung expansion.

Previous reports by other investigators suggest that postpneumonectomy compensatory growth of alveolar septal tissue is more extensive than that of nonseptal tissue (conducting airways and blood vessels). Such evidence has been inferred from a lower maximal

Table 1. Lung volumes 1 yr after surgery

<table>
<thead>
<tr>
<th></th>
<th>R-Pnx</th>
<th>Sham</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of animals</td>
<td>5</td>
<td>6</td>
<td>0.81</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>31.2 ± 1.2</td>
<td>31.9 ± 2.3</td>
<td>0.81</td>
</tr>
<tr>
<td>Rebreathing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vair</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lung</td>
<td>81.9 ± 6.7</td>
<td>42.0 ± 2.8</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Total lung</td>
<td>81.9 ± 6.7</td>
<td>100.1 ± 6.7</td>
<td>0.09</td>
</tr>
<tr>
<td>Vtisept</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lung</td>
<td>8.20 ± 0.44</td>
<td>3.63 ± 0.24</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total lung</td>
<td>8.20 ± 0.44</td>
<td>8.64 ± 0.57</td>
<td>0.56</td>
</tr>
<tr>
<td>CT scan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vair</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lung</td>
<td>70.5 ± 5.3</td>
<td>40.2 ± 3.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total lung</td>
<td>70.5 ± 5.3</td>
<td>95.3 ± 6.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Vtinepsept</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lung</td>
<td>10.11 ± 0.25</td>
<td>5.96 ± 0.22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total lung</td>
<td>10.11 ± 0.25</td>
<td>14.60 ± 0.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CT-rebreathing</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. All volumes are in ml/kg. Vair, lung air volume; Vtisept, septal lung tissue volume; Vtinepsept, nonseptal lung tissue volume; R-Pnx, right pneumonectomy; CT, computerized tomography; Vtinepsept, total tissue volume. *Left lung volume is calculated as 42% of total volume.
expiratory flow rate in dogs after L-Pnx (7, 8, 18) and a lower-than-expected airway cross-sectional area (17) as well as lengthening of peripheral airways (16) as seen in postmortem examination of immature ferrets after R-Pnx. Although these reports support the occurrence of dysanapsis, dysanaptic compensatory lung growth is not the only possible explanation. These findings are also consistent with a loss of radial traction on the small airways related to the reduction of elastic recoil of the remaining lung after pneumonectomy. The only data on airway and parenchymal tissue volume after pneumonectomy are from Burri and Sehovic (2), who found a less-than-expected increase in total airway tissue volume in rats after bilobectomy. The present report demonstrates for the first time the divergent
responses of septal and nonseptal tissue during the period of maturation in a large animal model. We found a complete restoration of normal \( V_t \) after R-Pnx, consistent with previous studies in immature dogs after L-Pnx, in which the amount of lung resected is smaller (14, 22). This vigorous acceleration of septal tissue growth occurred within 7 wk after pneumonectomy; during this period, the increase in \( V_t \) exceeded the increase in \( V_a \). Subsequently, \( V_t \) and lung \( V_a \) continued to increase at a matched developmental rate until maturity. These data support and extend the previous short-term findings of Thurlbeck et al. (22).

On the other hand, although there was an early increase in \( V_t \) after R-Pnx, subsequently the rate of its increase failed to match that of developmental growth. At maturity, \( V_t \) in dogs after pneumonectomy was only 30% of that in two normal lungs.

Table 2. Thoracic volumes measured by CT scan

<table>
<thead>
<tr>
<th></th>
<th>R-Pnx</th>
<th>Sham</th>
<th>P Value, R-Pnx vs. Sham, ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total volume</td>
<td>154.4 ± 4.3</td>
<td>187.3 ± 8.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Left hemithorax</td>
<td>79.8 ± 1.7</td>
<td>95.9 ± 5.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Right hemithorax</td>
<td>74.6 ± 2.9</td>
<td>91.4 ± 3.3</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>P value, left vs. right hemithorax, paired t-test</td>
<td>&lt;0.05</td>
<td>0.16</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE; all volumes are in ml/kg. ANOVA, analysis of variance.
Topographical distribution of V\textsubscript{l} and thoracic volume. Using cine X-ray CT scan, Olson and Hoffman (19) found in studies of adult rabbits that the topographical distribution of air content of the lung was influenced by V\textsubscript{l} as well as by the gravitational effect of the mediastinum and abdominal content in different postures. Pneumonectomy did not significantly alter these distributions in the supine or prone position. In this study, we found that the increase in Vair and VTi of the left lung after R-Pnx occurred at all anatomic levels, but the relative increase in VTi was most pronounced in the regions just cranial and caudal to the heart and least pronounced in the apex and the costophrenic angles. Thus compensatory growth occurs most markedly in the midregion of the lung.

Johnson et al. (14) previously found, in studies of beagles that received L-Pnx as puppies, that thoracic compliance above FRC increased above that in control animals. Dimensions of the thorax measured by CT scan diminished commensurate with a reduced Vl at any given Ptp. From plain chest X-rays taken previously of dogs and human subjects studied after pneumonectomy, we had observed that, although the hemithorax on the side of resection appeared smaller, as expected, the hemithorax on the side of the remaining lung often appeared larger than before pneumonectomy. However, conclusions cannot be drawn from such observations, because the entire thoracic cage, including the spine, is variably distorted by pneumonectomy. We wondered whether growth and expansion of the remaining lung, in addition to causing displacement of the mediastinum across the midline, also caused expansion of the ipsilateral rib cage. If so, after R-Pnx the volume of the right hemithorax should be smaller than control values while volume of the left hemithorax should exceed control values. Measurements of hemithoracic volumes from serial CT images show that this is not the case. The reduction of thoracic volume after R-Pnx was similarly distributed in the cranial-caudal direction. After R-Pnx, both left and right hemithoraces were significantly smaller than the corresponding hemithorax in control animals, i.e., there was no evidence of greater expansion and growth of the left rib cage. In both groups, the left hemithorax was slightly larger (by 5–7%) than the right by paired analysis. This finding is unexpected and raises the possibility that early thoracotomy may have adversely affected subsequent development of the right rib cage in both groups. This issue cannot be resolved by the present study because of a lack of matched, unoperated dogs.

In conclusion, in this study we compared two noninvasive, in vivo techniques of estimating lung Vair and VTi in immature dogs raised to maturity after R-Pnx. Total lung VTi was restored during an initial phase of accelerated compensatory lung growth, followed by a normal rate of developmental growth that persisted until maturity. Compensatory growth involved mainly septal lung tissue, with very limited growth of nonseptal lung tissue. The disparity between VTi\textsubscript{sept} and VTi\textsubscript{nonsept} persisted throughout maturation. Early R-Pnx was not associated with a selective alteration in thoracic development.

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Present address of S. Takeda: First Dept. of Surgery, Osaka University Medical School, 202 Yamadaoka, Suita, Osaka 565, Japan.

Address for reprint requests: C. C. W. Hsia, Dept. of Internal Medicine, Univ. of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75235-9034.

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