Progressive adaptation in regional parenchyma mechanics following extensive lung resection assessed by functional computed tomography

Cuneyt Yilmaz, Nicholas J. Tustison, D. Merrill Dane, Priya Ravikumar, Masaya Takahashi, James C. Gee, and Connie C. W. Hsia

Department of Internal Medicine and Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, Texas; and Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania

Submitted 28 April 2011; accepted in final form 23 July 2011

Yilmaz C, Tustison NJ, Dane DM, Ravikumar P, Takahashi M, Gee JC, Hsia CC. Progressive adaptation in regional parenchyma mechanics following extensive lung resection assessed by functional computed tomography, J Appl Physiol 111: 1150–1158, 2011. First published July 28, 2011; doi:10.1152/japplphysiol.00527.2011.—In adult canines following major lung resection, the remaining lobes expand asymmetrically, associated with alveolar tissue regrowth, remodeling, and progressive functional compensation over many months. To permit noninvasive longitudinal assessment of regional growth and function, we performed serial high-resolution computed tomography (HRCT) on six male dogs (9 mo old, 25.0 ± 4.5 kg, ±SD) at 15 and 30 cmH2O transpulmonary pressure (Ptp) before resection (PRE) and 3 and 15 mo post resection (POST3 and POST15, respectively) of 65–70% of lung units. At POST3, lobar air volume increased 83–148% and tissue (including microvascular blood) volume 120–234% above PRE values without further changes at POST15. Lobar-specific compliance (Cs) increased 52–137% from PRE to POST3 and 28–79% from POST3 to POST15. Inflation-related parenchyma strain and shear were estimated by detailed registration of corresponding anatomical features at each Ptp. Within each lobe, regional displacement was most pronounced at the caudal region, whereas strain was pronounced in the periphery. Regional three-dimensional strain magnitudes increased heterogeneously from PRE to POST3, with further medial-lateral increases from POST3 to POST15. Lobar principal strains (Ps) were unchanged or modestly elevated post resection; changes in lobar maximum Ps correlated inversely with changes in lobar air and tissue volumes. Lobar shear distortion increased in coronal and transverse planes at POST3 without further changes thereafter. These results establish a novel use of functional HRCT to map heterogeneous regional deformation during compensatory lung growth and illustrate a stimulus-response feedback loop whereby post resection mechanical stress initiates differential lobar regrowth and sustained remodeling, which in turn, relieves parenchyma stress and strain, resulting in progressive increases in lobar Cs and a delayed increase in whole lung Cs.

measured by high-resolution computed tomography (HRCT) correlates with lobar alveolar tissue volume following pneumonectomy (PNX) (20) and that preventing post-PNX lung expansion using an inflatable silicone prosthesis significantly blunts structural and functional compensation (11, 12, 26). Until now, the relationship between lung expansion and mechanical tissue stress has been inferred; in vivo magnitude and distribution of parenchyma deformation have not been directly measured. Furthermore, in large animals, such as the dog, post resection parenchyma remodeling progresses over many months, associated with continuing improvement in lung diffuse capacity (10, 13, 18); hence, there is a need for noninvasive techniques that can follow growth and remodeling in correlation with their functional consequences. To this end, we developed a lobe-based HRCT image analysis technique to directly map regional air and tissue (including microvascular blood) volumes, as well as fractional tissue volume (FTV) during postnatal and post PNX lung growth (19, 20, 27). With the use of this technique, we demonstrated significant intra- and interlobar spatial heterogeneity in the compensatory response in correlation with postmortem alveolar tissue volume. In the present report, we extended this technique to longitudinally map regional mechanical strain and shear during inflation from images obtained at two transpulmonary pressures (Ps) in adult canines before (PRE) and 3 and 15 mo following (POST3 and POST15, respectively) extensive lung resection. Our objectives were to define the distribution of regional lung deformation and shear distortion, describe the time course of mechanical compensation during post resection growth and remodeling, and establish the feasibility of this technique for longitudinal followup of regional lung mechanics. We tested the hypothesis that post resection regional mechanical function continues to improve beyond the early period of active cellular growth.

MATERIALS AND METHODS

Animals. The Institutional Animal Care and Use Committee of the University of Texas Southwestern Medical Center approved all procedures. Six litter-matched male mixed-breed hounds (~9 mo old) were studied before and after undergoing surgical resection of 65–70% of lung tissue by a two-stage procedure performed 1 mo apart. The surgical procedure and physiological measurements have been described in detail elsewhere (9). Briefly, under general anesthesia and lateral thoracotomy, the appropriate lobar arteries and veins were ligated and cut. The appropriate lobar bronchi were stapled and the lobes removed. The stumps were immersed in warm saline to check for leaks. The chest wall was closed in layers, and a chest tube with a one-way valve was placed for 24 h. Analgesics were administered postoperatively for 48 h and then as needed. In the first procedure, a left lateral thoracotomy was performed and the left caudal lobe removed. Following recovery 1 mo later, a right lateral thoracotomy was performed...
where the right middle, caudal, and infracardiac lobes were removed. Three lobes remained: right cranial (RC), left cranial (LC), and left middle (LM). These remaining lobes comprised 12%, 12%, and 7%, respectively, of the original lung units (9). The LM lobe has been considered the inferior part of the LC lobe because its bronchus arises immediately next to the LC lobe (14). Here, we considered the two parts as distinct lobes because sometimes they are completely separated by fissures in the foxhound and because the mechanical behavior of the LM lobe was distinct from that of the other two remaining lobes (see RESULTS). Because roughly similar amounts of lung remained in each side (12% and 19%), the mediastinum maintained its midline position. The animals tolerated the resection well and without complications. HRCT was performed 1 mo before surgery and 3 and 15 mo following the second surgery.

HRCT. These procedures have been described previously (19, 20, 27). The animals were fasted overnight and premedicated, and a peripheral IV catheter was inserted. Anesthesia was induced with intravenous propofol and maintained with an infusion of ketamine and diazepam. The animal was intubated with a cuffed endotracheal tube, placed supine on the computed tomography (CT) table and mechanically ventilated using a volume-controlled ventilator (Model 613, Harvard Apparatus, Holliston, MA) at a tidal volume of 12 mL/kg and a rate (18 breaths/min) sufficient to eliminate spontaneous breathing efforts. Esophageal and mouth pressures were measured simultaneously to estimate Ptp. Initially, a General Electric (GE) High-Speed CTI (Milwaukee, WI) was used (3 × 3 mm collimation, 120 kV, 250 mA, a pitch of 1.0, and a rotation time of 0.8 s). Images were reconstructed at consecutive, 1-mm intervals, resulting in 300–325 images/animal. Later, a GE LightSpeed 16 CT scanner became available (1.25 × 1.25 mm collimation, 120 kV, 190 mA, pitch 1.0, and rotation time 0.5 s) and was used to obtain consecutive images at 1.25-mm thickness. Scout images were obtained to ensure the field of scan included the entire lung from the apex to the diaphragm and halfway between them; average CT value (in HU) of a lobe. Specific lobar volumes (Vlobe) between two levels of Ptp (ΔPtp) normalized by Vlobe:

\[
C_s = \frac{\Delta V_{\text{lobe}}}{\Delta P_{\text{tp}} \cdot V_{\text{lobe}}} \tag{4}
\]

Deformation analysis. Deformation of anatomical pulmonary landmarks between the two levels of Ptps (15 and 30 cmH2O) was analyzed using a nonrigid image registration software, Advanced Normalization Tools (ANTS; University of Pennsylvania, Philadelphia, PA), which has been described in detail elsewhere (2–4, 6, 21, 24). Briefly, the algorithm estimates regional lung displacement by maximizing a specified similarity metric over the paired registered images to identify corresponding locations between the images (6). The estimated displacements were used to model the deformation of the lung parenchyma. The Lagrangian strain, derived from the calculated displacement vectors, was used to quantify lung-tissue deformation between the two inflation levels. We explored several transformation models and similarity metric options to ensure accurate image registration. The optimal ANTS configuration was determined based on visual inspection and a computer algorithm that labeled overlapping voxels and measured the displacements of paired voxels between the registered images (4). This optimal configuration included the use of the directly manipulated free-form deformation model (24) and a local, normalized cross-correlation similarity metric to account for the variation in CT attenuation between the paired images. The computed correspondences yielded three-dimensional (3D) displacement vector field maps that describe regional movement of the parenchyma. The magnitude and direction of regional displacement vectors and the principal strains (PSs) and shear distortion were derived from tensor eigenvalues.

Statistical analysis. Results were expressed (mean ± SD) in absolute units or as ratios with respect to baseline values. Each lobe served as its own reference space for comparisons across time points, and whole lung values were derived separately. Comparisons with respect to time points and inflation volumes used repeated measures ANOVA. Comparisons among lobes used one-way ANOVA. Post hoc analysis was by Fisher’s Protected Least Significant Difference. A P value of 0.05 or less was considered significant.

RESULTS

Body weight did not change with time: 25.0 ± 4.5, 25.6 ± 3.9, and 24.6 ± 4.1 kg at PRE, POST3, and POST15, respectively (mean ± SD). The airways, vascular trees, and lobes were reconstructed at the three time points (Fig. 1). Postresection, the remaining lobes expanded primarily in a caudal direction, accompanied by bronchovascular elongation, rotation, and distortion. The magnitude and distribution of CT-derived regional air and tissue volumes and Cs in these animals at PRE and POST3 have been published (27). Since a given inflation volume is distributed among three lobes postresection, instead of seven PRE, the fraction of inflation volume received by each remaining lobe increased more than fourfold (27). The fractional increase in lobar volume from 15 to 30 cmH2O of Ptp, calculated as [(air volume_{ POST3} – air volume_{ PRE})/air volume_{ PRE}] at PRE, POST3, and POST15, is shown in Table 1. Normally, the fractional volume increase during inflation was higher in both caudal lobes and the right infracardiac lobe (0.21–0.31) compared with the cranial and middle lobes (0.05–0.11). After the caudal and infracardiac lobes were removed (POST3), fractional increase in air volume during inflation was greater and more uniform among the remaining lobes, with further improvement in uniformity by POST15. The small LM lobe experienced the largest increase in fractional volume change during inflation. The relative changes in air and tissue volumes, FTV, and Cs are shown in Table 2. By POST3, the
remaining lobes enlarged by 83–148% in air volume and 120–234% in tissue + microvascular blood volume, associated with a 21–31% increase in FTV above PRE baseline. The LM lobe exhibited the largest relative increase in air and tissue volumes. Whole lung air and tissue volumes were restored to ~73% and 91%, respectively, of PRE baseline. There was no further change in these parameters between POST3 and POST15. In contrast, lobar Cs increased 52–137% at POST3 compared with PRE and another 28–79% between POST3 and POST15 to reach final levels 170–196% above PRE baseline (Table 2 and Fig. 2). Whole lung Cs was similar to PRE at POST3 but ~50% higher by POST15.

Fig. 1. Representative 3-dimensional (3D) reconstruction of airways (1st row), superimposed blood vessels (2nd row), and individual lobes in anteroposterior and caudal oblique views (3rd and 4th rows, respectively) before (PRE) and at 3 and 15 mo following (POST3 and POST15, respectively) resection.
Displacement vectors obtained between 15 and 30 cmH₂O Ptp are shown in 3D color field maps and representative 2D cross-sections (Fig. 3). Normally, the displacement vectors were oriented toward the diaphragm with a clear cranial-to-caudal gradient of increasing magnitude within and among lobes. The largest displacements were seen next to the diaphragmatic surface near the posterior costophrenic angle. At POST3, displacement magnitude was generally reduced, especially at the cranial end and periphery, although the cranial-to-caudal gradient was preserved. By POST15 compared with PRE, displacement magnitudes, which increased back to or in some regions, exceeded that in the corresponding regions of the same lobe(s) before resection. There was marked spatial heterogeneity in displacement within and among lobes, with the largest postresection changes occurring in the LM lobe, which came to lie adjacent to the costophrenic angle.

The corresponding strain vectors are shown in 3D color field maps and representative 2D cross-sections (Fig. 4). Normally, strain vectors were oriented toward the hila with larger magnitude in the peripheral and mid-to-lower lung zones compared with the central and cranial lung zones. Strain magnitude in the central/perihilar regions and the LM lobe increased at POST3 and then declined toward baseline by POST15.

Mean lobar strain magnitude was expressed along mediolateral (xx), anteroposterior (yy), and craniocaudal (zz) directions (Fig. 5, top panels). Mean lobar strain was not significantly different among lobes PRE but increased heterogeneously postresection, with the largest increases in the LM lobe along anteroposterior and craniocaudal directions. In all lobes, strain magnitude along the mediolateral axis continued to increase between POST3 and POST15. Lobar PSs derived from the eigenvectors (Fig. 5, middle panels) were also higher in the LM lobe than in other lobes and higher at POST15 than PRE but not significantly different between POST3 and POST15. Lobar shear distortion was negligible PRE (Fig. 5, bottom panels). Significant shear (P < 0.05 vs. 0) developed POST3 and POST15 in the coronal (xz) plane of all remaining lobes and in the transverse (xy) plane of the LM lobe. In the coronal plane, the directions of shear distortion of the right and LC lobes mirrored each other.

There was no significant correlation PRE between absolute PS and lobar air or tissue volumes (data not shown). At POST3 and POST15, the relative changes (POST/PRE ratio) in lobar air and tissue volumes were directly and significantly correlated (Fig. 6, left panels); i.e., greater expansion was associated with greater tissue growth. The POST/PRE ratio in lobar specific lung compliance from PRE to POST3 and POST15

<table>
<thead>
<tr>
<th>Lobe</th>
<th>PRE</th>
<th>POST3</th>
<th>POST15</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Cranial</td>
<td>0.110 ± 0.042</td>
<td>0.171 ± 0.008</td>
<td>0.268 ± 0.111</td>
</tr>
<tr>
<td>R Middle</td>
<td>0.048 ± 0.040</td>
<td>0.312 ± 0.113</td>
<td>0.214 ± 0.074</td>
</tr>
<tr>
<td>R Infracardiac</td>
<td>0.089 ± 0.053</td>
<td>0.211 ± 0.037</td>
<td>0.247 ± 0.032</td>
</tr>
<tr>
<td>L Cranial</td>
<td>0.113 ± 0.030</td>
<td>0.290 ± 0.022</td>
<td>0.310 ± 0.056</td>
</tr>
<tr>
<td>L Middle</td>
<td>0.307 ± 0.160</td>
<td>0.193 ± 0.066</td>
<td>0.205 ± 0.009</td>
</tr>
<tr>
<td>L Caudal</td>
<td>0.111 ± 0.030</td>
<td>0.290 ± 0.022</td>
<td>0.310 ± 0.056</td>
</tr>
<tr>
<td>Whole Lung</td>
<td>0.193 ± 0.066</td>
<td>0.205 ± 0.009</td>
<td>0.258 ± 0.051</td>
</tr>
</tbody>
</table>

Mean ± SD. Whole lung values represent 7 lobes preresection (PRE) and 3 lobes postresection. POST3, 3 mo postresection; POST15, 15 mo postresection; R, right; L, left.

**DISCUSSION**

**Summary and significance.** This is the first study to directly measure noninvasively in vivo parenchyma deformation and map regional parenchyma strain and shear distortion in a robust model of compensatory lung growth. The main findings follow:

1) During normal inflation, parenchyma displacement was greater at the caudal rather than the cranial region of each lobe, whereas strain was greater in the peripheral rather than the central region of each lobe. Lobar shear distortion was negligible. 2) At POST3, lobar air volume increased by 83–148% and tissue-microvascular blood volume 120–234% above PRE baseline values without further changes from POST3 to POST15. In contrast, lobar Cs continued to increase 52–137% from PRE to POST3 and 28–79% from POST3 to POST15, resulting in a delayed 50% increase in whole lung Cs. This pattern is consistent with the consequences of progressive alveolar tissue and architectural remodeling beyond the early period of active cellular proliferation and tissue growth (POST3). 3) Lobar strain increased heterogeneously PRE to postresection, with further increases in the mediolateral direction from POST3 to POST15. 4) Heterogeneous lobar shear distortion developed postresection in the transverse and coronal planes. 5) The remaining LM lobe experienced significantly larger postresection strain and shear, as well as larger increases in air and tissue volumes and Cs than the other remaining lobes. 6) Postresection changes in lobar expansion correlated directly with compensatory lung growth and correlated inversely with changes in mechanical strain; i.e., greater...
lobar expansion was associated with greater tissue growth and smaller increases in inflation-related mechanical strain. These novel results establish our HRCT technique for the longitudinal quantification and intra- as well as interlobar comparisons of asymmetric regional lung expansion, growth, Cs, strain, and shear. Results support an in vivo stimuli-response feedback mechanism between parenchyma deformation and progressive compensatory lung growth and remodeling (Fig. 7; discussed below in Regional parenchyma deformation).

Measuring in vivo mechanical lung strain. With the use of lung volume expansion following PNX as a surrogate marker of parenchyma stress, we reported that lobar air and tissue volumes estimated by HRCT correlated significantly with alveolar septum (tissue + capillary blood) volume, measured postmortem by morphometry. However, because HRCT-derived tissue volume also incorporates blood in microvessels, up to ~1 mm in diameter, it is systematically higher than the morphometric estimates (20). Serial HRCT tracked longitudinal changes in lobar air and tissue volumes during postnatal as well as post-PNX lung growth (19, 20). In a separate series of studies, we showed that preventing mediastinal shift and lateral lung expansion following right PNX, using an inflatable silastic coneprosthesis, impaired the expected activation of growth-related cellular signaling (28), the anatomical growth of alveolar-capillary tissue volume and surface areas (12), and the compensatory increases in diffusing capacity for O2 and CO at rest and during exercise in the remaining lung (11, 26). These data demonstrate directly that mechanical lung stresses provide major stimuli for initiating and perpetuating the compensatory responses. However, owing to the asymmetry of intrathoracic structures and rigidity of the mediastinum, postresection increase in lobar volume was heterogeneous, ranging from negligible in some lobes to more than threefold in others. Regional expansion within the remaining lobes was also heterogeneous, exhibiting significant 3D gradients in air and tissue volumes, as well as FTV (27). In addition, moderate lobar expansion may cause unfolding of alveolar septa without increasing cell/tissue stress. These caveats make lung volume an imprecise surrogate measure of parenchyma strain. Furthermore, compensatory lung growth and remodeling in large animals, such as the dog, progress over many months following lung resection (10, 13, 18), thus prompting us to explore noninvasive, functional imaging methods to map regional lung anatomy and mechanics in the presence of gross architectural distortion.

HRCT-based deformation analysis. The various image registration algorithms developed and characterized extensively by Gee and colleagues (6, 22–24) have been used to analyze motion and deformation of solid organs as well as the lung obtained by MRI during normal respiration. In healthy volunteers, regional parenchyma strain was oriented toward the hilum with maximal strain magnitude seen at midexpiration (6). Subsequently, Kiryu et al. (15) applied this approach to describe heterogeneity of regional lung motion in mice. In normal mice, the right and left lungs moved symmetrically with greater movement in the lower than the upper regions and uniform calculated strain through the entire lung. In transgenic mice with sickle cell disease, pulmonary motion was normal at baseline but became distorted upon exposure to hypoxia. In these MRI studies, image registration relied on vascular landmarks because parenchyma features and individual lobes could not be resolved. One advantage of HRCT is the high resolution of parenchyma details that allow bronchial, vascular, and pleural features to be used for registration. However, the calculated regional parenchyma displacement from HRCT obtained at two inflation levels reflects static deformation rather than dynamic respiratory motion.

Regional parenchyma deformation. Normally, parenchyma displacement during inflation is larger near the diaphragm, reflecting preferential ventilatory distribution to the caudal and infracardiac lobes, which were later removed. Postresection displacement near the diaphragm reflects movement of the LM lobe and the caudal end of the RC lobe, which normally receive less fractional inflation vol-
Postresection asymmetric expansion and vigorous tissue growth more than doubled the size of these lobes. Ventilation was redistributed, such that each remaining lobe received more than four times its normal fraction of inflation volume (27). For a given ΔPtp, regional displacement magnitude at POST3 was globally reduced, reflecting hyperinflation; however, the total lobar volume increase was greater, i.e., a higher lobar Cs. In addition to hyperinflation

Fig. 3. Color maps of displacement vector field are shown in 3D (top 2 rows) and 2D cross-sections in the coronal, sagittal, and transverse planes (bottom 3 rows, respectively) at 3 time points (PRE, POST3, and POST15).

Fig. 4. Color maps of strain field are shown in 3D (top 2 rows) and 2D cross-sections in the coronal, sagittal, and transverse planes (bottom 3 rows, respectively) at 3 time points (PRE, POST3, and POST15).
and growth, structural remodeling must have contributed to tissue relaxation between POST3 and POST15, such that regional displacement, particularly in the LM lobe and caudal end of the RC lobe, continues to increase toward restoring the normal topographical pattern associated with an increase in lobar Cs without evidence of further lobar growth. Whole lung Cs reflects seven lobes PRE and three lobes postresection. At POST3, the increase in lobar Cs was enough to normalize whole lung Cs; further increases in lobar Cs between POST3 and POST15 led to a delayed increase in whole lung Cs.

Ongoing distal lung remodeling may consist of rearrangement of alveolar septal constituents (cells, fibers, matrix, and capillaries), thinning of the membrane-blood barrier, and normalization of alveolar duct and sac volumes, as well as their architecture. Adjustment of the 3D relationships among septal ultrastructure and acinar components is often difficult to quantify but could contribute significantly to lowering tissue stresses and optimizing gas exchange. With the use of postmortem morphometry, we have shown that these remodeling events occur and continue for more than 5 mo in adult dogs following PNX and are associated with progressive improvement in gas exchange, as well as mechanical function (13, 18).

Several observations support a causal relationship between parenchyma deformation and compensatory alveolar growth and remodeling. 1) Owing to a lack of rigid bronchovascular support in the lobar periphery, it is not surprising to find accentuated strain in this region. Interestingly, the periphery also experiences the fastest rate of cell proliferation and turnover during postnatal maturation and following PNX (5, 17). 2) Compared with the other remaining lobes, the LM lobe consistently exhibited a larger postresection increase of mean strain and shear magnitudes (Fig. 5), which correlated with larger relative increases in air and tissue volumes, FTV, and Cs (Table 1). 3) By POST15, the change in lobar maximum PS tensor correlated inversely with that in lobar air and tissue volumes, i.e., the greater the lobar growth, the smaller the increase in mechanical strain during inflation (Fig. 6). Shear stress postresection in the coronal plane of RC and LC lobes mirrors each other, reflecting the predominantly caudal direction of distortion, whereas the significant postresection shear in the transverse plane of the LM lobe reflects rotation of the middle lobe as it expanded around the heart.

The above observations, taken together with our previous reports (11, 12, 19, 20, 26 – 28), support the interpretation that postresection heterogeneous parenchyma deformation triggers and sustains compensatory lung growth and/or remodeling in a manner dependent on the stimulus intensity (i.e., severity of resection). Growth and remodeling in turn mitigate tissue stress and strain in a feedback mechanism (Fig. 7), which continues with gradually diminishing intensity until regional stress/strain declines below a critical threshold where tissue responses become negligible. Threshold for the initiation, as well as cessation of tissue responses, is likely reached at a variable rate in different lobes or regions, thus explaining our observations of slow, progressive alveolar remodeling and functional improvement over many months following major resection. We can further speculate that as long as the local mechanical stresses remain suprathreshold, the regionally active, growth-related regulatory pathways will be amenable to intervention; this possibility would explain our previous observation that oral supplementation of exogenous growth promoters (all-trans retinoic acid) continues to exert an enhancing effect on alveolar septal tissue growth more than 4 mo following right PNX (18). However, enhancement of cellular and tissue growth may not lead to functional augmentation unless growth is accompanied or followed by appropriate remodeling to preserve and/or...
restore the optimal architectural relationships among septal and acinar components.

Limitations of the study. Regional lung mechanics during passive inflation may not reflect spontaneous breathing in the conscious state. At functional residual capacity, boundary definition is suboptimal, and it is difficult to breath-hold through the duration of scanning without incurring spontaneous breathing efforts; hence, HRCT was performed at higher lung volumes. Postresection, the hyperinflated, remaining lobes operated at or near the pressure-volume plateau. The pressure excursion at HRCT ($P_{tp}$ $15$ cmH$_2$O) exceeds that during conscious, spontaneous tidal breathing at rest ($P_{tp}$ $6$ and $9$ cmH$_2$O PRE and postresection, respectively) but is in the range of the excursion at peak exercise ($\Delta P_{tp}$ $19 \pm 7$ and $39 \pm 17$ cmH$_2$O PRE and postresection, respectively). Measurements were made supine and do not account for potential postural changes. We assume a uniform pleural pressure distribution. In normal canine lobes, small pressure variations can exist that do not follow any clear topographical orientation and are indicative of variable lung $C_s$ within small regions (16).

Whereas heterogeneity in the distribution of inflation volume within and among lobes was evident both PRE and postresection, there was no net increase in physiological measures of ventilatory heterogeneity (9, 27). Postresection, the distribution of inflation volume among the remaining lobes became more uniform than PRE and continued to improve with time (Table 1). In other models of destructive lung disease, e.g., canine unilateral emphysema, mean pleural pressure in the two hemithoraces remains equal, and regional volume distribution between the emphysematous and nonemphysematous lungs is determined only by differences in lung recoil and $C_s$ (16). Furthermore, substantial distortion of thoracic shape produces little change in local pleural pressures (7, 25). Thus any uncertainty regarding regional pleural pressure distribution does not detract from our major conclusion of progressive, topographically heterogeneous structural adaptation, leading to overall tissue relaxation and improved lobar $C_s$.

Conclusion. We describe a novel technique of noninvasive, functional CT to map regional mechanical function of lung parenchyma during canine compensatory growth following extensive resection. The findings of heterogeneous regional displacement, strain, and shear clearly reflect variable regional
mechanical forces, the patterns of which correlate quantitatively as well as qualitatively with cellular and structural adaptation. Results also demonstrate progressive improvement of mechanical lung function beyond the first POST3 in a way analogous to the previously reported progressive improvement in gas exchange and structural dimensions (10, 13, 18), consistent with persistent parenchyma remodeling following the initial phase of cellular proliferation and tissue growth. Given the complexity of acinar structure and the difficulty of remodeling a highly stratified scaffold to balance the often-conflicting requirements for optimal gas exchange and mechanical strength, a protracted time course of anatomical adjustment is probably unavoidable. In fact, gradual adjustment may be preferable to rapid adaptation to minimize structure-function distortions that could detract from maximum long-term compensation. Thus longitudinal followup is needed to establish the full extent, as well as distribution of postresection lung regrowth and functional outcome in large mammalian lungs. Our analysis of serial, functional CT could facilitate the longitudinal assessment of regional, anatomical-mechanical correlation, not only in this model but also during lung development and in other focal or diffuse pulmonary pathologies.

ACKNOWLEDGMENTS

The authors thank Greg Horton, Jennifer Fehmel, and Corie Thorson for technical assistance, the staff of the Animal Resources Center for assistance with veterinary care, and Jeanne-Marie Quevedo for administrative assistance.

GRANTS

The research was supported by the National Heart, Lung, and Blood Institute Grants R01 HL040070 and HL062873.

DISCLOSURES

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Heart, Lung, and Blood Institute or of the National Institutes of Health.

REFERENCES