Effect of lung inflation and airway muscle tone on airway diameter in vivo

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Brown, Robert H., and Wayne Mitzner. Effect of lung inflation and airway muscle tone on airway diameter in vivo. J. Appl. Physiol. 80(5): 1581–1588, 1996.—How normal airway dimensions change with lung volume is of great importance in determining flow limitation during the normal forced vital capacity maneuver as well as in the manifestation of obstructive lung disease. The literature presents a confusing picture, with some results suggesting that airway diameter increases linearly with the cube root of lung volume and others showing a highly nonlinear relation. The effect of smooth muscle contraction on lung-airway interdependence is even less well understood. Recent morphological work explicitly assumes that airway basement membrane is nondisposable, although the lung volume at which this maximal airway size is reached is unknown. With smooth muscle contraction, folding of the epithelium and basement membrane accounts for the changes in luminal area. In this study, we measured the effect of lung inflation on relaxed and contracted airway areas by using high-resolution computed tomography at different transpulmonary pressures, each held for 2 min. We found that fully relaxed airways are quite dilatable up to a pressure of 5–7 cmH₂O (P < 0.001), where they reach a maximal size with no further distension up to an airway pressure of 30 cmH₂O (P = 0.49). Thus relaxed airways clearly do not expand isotropically with the lung. With smooth muscle tone, the airways in different animals responded differently to lung inflation, with some animals showing minimal airway dilation up to an airway pressure of 20 cmH₂O and others showing airways that were more easily dilated with lung expansion. However, maximal diameter of these moderately constricted airways was not usually achieved even up to an airway pressure of 30 cmH₂O. Thus a transient deep inspiration in vivo would be expected to have only a small effect on contracted airways.

How airways respond to inflation of the lung has fascinated physiologists since the time of Leonardo da Vinci (25). More recently, in this topic has come from general questions of pulmonary interdependence (11, 13, 31) and from empirical observations that the normal dilatory response to deep inspiration seems to be absent in the airways of asthmatic subjects (7–9, 27, 28). How normal airways respond to lung inflation has been assessed primarily in isolated lungs, where the airways were dusted with tantalum (14–17, 23, 29). Many of these studies (14, 15, 19) conclude that airway diameter increases as the cube root of lung volume over the entire range of normal lung volumes. That is, the diameter of the airways changes at the same rate as any linear dimension within the lung parenchyma. The implications of these results are that, during a deep inspiration from functional residual capacity (FRC) to total lung capacity (TLC) where the lung volume roughly doubles, the airways should continually dilate to ~125% of the size at FRC, showing no maximal diameter at least within the range of normal transpulmonary pressures (PtP). This conclusion, however, is not consistent with several in vitro smooth muscle studies (10, 14, 17) that show a maximal airway diameter being reached at a relatively low PtP, typically in the range of 4–10 cmH₂O. Airway smooth muscle tone may be responsible for these different results.

How airway smooth muscle contraction affects the pressure-diameter relationship in vivo, however, is also poorly understood. This situation largely results from a paucity of data that can be directly applied to the in vivo situation. The effects of lung inflation on airway dimensions in vivo are usually assessed with global measures of resistance or spirometric variables, and most studies have looked primarily at the effect of a deep inspiration with measurement at the same lung volume (7–9, 27, 28). This scarcity of detailed experimental data, however, has not limited speculation on this process, and an inability to dilate airways during lung inflation has been suggested as a primary defect in asthma (7–9, 27, 28).

In the present study, we attempt to address these problems by using computed tomography (CT) to make direct in vivo measurements of relaxed and contracted individual airways at different lung volumes. Our results indicate that relaxed airways behave as would be predicted if there were a stiff basement membrane that reached its full size at relatively low PtP values (5–7 cmH₂O). Results also indicate that airway muscle contraction prevents full distension of the airways at maximal lung inflation.

METHODS

Our study protocol was approved by The Johns Hopkins Animal Care and Use Committee. Ten studies were performed on five dogs weighing ~20 kg. The dogs were anesthetized with thiopental sodium (15 mg/kg induction dose followed by 10 mg·kg⁻¹·h⁻¹ iv maintenance dose). After induction of anesthesia, the dogs were paralyzed with 0.5 mg/kg of succinylcholine, with supplemental doses given as required. After tracheal intubation with an 8.5-mm-ID endotracheal tube, the dogs were placed in a supine position and their lungs were ventilated with 100% oxygen with a volume-cycled ventilator (Harvard Apparatus, Millus, MA) at a tidal volume of 15 ml/kg and a rate of 18 breaths/min. A thin-walled latex esophageal balloon inflated with 0.8 ml of air was positioned in the lower one-third of the esophagus to estimate pleural pressure changes (24). PtP, measured with a differential pressure transducer, was estimated as the difference between

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the esophageal pressure and the airway pressure measured at the end of the endotracheal tube. A stable depth of anesthesia was maintained by monitoring heart rate changes and eyelash reflex.

**Imaging of airways.** High-resolution CT (HRCT) scans were obtained with a Somatom Plus Scanner (Siemens, Iselin, NJ) by using a 1-s scan time, 137 kVp, and 220 mA. Scanner accuracy was measured weekly and recalibrated if the measurement of water was off by >1%. The images were reconstructed as a 256 × 256 matrix by using a maximum zoom of 4.0 (12-mm field of view). The optimal spatial resolution of the scanner was 0.35 mm. Twenty-five to fifty contiguous sections were obtained, starting at the carina and moving caudally by using a 1-mm table feed and a 2-mm slice thickness. The dogs were anemic, with a constant controlled airway pressure for the duration of the scans (~2 min).

Images were reconstructed with the use of a high spatial frequency (resolution) algorithm that enhanced edge detection, at window level of -450 Hounsfield units (HU) and window width of 1,350 HU. These window settings have been previously shown to allow optimal lung resolution (32). All airways visualized approximately perpendicular to the scan plane (long-to-short axis ratio <1.5:1) were measured. For repeated airway measurements in a given dog within each experimental protocol and across experiments on different days, adjacent anatomic landmarks such as airway or vascular branching points were defined, and the airways were matched by these adjacent landmarks and measured.

**Imaging and measuring lung volume.** Standard-resolution CT scans were obtained with a Somatom Plus Scanner (Siemens) by using a 1-s scan time, 137 kVp, and 210 mA. The images were reconstructed as a 256 × 256 matrix by using a maximum zoom of 2.0. Twenty-five to fifty contiguous sections were obtained, starting at the apex of the lungs and moving caudally to the bases by using an 8-mm table feed and an 8-mm slice thickness. Images were reconstructed with the use of a standard lung algorithm at the same window settings described above, and lung volume at each inflation pressure was measured as described below.

**Image analysis.** The HRCT images were transferred as 16-bit data images to a UNIX based workstation and reduced to 8-bit images, which were then analyzed by using the airway-analysis module of the Volumetric Image and Display Analysis image-analysis software package (Department of Radiology, Division of Physiologic Imaging, University of Iowa, Iowa City, IA). To measure airway areas, the operator drew a rough estimate of the lumen isocontour within the lumen of the airway. The software program then automatically located an isocontour perimeter of the airway lumen by sending out rays in a spoke-wheel fashion to a predesignated pixel-intensity level that defined the luminal edge of the airway wall. The length of the rays was set at 6 pixels. The software program used an algorithm for edge detection based on the “full-width-half-maximum” principle. The edge of the wall was defined by the program by the points along the rays where the pixel intensity changed to one-half its maximum through the wall. All full and partial pixels (full pixel size equals 0.93 mm² with our settings) within the adjusted isocontour were counted and represented the airway area. For consistency and comparison with most other studies, the airway areas (A) were converted to an equivalent diameter as (4A/π)0.5. Accuracy and variability of the software program to measure known areas has been previously documented (1).

To measure lung volume, the total lung area of each standard-resolution CT slice was measured by using the same computer program described above. The length of the rays was set at 8 pixels for measurement of lung volume. The area of the lung on each CT scan was defined as the area within the pleural border, excluding the heart and diaphragm. The edge of the lung was defined by the same full-width-half-maximum principle described above. All lung standard CT slice areas were multiplied by the slice thickness and summed to calculate the total lung volume for each condition.

**Protocol.** Each dog served as its own control. The dogs were anesthetized and ventilated as described above. On separate days, in random order, the dogs received a continuous intravenous infusion of 67 μg/min methacholine (Sigma Chemical, St. Louis, MO), a dose previously demonstrated to decrease the size of the airways to 60% of baseline (6), or 0.2 mg/kg intravenous atropine, a dose previously shown to completely block vagal tone (6). To standardize lung volume history, before each measurement the airway pressure was increased to 35 cmH₂O, held for 5 s, and then decreased and maintained at the designated airway pressure for the duration of each set of scans. At each pressure, HRCT scans were acquired to measure airway areas, and standard CT scans were acquired to measure lung volumes. During methacholine infusion, scans were acquired at airway pressures of ~0, 10, 20, and 30 cmH₂O. After intravenous atropine, scans were acquired at approximately ~2, 0, 10, 20, and 30 cmH₂O. Between each experimental condition, the animals were ventilated normally.

**Analysis.** In each dog, 13 airways (range 1.8–19.1 mm diameter) were identified and measured under all conditions. Data are expressed as absolute diameter and as a percentage of maximal airway diameter at 30 cmH₂O after atropine. Data were analyzed by linear regression, and significance of the slope of the regression lines was determined from zero was tested.

**RESULTS**

With atropine treatment, the airway pressures of −2, 0, 10, 20, and 30 cmH₂O corresponded to average Ptp values of 0 ± 0.2, 0.6 ± 0.4, 14.0 ± 1.1, and 21.0 ± 0.9 cmH₂O, respectively. After methacholine, the airway pressures of 0, 10, 20, and 30 cmH₂O corresponded to Ptp values of 2.5 ± 0.3, 7.8 ± 1.2, 14.2 ± 1.1, and 22.0 ± 0.6 cmH₂O, respectively. Figure 1 shows an example of HRCT scans of matched airways in one dog after atropine administration (top row) at low (top left) and high (top right) lung volumes and during methacholine line infusion (bottom row) at low (bottom left) and high (bottom right) lung volumes.

The top graphs in Fig. 2, A-E, show the relationship between Ptp and airway diameter for each individual airway measured after atropine in each dog. The bottom graphs in Fig. 2, A-E, show the mean airway responses plotted as a percentage of atropine diameter at maximal Ptp for both the relaxed and methacholine-contrasted airways. Figure 2 clearly demonstrates that airways with no smooth muscle tone reach a maximal diameter at a very low Ptp (5–7 cmH₂O). There were no significant changes in diameter in any airway >7 cmH₂O (P = 0.49). Below 7 cmH₂O in each lung, the airways are extremely distensible, increasing 3.9% of maximal diameter for each centimeter of water increase in Ptp (P < 0.001). Indeed, over this low pressure
range, the airways appear even more distensible than the lung itself, with airway diameter increasing 1.2% for each 1% increase in the cube root of lung volume ($P < 0.001$).

Contraction of the airways with methacholine had a variable effect among dogs on the airway pressure-diameter relationship. At FRC (airway pressure = 0), mean airway diameter during methacholine infusion decreased by $46 \pm 2\%$ (SE). Increases in Ptp resulted in linear, convex, or S-shaped relationships in the different animals. In only one animal (dog 5) did the airways approach maximal size at the highest Ptp. Because of this variable response, airway distensibility in the contracted airways cannot be calculated for the group. In each animal, airway compliance changes greatly over the pressure range studied. For example, in dog 2 the airways appear extremely stiff $<15$ cmH$_2$O and become quite compliant at higher pressure, where they approach the maximal plateau.

It is worth noting that some airways in each dog actually decreased in size, approaching highest pressures (Fig. 2, A-E, top graphs). The location and size of such airways seemed random, but if this phenomenon occurred in an airway, it was quite reproducible, often occurring in the relaxed airway and after methacholine challenge.

Figure 3 shows the lung pressure-volume curves for the five dogs. Contraction of the airways with methacholine at the dose we used had negligible effects on the pressure-volume curves.

**DISCUSSION**

Our results clearly demonstrate that airways do not expand isotropically with the lung. When the airways are in a completely relaxed condition, airway diameter during atropine than methacholine administration at low lung volumes. Even at high lung volumes, airways are larger during atropine than methacholine administration, demonstrating inability of large lung volume to fully "pull-out" induced airway constriction. Ptp, transpulmonary pressure.
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Figure 2. A-E. dogs 1–5. Top graphs show individual airway pressure-diameter curves for all measured airways (different symbols) in each dog during atropine administration. Bottom graphs show average airway pressure-diameter curves (means ± SE) for all airways in each dog during atropine (solid line) and methacholine (dashed line) as a percentage of atropine airway diameter at maximal transpulmonary pressure.

The position of this limb after methacholine could not account for the observed variability in airway responses.

Recent histological studies have assumed that the epithelial basement membrane is not distensible, thereby allowing its fixed perimeter to be used to determine the size of the relaxed airways (18). Our results in vivo support this conjecture. Below the plateau, we found the relaxed airways to be extremely compliant, with changes in airway diameter at least as great as the cube root of lung volume changes. This is a surprising finding because one might expect the highly structured airway wall to have greater stiffness than the lung parenchyma. However, how the actual airway wall diameter changes with Ptp in relation to how an imaginary circular wall in the lung parenchyma changes with Ptp depends not only on the structure of the wall but also on what exists inside the epithelial border. This situation can be modeled with a continuum-mechanics analysis, considering the shear moduli of airway and parenchyma (20). However, one can intuitively envision an imaginary thin circular wall in the lung where there would be parenchymal tissue inside as well as outside the wall. In such a case, the diameter of the imaginary wall must then increase proportionally to the cube root of lung volume. If we now add a normal structure to the airway wall, maintaining the imagined parenchyma inside as well as outside the wall, this added wall structure might be expected to make this composite airway tube less distensible than the lung. However, if we next remove this theoretical elastic parenchyma inside the airway wall, this must increase the distensibility of the tubular airway. How much it would increase is not known, but it is conceivable that, if the airway wall is not very stiff, the airway could appear more compliant than the lung. Indeed, if the airway gets smaller by buckling its lumen, then it is reasonable to expect the relaxed airway to be very compliant over the pressure range where the lumen is simply being unfolded.

In previous work, we observed a markedly variable response to agonist challenge in individual airways within and among dogs (4, 5). In this study, we also found a variable contractile response, but in addition we also found widely variable sensitivities of contracted airways to lung inflation among the dogs. For example, in dog 3 initial increases in pressure have almost no effect on the mean diameter. Once pressure reaches 12 cmH2O, the smooth muscle contraction is pulled out and the airways enlarge. Furthermore, once this enlargement begins, the airways then appear very compliant over a narrow pressure range. In such cases, the methacholine causes the pressure-diameter curve to take on an S-shaped appearance. In dogs 1 and 2, a similar observation occurs, albeit to a lesser degree. In dog 5, the pressure-diameter curve has a similar shape as the relaxed curve, with only a slight shift to the right. At the present time, we have no satisfying explanation for this variability among animals. It seems not directly related to the initial response to methacholine because the initial constrictions at FRC in dogs 2 and 5 are similar. However, it is our expectation that, given enough contractile agonist, all the animals would eventually show curves that look like those in dog 2. Gunst et al. (12) have suggested that, if the smooth muscle contraction is high enough, physiological increases in Ptp might be insufficient to cause any increase in airway size. This latter speculation has obvious and direct clinical implications. In clinical asthma, the intrinsic forces of constriction may be greater than those which lung inflation can overcome. This would be consistent with several observations showing that a deep inspiration does not relieve bronchoconstriction in asthmatic patients (2, 3, 7–9, 27, 28). A model of asthma based on this ineffectiveness of a deep inspiration has recently been described by Skloot et al. (30). If humans showed the same degree of variability that we have seen in our animals, then we might speculate that those subjects behaving like dog 2 might be more prone to developing asthma.

There have been no previous in vivo studies that have examined the role of smooth muscle tone on the response of individual airways to lung inflation. How-
ever, there are several relevant studies in the literature that relate to our results. In a study of human subjects, Marshall and Holden (22) used bronchography to measure airway diameter at three lung volumes: FRC, TLC, and residual volume. They observed that, compared with FRC, airway diameter increased from 5–28% at TLC and decreased from 7–13% at residual volume. Because they only studied two volume extremes, their data unfortunately cannot be used to obtain nonlinear pressure-diameter relationships.

An often-cited study by Hughes et al. (15) in the isolated dog lung tentatively concluded that airway diameter changes linearly with the cube root of lung volume. In the present in vivo study, we found no evidence that relaxed airways behave in this manner. As noted by the authors, one possible explanation for the results of Hughes et al. (15) is the presence of residual intrinsic airway tone. Such intrinsic tone can exist in excised lungs for a period of time (14, 29). If there were airway tone in the excised lungs they studied, they would have observed results such as we found in dog 1. The large variability they observed within and among animals is also consistent with a variable and inconsistent degree of tone.

Several other studies done in isolated lobes and bronchi of dogs by using tantalum bronchography are more consistent with our findings. Hahn et al. (14) found that, when airways had low tone, they were very compliant below 10 cmH₂O but quite stiff above 10 cmH₂O. With high airway tone, airway diameter did not plateau up to a Ptp of 25 cmH₂O. Additionally, they found that the airways correlated in a linear fashion with the cube root of lung volume in the high airway tone state but not in the low airway tone state. Marshall (21) found similar results in isolated canine lungs, where maximal airway diameter was quickly reached at pressures <10 cmH₂O. In isolated canine bronchi in vitro without tone, Gunst et al. (12) also found that maximal airway diameters were reached below 10 cmH₂O. With high tone, sufficient to contract the airways to <10% of maximal size, the airways were not distensible even up to pressures of 25 cmH₂O. The rigidity they observed in the contracted airways probably results from much greater contraction than they were able to elicit in vitro. Studies in isolated bronchi by Martin and Proctor (23) showed that bronchi were highly compliant near end-expiratory volumes, i.e., at FRC, and noncompliant near end-inspiratory volumes, i.e., at TLC. However, they did not observe a plateau of airway diameter until much higher pressures were achieved (between 10 and 20 cmH₂O transmural pressure).

Consistent with our results are the several reports by Hyatt et al., who found that both intact and dissected canine bronchi reached a maximal plateau in diameter at a Ptp by 4–6 cmH₂O (16) and 8 cmH₂O (17). Sasaki et al. (29) also found that the relaxed airways increased in

Fig. 3. Lung volume (as percentage of maximal volume in atropine-relaxed state) vs. transpulmonary pressure for each dog in atropine-relaxed state and in methacholine-constricted state.
diameter up to 10 cmH\textsubscript{2}O and then plateaued above that pressure. However, in constricted airways they found airway diameter plateaued at a decreased maximal size. Such a decrease in maximal diameter was also observed by Murtagh et al. (26) in situ and Gunet and Mitzner (10) in vitro. In the present in vivo experiments, however, we never observed such a decreased plateau. At present, we can only speculate on what might cause such a plateau to occur in excised lungs and in vitro bronchi. The difference may result from variations in methodology, especially those related to dose and volume history. Allowing the contracted airways to reach very low (unphysiological) distending pressures may allow latch phenomena to strengthen, and this could be manifested as a decreased plateau.

Our observation that some airways actually decreased in size at the highest P\textsubscript{tp} is consistent with several published studies (14, 21). Whereas some investigators only observed the decrease in airway size with increasing pressure in larger airways (>9 mm in diameter) (14), we observed these changes in a wide range of airways (3.2–13.4 mm in diameter at FRC after atropine). Every dog in our study showed some airways that decreased in diameter when airway pressure was increased from 20 to 30 cmH\textsubscript{2}O. The number of airways that showed a decrease in diameter ranged from 1 to 6 in each dog (Fig. 2, A–E). There did not appear to be a specific effect by size or location of the airway (right vs. left lung). This decrease in size may be due to increased axial stresses with continued increases in P\textsubscript{tp}. Increasing stress on the spirally oriented airway smooth muscle and elastic fibers could narrow the airway diameter; however, why this would occur only in selected airways is not at all clear.

In conclusion, we found that airways with no smooth muscle tone are quite distensible up to a pressure of 5–7 cmH\textsubscript{2}O, where they reach a maximal size. Thus relaxed airways clearly do not expand isotropically with lung volume. With smooth muscle tone, the airways in different animals respond differently to lung inflation, with some animals showing minimal airway dilation up to airway pressures of 20 cmH\textsubscript{2}O. Maximal diameter of these moderately constricted airways is not usually achieved, even up to an airway pressure of 30 cmH\textsubscript{2}O.

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