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Imaging alveolar-duct geometry during expiration via $^3$He lung morphometry


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Hajari AJ, Yablonskiy DA, Quirk JD, Sukstanskii AL, Pierce RA, Deslée G, Conradi MS, Woods JC. Imaging alveolar-duct geometry during expiration via $^3$He lung morphometry. J Appl Physiol 110: 1448–1454, 2011. First published February 24, 2011; doi:10.1152/japplphysiol.01352.2010.—Acinar geometry has been the subject of several morphological and imaging studies in the past; however, surprisingly little is known about how the acinar microstructure changes when the lung inflates or deflates. Lung morphometry with hyperpolarized $^3$He diffusion MRI allows non-destructive evaluation of lung microstructure and acinar geometry, which has important applications in understanding basic lung physiology and disease. In this study, we have measured the acinar and acinar duct sizes at physiologically relevant volumes by $^3$He lung morphometry in six normal, excised, and unfixed canine lungs. Our results imply that, during a 37% decrease in lung volume, the acinar duct radius decreases by 19%, whereas the alveolar depth increases by 9% ($P < 0.0001$ and $P < 0.05$, respectively via paired $t$-tests with a Bonferroni correction). A comparison to serial sections under the microscope validates the imaging results and opens the door to in vivo human studies of lung acinar geometry and physiology during respiration using $^3$He lung morphometry.

AN ABILITY TO MORPHOMETRICALLY characterize the lung in vivo and measure geometric changes in terminal airspaces at varying levels of lung inflation would have great potential benefit for understanding lung physiology and diseases that affect lung microstructure. Many studies of acinar lung geometry have been performed on animals by means of invasive techniques, but the absence of a modality for in vivo measurement has resulted in a lack of such data for human lungs. A recently introduced imaging technique, lung morphometry with hyperpolarized $^3$He diffusion MRI (17, 24, 25), allows for measurements of micro-geometrical parameters of lung acinar airways. This technique is non-invasive, allows multiple measurements on the same lungs, and is suitable for in vivo human experiments. Here, we apply this technique to study excised dog lungs at different levels of inflation and compare the results to histological measurements taken from those same lungs and to histological results acquired by other researchers (6, 16).

The precise microscopic geometrical changes that occur during lung volume changes (i.e., during respiration) have been a topic of scientific discussion for over 50 years. Four likely possibilities that have emerged as top contenders for volume change mechanisms are 1) recruitment/derecruitment of alveoli, 2) isotropic changes in the dimensions of alveolar ducts, 3) simultaneous changes of alveolar size and shape, and 4) the folding or crumpling of the alveolar surface in an accordion-like deformation of the entire alveolar duct unit (7). Past studies have each concluded that airspace expansion is a result of one or more of these mechanisms but disagree about the degree to which each mechanism contributes. The disagreement is, at least in part, a result of differences in measurement methods. Histological assessment led Macklin (10, 11) to conclude that the bulk of physiological changes occur by elongation and radial expansion of alveolar ducts with no change in alveolar surface area. In 1970, Forrest performed a more quantitative histological study in which he measured alveolar duct diameters after rapidly freezing guinea-pig lungs at different levels of inflation and found that the alveolar duct diameter increased by 40% during inflation (6).

More recently, two studies by Carney et al. (2) and Albert et al. (1) using in vivo optical microscopy of subpleural alveoli (in dogs and rats, respectively) found that alveolar volume changes very little during inflation/deflation and concluded that alveolar recruitment/derecruitment is the dominant mechanism in lung volume change. Carney explains the discrepancy between his and previous results by noting that histological studies suffer from distortion of lung tissue during fixation/freezing and an inherent difficulty in distinguishing between alveolar ducts and alveolar sacs. In addition, histological studies also lack the ability to take measurements at multiple levels of inflation from the same tissue. However, both histological measurements and subpleural microscopy are limited to making inferences of a complex, three-dimensional structure from two dimensional measurements. In addition, measurements from in vivo microscopy are limited to alveoli at the lung periphery, which might not be representative of the majority of alveoli and alveolar ducts.

In recent years, hyperpolarized gas diffusion MRI has proven to be a useful tool for investigating various porous media via both direct magnetic resonance (MR) imaging and MR diffusion-imaging measurements. Although the boost in signal from hyperpolarized gas gives more than sufficient signal for conventional MR imaging, MRI resolution is limited by finite magnetic field gradients and gas diffusion. Consequently, researchers have used $^3$He diffusion MRI to study microscopic lung features at the alveolar level by measuring the diffusive properties of the gas restricted within acinar-airways (21). In canines, the mean acinar airway radius was reported by Tanoli et al. to be $\sim 0.3$ mm (18). Within 2 ms (a typical diffusion time used in experiments), a freely diffusing $^3$He atom dilute in air is displaced a root-mean-square distance on the order of 1 mm. Since this diffusion length is larger than the alveolar size and duct diameter, the diffusion of a typical $^3$He atom within the acinus is substantially restricted, and the apparent diffusivity is less than that of freely diffusing gas. We and others have shown that $^3$He diffusion MRI is very sensitive

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ALVEOLAR GEOMETRY DURING EXPIRATION VIA $^3$He LUNG MORPHOMETRY

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Methods

Normal lungs were excised from six dogs after death following unrelated cardiac experiments; approval was obtained from the Washington University Animal Studies Committee. All dogs were purpose-bred adult (usually over 8 mo of age) mongrel hounds (male and female) weighing between 20 and 25 kg with no pulmonary abnormalities. A single lung was removed from dogs 1–4, whereas both left and right lung were removed from dogs 5 and 6. The main bronchus of each lung was cannulated, and all leaks were repaired. Four lungs were imaged immediately after removal, and two were refrigerated at 4°C for <12 h before imaging.

Before imaging, each lung was filled with N$_2$ and passively deflated at least five times to purge the lung of O$_2$ and increase the T$_1$ relaxation time of $^3$He. The lung was gently massaged while inflating to ensure that all visible atelectatic regions were well ventilated before imaging. The lung was then placed in the MR scanner and ventilated with a syringe containing $\sim$300 ml of $^3$He and 700 ml of N$_2$ to a maximum transpulmonary pressure of 23 cmH$_2$O. The gas mixture was then partially evacuated by free collapse to obtain one of three desired pressures ($\sim$18, 7.5, or 2.5 cmH$_2$O) and imaged at near-static pressure for between 15 and 50 s. This process was repeated a total of three times to obtain images at high, medium, and low levels of lung inflation.

The hyperpolarized $^3$He used in these experiments was prepared with either a IGI.9600.HE commercial polarizer (GE Medical) or a home-built polarizer. Nuclear spin polarization was $\sim$35% for all experiments. Imaging took place in a 1.5-T Siemens Magnetom Sonata whole body scanner at 48.47 MHz. A solenoid-like, single-turn radio frequency (rf) coil, custom built for explanted lungs, gave high signal to noise and allowed for low flip angles and multiple measurements from each liter of gas.

Diffusion weighted images were acquired by means of a two-dimensional gradient echo pulse sequence with a biphasic diffusion sensitizing gradient (Fig. 1) characterized by a diffusion weighting parameter b:

$$b = (\gamma G m)^2 \left[ \delta^2 - \frac{\delta}{3} + \tau \left( \delta^2 - 2\Delta \delta + \Delta^2 + \frac{7}{6} \delta \tau + \frac{8}{15} \tau^2 \right) \right]$$

(1)

Here $\gamma$ is the gyromagnetic ratio, $G_m$ is the maximum gradient amplitude, $\delta$ is the total width of each pulse, $\Delta$ is the diffusion time (time between pulses), and $\tau$ is the gradient ramp time (12, 24). For all experiments, the timing parameters were kept constant ($\tau = 0.3 \text{ ms}$, $\delta = \Delta = 1.8 \text{ ms}$), whereas $G_m$ was varied to produce a complete set of multiple b-value, diffusion-weighted images at each inflation pressure. Nine diffusion-weighted images were obtained for all slices at each inflation pressure using values of b ranging from 0 to 14 s/cm$^2$. Slices were each 30 mm thick with an in-plane resolution of 5 mm $\times$ 5 mm. For each set of images, the field of view was sufficiently large to contain the entire lung so that volume measurements of the whole lung could be made from the MR images. Each lung’s reported high volume (HV) corresponds to a pressure for which there was no visual change in lung volume for incremental increases in pressure. This volume is nearly equal to the lung’s volume at total lung capacity.
The equations used in this study are given in the APPENDIX.

The alveoli and alveolar ducts are modeled as annuli with inner radii \( r \) and outer radii \( R \) periodically spaced along the inside of a long cylinder; the space between the annuli is further segmented by eight walls that extend between the annuli (see Fig. 2). The outer cylinder of radius \( R \) represents the alveolar duct, and the alveolar depth, \( h \), is given by \( R - r \). [Because alveolar ducts comprise ~95% of the acinus (20), we use the terms “alveolar duct” and “acinar airway” interchangeably. Both refer to the entire airway unit in Fig. 2 with cross-sectional area \( \pi R^2 \) (10).]

Diffusion of \(^3\)He within the lung is restricted by airway walls. In cylindrical airways, diffusion is anisotropic and can be described by two distinct diffusion coefficients, \( D_L \) and \( D_T \), which correspond to diffusion in directions transverse and longitudinal to the airway axis (17). For an isotropic mixture of cylindrical airways, the signal attenuation from each diffusion-weighted voxel is the average signal (averaged over all airway orientations) from all of the airways in that voxel and is represented by the following equation (24):

\[
S_{\text{voxel}} = S_0 e^{-bD_T}\left(\frac{\pi}{4b(D_L - D_T)}\right)^{1/2} \text{erf}\left[b(D_L - D_T)\right]^{1/2} \tag{2}
\]

where \( S_0 \) is the MR signal in the absence of diffusion gradients and \( \text{erf} \) is the error function. The values of \( D_L \) and \( D_T \) in Eq. 2 are related to the parameters \( R \) and \( h \) by a set of empirical equations determined by computer simulations of \(^3\)He diffusion in the structure of Fig. 2. The procedure for obtaining these equations is detailed in Refs. 17 and 25 where diffusion is simulated in airways with radii between 280 and 400 \( \mu \)m (the physiologically relevant range for healthy and slightly emphysematous human lungs). Because the average size of canine acinar airways falls just outside this range, we use a new set of empirical equations suitable for measurements in dog lungs (\( R \) between 140 and 260 \( \mu \)m) based on additional computer simulations. The equations used in this study are given in the APPENDIX.

Signal from each voxel was fit by Eq. 2 with the dependence of \( D_L \) and \( D_T \) on \( R \) and \( h \) given by Eqs. A1 and A2, using nine \( b \) values ranging from 0 to 14 s/cm\(^2\). This analysis provided average values of the radius \( R \) and alveolar depth \( h \) within each voxel. Voxels containing large airways, with insufficient S/N, or with low fitting confidence were excluded from the analysis. For each lung at each volume, \( R \) and \( h \) values from all voxels included in the analysis were averaged. The effects of lung volume on the parameters \( R \) and \( h \) were determined for all six lungs by performing repeated-measures ANOVA. Comparisons between each pair of results were performed using paired \( t \)-tests with a Bonferroni correction. \( P \) values of <0.05 were considered statistically significant. All statistical analysis was performed using SPSS Statistics 19.0.0.

After imaging, the right and left lungs from dogs 5 and 6 were frozen at different levels of inflation for quantitative histological studies. Each lung from the pair was first inflated to 23 cmH\(_2\)O and then passively deflated to one of two pressures and suspended at constant pressure in cold \( N_2 \) vapor (over a bed of LN\(_2\)) in an insulated container for 30 min (21). The left lungs from dogs 5 and 6 were frozen at the pressure corresponding to each lung’s high volume from the MRI experiments, and the right lungs from the same dogs were frozen at pressures corresponding to low volumes from the MRI experiments. Each lung was then cut and sampled while frozen over dry ice, and each sample was sectioned at 6 \( \mu \)m for immunohistochemistry (in this case, a Hart’s stain) to distinguish elastic fibers (5).

Low resolution (\( \times 5 \)) microscope images were acquired across the entire slide. These images were seamlessly stitched together using Adobe Photoshop and saved as a high-resolution composite image of the whole slide. By serial sectioning, in most cases we were able to distinguish acinar airways that were parallel, perpendicular, and at oblique angles relative to the slide. All airways deemed to be perpendicular (which are subject to the least error in transverse measurements) within the \( 2 \times 2 \) cm sample were then measured for morphometric parameters \( R \) and \( h \) using ImagePro Plus software. Shrinkage was accounted for by measuring several dimensions of the cut samples before and after histological processing. A total of 550 measurements were made in 62 different airways in the two lungs frozen at high inflation, and 689 measurements were made in 74 different airways in the two lungs frozen at low inflation.

RESULTS

Results: Figure 3 shows examples of diffusion attenuated MRI signal at three different levels of deflation and the corresponding

![Fig. 3. Plot of diffusion-weighted magnetic resonance (MR) data averaged over 4 voxels in dog lung 3 and the corresponding curve fits from Eq. 1.](https://jap.physiology.org/)

(TLC). All other volumes are reported as a percentage of HV as measured by counting voxels from the \(^3\)He MR images containing the lung.
fitting curves to Eq. 2. Clearly, from Fig. 3, the mean diffusivity is larger at high volume, in accord with the qualitative notion of lung airspaces being “more open” at higher inflation.

Histograms of the parameter $R$, from different volumes over all voxels, illustrate a clear difference in airway sizes as expected (Fig. 4). All MR data included in analysis demonstrated more than sufficient signal-to-noise to confidently fit to the airway model in Eq. 1 (SNR exceeded 100 for $b = 0$ in all images). Data were analyzed on a voxel-by-voxel basis. For each lung, $R$ and $h$ values from all voxels included in the analysis were averaged. The results for the outer radii and alveolar depth ($R$ and $h$, respectively) are shown in Table 1. Each lung showed significant microgeometrical changes with deflation across all volumes in both $R$ ($P < 10^{-6}$) and $h$ ($P < 0.01$) via repeated-measures ANOVA. On average, a 37% decrease in volume (high to low volume) led to a 19% decrease in $R$ and a 9% increase in the alveolar wall depth $h$ ($P < 0.0001$ and $P < 0.05$, respectively, via paired $t$-tests with a Bonferroni correction). Differences between values of $h$ at high and medium volume were not significant ($P > 0.05$); all other pairwise comparisons of $R$ and $h$ at different volumes were significant. Regional variation (on average ~15% for $R$ and 24% for $h$) was seen in each case but was consistent across all volumes, implying the spatial variations were physiological.

Figure 5 shows maps of $R$ and $h$ for a representative slice from dog lung 6 at HV, 78% HV, and 54% HV.

From the composite histological images, all acinar airways judged by serial section to be perpendicular to the slide within each 2 x 2 cm sample were identified and measured for morphometric parameters $R$ and $h$, after correcting for shrinkage (Fig. 6). The shrinkage factor (post-processed sample size/pre-processed sample size) was $0.47 \pm 0.03$ (mean $\pm$ SD). Although serial sections reduce the probability of error, we note that our method for histological measurements of $R$ and $h$ are still subject to some error due to subjective judgments made in determining which alveolar ducts are perpendicular enough to measure. A summary of the histology and MR measurements from the same lungs is shown in Table 2. The comparison is quite favorable, and in each case the difference between histology and MRI was well within 1 SD of either average measurement.

**DISCUSSION**

For the first time we have employed lung morphometry with $^3$He MR diffusion imaging to study lung microstructure at different levels of inflation. We believe this morphometric imaging technique holds important advantages over both histology and subpleural microscopy in studying lung microstructure. MR data are obtained here from $5 \times 5 \times 30$ mm voxels, each containing thousands of acinar airways. Histological measurements, which are generally taken from hundreds of acinar airways over the course of many hours, only represent a relatively few 6-μm slices of tissue and are naturally not volume averages, in contrast to MRI data. Our model takes into account the signal from all acinar airways within each voxel.

<table>
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<th>Table 1. $^3$He morphometry results</th>
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<td><strong>Dog 1</strong></td>
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<tr>
<td>High volume</td>
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<tr>
<td>$R$ (μ)</td>
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<td>$h$ (μ)</td>
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<td>Medium volume</td>
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<tr>
<td>Low volume</td>
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<tr>
<td>$R$ (μ)</td>
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<td>$h$ (μ)</td>
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Values for individual dogs (columns 1–6) are means ± SD of all voxels included in analysis at each volume. Mean ± SD of columns 1–6 are reported in column 7. $R$, outer radius; $h$, alveolar depth.
and assumes a near-isotropic mixture of airway orientations, accounting for the three-dimensionality of the airway network. Voxels are large enough to contain a sufficient number of airways to ensure a uniform distribution of orientations and to ensure that most voxels contain sufficient signal to fit Eqs. A1 and A2. Voxels are also small enough to perform regional analysis from the images and exclude large (non-acinar) airways from the analysis. In addition, because hyperpolarized $^3$He gas is inert and has a very low solubility in lung tissue, the technique is suitable and safe for in vivo human studies (9).

Our imaging method is currently limited to measuring only two independent parameters (radius $R$ and alveolar depth $h$) within the cylindrical acinar airways and is insensitive to changes in alveolar length, $L$ (25). Thus it is not possible to determine either alveolar volume or alveolar-duct volume from these measurements without making assumptions about the alveolar length. However, in the reasonable scenario where $L$ changes proportionally to $R$, the average 19% decrease in $R$ measured with diffusion MRI indicates that there is a change in alveolar duct volume of 46% from full inflation to deflation. This is remarkably similar to the change in macroscopic volume (37%) measured from MR images. Although $h$, the alveolar depth, increases slightly as the total lung volume decreases, the alveolar volume in our model depends on both $h$ and $R$ (Eq. 3), and decreases with decreasing macroscopic lung volume:

$$V_a = \pi \cdot h \cdot (2R - h) \cdot \frac{L}{8}$$  \hspace{1cm} (3)

From the MR measurements, assuming $L$ is proportional to $R$, alveolar volume decreases by 31% from high volume to low volume.

Using photomicroscopy at subpleural surfaces, Carney et al. determined that during inflation there is little change in alveolar volume from low inflation to 80% of TLC. They concluded that recruitment/derecruitment is the predominant mechanism for changes in lung volume in canines and that there is little change in alveolar volume through most of the deflation curve. Since MR signal is only obtained within open airspaces, our results do not directly address alveolar derecruitment. However, our results unambiguously indicate that there is a significant decrease in both alveolar duct volume and alveolar volume during deflation even between medium inflation volumes and low inflation volumes, implying that alveolar derecruitment is likely not the only significant mechanism involved in lung deflation. Furthermore, the volume changes of alveolar ducts and alveoli calculated above are consistent with those volumetric changes being largely responsible for the macroscopic decrease in volume. A possible explanation for the discrepancy between our imaging results and the photomicroscopy results is that subpleural alveolar measurements do not account for changes in alveolar duct volume in the bulk of the lung, which our results show contribute significantly to the total change in lung volume.

Our findings are supported by those of Macklin (10, 11), Storey and Staub (16), and Forrest (6). Forrest showed that, in guinea pigs, the mean alveolar duct diameter was 29% smaller in lungs that were nearly collapsed than in lungs that were fully inflated. Storey reported that, in rapidly frozen cat lungs, alveolar duct diameters were 26% smaller at low levels of lung inflation than at high levels of inflation. Our histological results showed a 20% decrease, and our MR results showed a 19% decrease in alveolar duct diameter from high volume to low volume, which is in good agreement with Forrest’s and Storey’s results. The 9% increase in $h$ during deflation is supported by Macklin’s observation in 1950 that alveoli change “from the shape of a cup to that of a saucer” during inspiration (10). This is consistent with an “accordion-like” model for acinar airway expansion in which the alveolar ducts become

<table>
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<th>Table 2. Comparison of histology and MR</th>
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Histology values over all measurements are means ± SD. $^3$He morphometry values over all voxels included in analysis are means ± SD.
longer while the alveolar depth becomes more shallow, with little change to alveolar surface area (8, 10).

Excised dog lungs were chosen in this study because they were available from unrelated cardiac experiments, could be imaged at reproducible pressures, and could be frozen for histological comparison with MR data. However, this study still leaves two open questions: 1) How does acinar geometry during respiration differ between canines and humans, and 2) what differences exist in acinar geometry between the ex vivo and in vivo lung? In vivo 3He lung morphometry has the potential to probe both of these topics in future work.

One major drawback of 3He MRI is the rising cost and limited availability of 3He gas. For this reason, some hyperpolarized gas researchers are turning to 129Xe as a potential alternative to helium. Although 129Xe may become an adequate substitute for 3He in ventilation and, in some cases, 2-b diffusion experiments, MRI gas diffusion morphometry is one area where the exceedingly high SNR of 3He is necessary and, at this time, cannot be matched by 129Xe. Although rising costs are an obstacle to the introduction of 3He into clinical environments, vigorous efforts are currently underway to implement 3He recycling programs and to collaborate with other industries that use 3He to manage usage and costs. Although we anticipate that these efforts will have a major impact on the cost and availability of 3He in the near future, even now 3He morphometry remains a valuable research tool in furthering our understanding of lung physiology and disease.

In summary, we have obtained morphological measurements of acinar airways from six canine lungs at various levels of deflation via lung morphometry with hyperpolarized 3He diffusion MRI. To substantiate our results, we froze two pairs of the lungs, with each lung at different volumes, for histological comparison. The imaging data indicate that in canine lungs alveolar depth, h, increases slightly during deflation and that changes in alveolar duct volume contribute significantly to changes in total lung volume; this is validated via histological finding in the same lungs. Our results help to illuminate mechanisms for lung volume change within perhaps the most fundamental pulmonary unit: acinar airways. In the future, we hope to apply 3He lung morphometry in an in vivo study of human lungs.

APPENDIX

The equations from Ref. 25 relating MR diffusion to acinar geometry were obtained by computer simulations of acinar airways with R values between 280 and 400 μm. However, histology and preliminary 3He morphometry results showed that a significant fraction of acinar airway radii in dog lungs are smaller than 280 μm. To extend the utility of 3He morphometry to smaller airways, we present here a new set of empirical relations between anisotropic diffusion coefficients $D_L$ and $D_T$ and the geometric parameters $R$ and $h$ based on computer simulations of 3He diffusion in alveolar ducts (described in Refs. 25 and 17) using values of $R$ between 140 and 260 μm. Tests with computer-simulated data show that, although based on 3He diffusion simulations in airways with $R < 260$ μm, Eqs. A1 and A2 accurately predict acinar geometrical parameters for values of $R$ up to 400 μm.

$$D_L = D_{L0} \cdot (1 - \beta_L \cdot bD_{L0})$$
$$D_{L0} = D_0 \cdot \exp[-2.87 \cdot (h/R)^{1.75}]$$
$$\beta_L = 96.4 \cdot (R/L)^{1.5} \cdot \exp[-4.86/\sqrt{h/R}]$$

$$D_T = D_0 \cdot 7/16 \cdot (R/L)^2 \cdot [1 + f(R, h)]$$
$$f(R, h) = \exp[-A \cdot (h/R)^2 \cdot \exp(-(5/h)^2) + 5 \cdot (h/R)^2 - 1]$$

Fig. 7. A–C: plots representing data obtained by Monte-Carlo simulation of $D_{L0}$ (A), $\beta_L$ (B), and $D_T$ (C) as a function of $h/R$ for $R = 140, 170, 200, 230, \text{and} 260$ μm. $D_{L0}$ and $\beta_L$ depend only on $h/R$ such that, in A and C, symbols for different values of $R$ collapse onto a single curve. D: a histogram of $h/R$ for all voxels from all lungs at all volumes after excluding voxels for insufficient S/N and low fitting confidence.
Here L₁ and L₂ are the characteristic free-diffusion lengths for one- and two-dimensional diffusion, respectively. We adopt the acinar airway model used in Ref. 25, in which each duct segment contains eight alveoli each with a length $L = 2R\sin(\pi/8)$. These equations, which are empirical fits to simulated results, were generated using the parameters $\Delta = 1.8$ ms, $D_0 = 0.88$ cm$^2$/s, and $R = 140–260$ μm. They are valid for $h/R \leq 0.75$, beyond which Eqs. A1 and A2 diverge from the simulated results. The histogram in Fig. 7 shows that, after excluding voxels for low S/N and low fitting confidence, $h/R$ is $>0.75$ for $<0.5\%$ of all voxels.

GRANTS
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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

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