Comparative respiratory system mechanics in rodents

R. F. M. Gomes, R. Ramchandani, R. S. Tepper, and J. H. T. Bates. Comparative respiratory system mechanics in rodents. J Appl Physiol 89: 908–916, 2000.—Because of the wide utilization of rodents as animal models in respiratory research and the limited data on measurements of respiratory input impedance (Zrs) in small animals, we measured Zrs between 0.25 and 9.125 Hz at different levels (0–7 hPa) of positive end-expiratory pressure (PEEP) in mice, rats, guinea pigs, and rabbits using a computer-controlled small-animal ventilator (Schuessler TF and Bates JHT, IEEE Trans Biomed Eng 42: 860–866, 1995). Zrs was fitted with a model, including a Newtonian resistance (R) and inertance in series with a constant-phase tissue compartment characterized by tissue damping (Gti) and elastance (Hti) parameters. Inertance was negligible in all cases. R, Gti, and Hti were normalized to body weight, yielding normalized R, Gti, and Hti (NHti), respectively. Normalized R tended to decrease slightly with PEEP and increased with animal size. Normalized Gti had a minimal dependence on PEEP. NHti decreased with increasing PEEP, reaching a minimum at ~5 hPa in all species except mice. NHti was also higher in mice and rabbits compared with guinea pigs and rats at low PEEPs, which we conclude is probably due to a relatively smaller air space volume in mice and rabbits. Our data also suggest that smaller rodents have proportionately wider airways than do larger animals. We conclude that a detailed, comparative study of respiratory system mechanics shows some evidence of structural differences among the lungs of various species but that, in general, rodent lungs obey scaling laws similar to those described in other species.

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Hz and permit us to compare interspecies respiratory mechanics in a frequency-independent fashion.

MATERIALS AND METHODS

Experimental procedures. We studied four different species of rodents: A/J mice ($n = 11$; 20.5–24.7 g), Sprague-Dawley rats ($n = 8; 260–290$ g), Dunkin-Hartley guinea pigs ($n = 5; 360–410$ g), and New Zealand White rabbits ($n = 6; 2.6–3.0$ kg). Mice and rats were sedated with an intraperitoneal bolus of xylazine (7 and 14 mg/kg, respectively). All animals were anesthetized [pentobarbital sodium in mice (50 mg/kg ip), rats (35 mg/kg ip), and guinea pigs (65 mg/kg ip); sodium thiopental in rabbits (35 mg/kg iv)] and tracheostomized. Except for the rabbits, which had their trachea cannulated with a rigid plastic tube and which were ventilated with a commercial version of the SAV (flexiVent, SCIREQ, Scientific Respiratory Equipment, Montreal, Quebec), all of the other animals had a snug-fitting metal tracheal cannula connected to a SAV prototype (34). Mice, rats, guinea pigs, and rabbits were mechanically ventilated with sinusoidal inspiration and expiration with tidal volumes of 6, 8, 9, and 7 ml/kg and breathing frequencies of 150, 90, 70, and 60 breaths/min, respectively. Positive end-expiratory pressure (PEEP) was set at 3 hPa by connecting the expiratory line of the ventilator to a water trap. Mice and rabbits were paralyzed with pancuronium bromide (0.8 mg/kg ip and 0.1 mg/kg iv, respectively). Rats and guinea pigs were paralyzed with succinylcholine chloride (20 and 13 mg/kg ip, respectively).

Every 3 min, the animals were ventilated against one of five different levels of PEEP (0–7 hPa) chosen randomly. Three total lung capacity maneuvers were performed by closing the expiratory line until an airway opening pressure ($P_{aw}$) of 30–35 hPa was obtained. We waited for 15 breathing cycles, the animals were allowed to expire passively to the relaxation volume as determined by PEEP (established by connecting the expiratory line of the ventilator to a water trap), and an 18-s small-amplitude, broad-band volume perturbation was applied to the airway opening. The volume perturbation waveform contained 12 discrete sinusoidal components having mutually prime frequencies from 0.25 to 9.125 Hz, and its peak-peak amplitude corresponded to 35% of the tidal volume of the animal. The individual amplitudes in flow and pressure at each frequency. The phases of the sinusoids were adjusted to minimize the peak-peak amplitude of the volume signal. The frequencies were chosen to be mutually prime to avoid harmonic distortion in the airway pressure ($P_{aw}$) signal (6). Also, this range of frequencies was selected because it is suitable for the partition of Newtonian resistive and respiratory tissue viscoelastic properties. Once measurements at all of the five different levels of PEEP had been taken, the procedure was repeated.

The SAV is a computer-controlled ventilator in which a linear motor drives a piston in a cylinder of known diameter (34). Calculations of $Z_{rs}$ are made from measurements of piston volume displacement ($V_{cyl}$) and the pressure inside the cylinder ($P_{cyl}$). $V_{cyl}$ and $P_{cyl}$ were recorded at 1,024 Hz after being passed through low-pass filters with cutoff at 200 Hz. The data were then digitally low-pass filtered at 30 Hz and decimated to 128 Hz before being stored on a personal computer for subsequent analysis.

Data analysis. Corrections for gas compressibility within the system and resistive and accelerative losses in the connecting tubing and tracheal cannula were performed as described previously (3, 17). Briefly, we first obtained dynamic calibration signals of $P_{cyl}$ and $V_{cyl}$ from the SAV before connecting the animal by applying the volume perturbation through the tracheal cannula first when it was completely closed and then again when it was open to the atmosphere. Subsequently, when the animal was connected to the SAV, we used these calibration signals to remove the contribution of both the tracheal cannula and the SAV itself from the measured animal $Z_{rs}$.

$Z_{rs}$ was calculated as the ratio between the cross-power spectrum of $P_{aw}$ with $V_{cyl}$ and the autopower spectrum of $V_{cyl}$ multiplied by $j_2\pi f$, where $j$ is the imaginary unit and $f$ is frequency. The first 2 s of each 18-s data record were discarded to avoid initial transients, and the remaining 16 s were divided into five 8-s blocks that overlapped by 75%. The cross- and autopower spectra for all blocks were averaged before being divided to yield $Z_{rs}$ to reduce the effects of measurement noise (13).

$Z_{rs}$ consists of a real part known as respiratory system resistance ($R_{rs}$) and an imaginary part known as respiratory system reactance ($X_{rs}$). We normalized $R_{rs}$ and $X_{rs}$ by multiplying them by body weight ($BW$) to obtain normalized $R_{rs}$ (NR$_{rs}$) and $X_{rs}$ (NX$_{rs}$), respectively.

We also fit $Z_{rs}$ data to a model consisting of a $R$ connected to a constant-phase tissue compartment. Thus

$$Z_{rs}(f) = R + j_2\pi f + \frac{G_{ti} - jH_{ti}}{(2\pi f)^\alpha}$$

where $I$ is inertance, $G_{ti}$ and $H_{ti}$ embody energy dissipation and storage, respectively, within the tissues, and

$$\alpha = \left(\frac{2}{\pi}\right)
\arctan\left(\frac{H_{ti}}{G_{ti}}\right)$$

The $\alpha$ determines the frequency dependence of both real and imaginary parts of $Z_{rs}$ and is related to the hysteresivity index ($\eta$) introduced by Fredberg and Stamenovic (9) where

$$\eta = \frac{G_{ti}}{H_{ti}}$$

To facilitate comparisons among species, we normalized the parameters $R$, $I$, $G_{ti}$, and $H_{ti}$ by multiplying them by $BW$ to obtain, respectively, NR, NI, NG$_{ti}$, and NH$_{ti}$.

We calculated the coherence between $P_{cyl}$ and $V_{cyl}$ at each of the frequencies used in the volume perturbation signal and fit the model to $Z_{rs}$ at only those frequencies for which the coherence was >0.9. On this basis, we discarded 0.15, 1.25, and 1.25% of the $Z_{rs}$ data in mice, rats, and rabbits, respectively. We also calculated the SD of the residuals between data and model fit and discarded those frequencies for which the real and/or imaginary parts of $Z_{rs}$ were more than two SDs away from the fit. All together, 1.97, 3.39, 0.41, and 2.78% of the $Z_{rs}$ data obtained in mice, rats, guinea pigs, and rabbits, respectively, were not used in the model fitting.

ANOVA was used to look for significant differences in the fitted model parameters due to the effects of species, PEEP, their interaction, and of a particular animal in one species. We found that the way in which the model parameter values depended on PEEP varied significantly among species; therefore, we used one-way ANOVA to investigate the effects of PEEP in each species. We also studied the differences in the parameter values among species for each PEEP. When appropriate, Tukey’s honestly significant difference multiple pairwise comparisons were performed. Statistical significance was considered when $P < 0.05$.

RESULTS

Figures 1 and 2 show, respectively, NR$_{rs}$ and NX$_{rs}$ as functions of frequency for each of the species studied.
at five different levels of PEEP. In each case, NRrs decreased monotonically, whereas NXrs increased monotonically with frequency. The resonant frequency was not attained in any of the animals by 9.125 Hz, as NXrs was always negative up to this frequency. Figure 1 also shows that mice had lower NRrs values at higher frequencies than did rats, guinea pigs, or rabbits. At the lowest frequency of 0.25 Hz and at 0-hPa PEEP, mice and rabbits had higher NRrs than did rats and guinea pigs. Above 6 Hz, NRrs decreased consistently with increasing PEEP. Figure 2 shows that mice and rabbits had lower NXrs at 0.25 Hz, in the absence of PEEP, than did rats and guinea pigs.

Figure 3 shows the PEEP dependence of the Zrs model parameters in the four species studied. NR tended to decrease with PEEP in all species and was very similar in rats and guinea pigs, lowest in mice, and highest in rabbits. NI was very small in magnitude and usually negative. Furthermore, when I was excluded from Eq. 1 and the model was refitted to the Zrs data, there was essentially no change in the values of the remaining parameters. We, therefore, consider the influence of NI to be negligible over the frequency range studied. Mice and rats had higher values of NGti in the absence of PEEP than when PEEP was applied. NGti did not show any PEEP dependence in rabbits, and in guinea pigs NGti tended to increase at higher levels of PEEP. Differences in NGti among species were minor and occurred at a PEEP of 0 hPa between mice and rats and at PEEPs of 2 and 7 hPa between rats and rabbits. In all species, NHti tended to decrease with increasing PEEP until 5 hPa when there was an inflexion point, except in mice. At lower PEEPs, mice and rabbits had higher values of NHti than did rats and guinea pigs. The $\alpha$ and $\eta$ were independent of PEEP in mice, but they showed a tendency to decrease and increase, respectively, with PEEP in rats and rabbits. In guinea pigs, the only difference noted was between PEEP levels of 0 and 2 hPa. Except when no PEEP was applied, mice showed values of $\alpha$ and $\eta$ that were significantly different from those of other species.

The repeat set of measurements that was made in each animal was analyzed to establish the reproducibility of the results in time. The first and second measurements of R, Gti, Hti, $\alpha$, and $\eta$ at each of the five different levels of PEEP were compared. Paired t-test analysis showed no significant differences in almost all the parameters. Exceptions were found for Gti in guinea pigs at a PEEP of 7 hPa, for Hti in guinea pigs at PEEPs of 5 and 7 hPa, for Hti in rabbits at a PEEP of 0 hPa, and for $\alpha$ and $\eta$ in mice at a PEEP of 2 hPa. However, the relative differences were always <9.1% for Hti and $\eta$, <3.1% for Gti, and <1% for $\alpha$.

DISCUSSION

The present study was motivated by the wide utilization of rodents in the investigation of lung development and processes related to respiratory-system diseases. Although the species we used have been studied in the past (3, 4, 10, 14, 16, 17, 19, 21, 25–30, 32, 35–37, 39), very little has been reported about the Zrs
of mice, no doubt in part because of the technical difficulties associated with making the necessary measurements. Also, most of the comparative studies on mammalian respiratory mechanics have been performed during spontaneous tidal breathing, which allows animals to choose (and vary) their tidal volumes, breathing frequencies, and functional residual capacities. Furthermore, existing comparative data have been gathered from different sources in the literature; therefore, the methods used to assess mechanics were not always the same in the various species. Considering the present need to perform accurate measurements of Zrs in small rodents and the fact that Zrs depends markedly on frequency and lung volume (Figs. 1 and 2), there is clearly a need for comparative measurements of Zrs in various rodent species over a broad range of frequencies and at different levels of PEEP. This was the purpose of our study.

Zrs by itself can provide useful information regarding the state of the respiratory system, but the utilization of suitable models can greatly facilitate its interpretation. The model we used consists of an R and I leading to a constant-phase tissue compartment characterized by the dissipative parameter Gti and the elastic parameter Hti. It has been shown previously that this model provides extremely accurate fits to normal Zrs over the range of frequencies that we studied (12, 15, 17, 22, 31), despite having only four independent parameters. As in our laboratory’s previous study in rats (17), we found I to make a negligible contribution to input impedance over the frequency range examined in the present study. Our laboratory’s previous studies in dogs (2) and rats (17) have also shown that R contains contributions from both the chest wall tissues and the pulmonary airways, respectively, to varying degrees, depending on the species. Gti and Hti characterize the viscoelastic properties of the respiratory tissues.

To compare Zrs, R, I, Gti, and Hti among species, we multiplied them by BW. Alternatively, we could have normalized to lung volume. However, this can be misleading because lung volume at any particular inflation pressure depends on the elastic properties of the lungs and chest wall (23), and because respiratory elastance (Hti) is one of the parameters in which we are interested, we would be effectively normalizing it to itself. On the other hand, we could have normalized to lung weight. However, it is known that guinea pigs undergo marked bronchoconstriction after death, probably due to the release of substance P, which can increase vascular permeability and enhance edema formation (20). Therefore, the postmortem measurement of lung weight in guinea pigs would likely overestimate its value in vivo relative to the other species. Consequently, we decided that normalizing to BW was the most appropriate thing to do, especially as our mechanics parameters reflect not only the lungs but also chest wall properties (8). Also, the lungs of an animal serve its entire body and not just its lung tissue; therefore, it would seem to make sense to consider how our parameters relate to the entire body. Finally, normalizing a parameter with respect to BW allows it to be easily associated with metabolic rate.

Fig. 2. Imaginary parts of respiratory system impedance normalized to BW (NXrs) in 4 different species. Values are means ± SE calculated for PEEPs ranging between 0 and 7 hPa in each species.
which has been shown to follow BW to the 0.75 power in mammals (33).

NR and Raw. Our results show that NR tends to decrease with PEEP (Fig. 3), presumably due to increasing parenchymal tethering forces causing an increase in airway caliber. Moreover, NR increased from the smaller to the larger species. This appears to suggest that the airways of smaller species are relatively larger than those of larger species, although we must be careful in drawing such a conclusion because R contains contributions from both the airways and the chest wall tissues, although the relative amounts may vary with species. In dogs, for example, the chest wall and airways have been shown to make approximately equal contributions to the Newtonian resistive properties of the respiratory system (2), whereas in humans the chest wall has been reported to contribute 27% of R (5). Data collected by Rotger et al. (32) suggest that the chest wall contributes roughly one-third of R in rabbits. We have observed in mice that the lung contributes up to 50% of R over a range of lung volumes (unpublished observations), whereas in rats (17, 30) and cats (12) the chest wall contributes very little to the Newtonian properties of the respiratory system. Therefore, it is possible that the rank ordering of NR that we found in the present study (Fig. 3) may not be the same rank ordering of actual normalized Raw.

However, the notion that the rank orderings are indeed the same comes from a comparative respiratory mechanics review by Leith (21), who showed that Raw is related to BW over a wide range of species by

$$\text{Raw} = a(BW)^b$$

where $a$ and $b$ were determined by linear regression analysis, and the value of $b$ varied between −0.86 and −0.70, depending on the source. The R data from our present study obtained at 0-hPa PEEP concur, insofar as R is an accurate reflection of Raw, giving an intermediate value of −0.75 (Fig. 4). These relationships again lead to the conclusion that relative Raw (i.e., normalized by the inverse of BW) increases with increasing animal size. Further support comes from Valerius (38), who studied silicone rubber lung casts of four species of myomorphic rodents and found that the volume of the conducting bronchial tree as a percentage of total lung volume was much smaller in the ~1.5-kg African giant pouched rat (Cricetomys gambianus) than in the 6-g harvest mouse (Micromys
Valerius also noted a progressive decline with animal size in the relative diameter of the left main bronchus.

Resonant frequency. The resonance frequency was not reached by 9.125 Hz in any of the species we investigated (Fig. 2). This agrees with data obtained from studies on low-frequency forced oscillations in rats (14, 17), guinea pigs (39), and rabbits (37). Petak et al. (30) were able to detect an inertive component in the respiratory system properties of rats using frequencies up to 21 Hz and concluded that the inertive component of Zrs is essentially determined by lung impedance, agreeing with data obtained from cats (12). The fact that our estimates of I were negligible for frequencies <9.125 Hz (Fig. 3) does not mean that there were no inertial elements in the airways but rather that inertial effects were minimal over the frequency range studied.

Effect of PEEP on tissue resistance. We found NGti in mice and rats to be higher at lower levels of PEEP (Fig. 3), agreeing with previous finding in rats (17). It has been shown in both rats and dogs that the chest wall resistance is independent of mean Pao (1, 17). Therefore, the negative dependence of Gti with lung volume is fully attributable to the lung and most likely reflects air space closure occurring at lower levels of PEEP. However, in rabbits, NGti was not dependent on end-expiratory volume, and in guinea pigs, there was a slight rise in NGti at the highest level of PEEP compared with intermediate lung volumes (Fig. 3). Because smaller animals are known to have more compliant chest walls, the relaxation volume normalized to lung size in these animals is usually lower than in larger animals (10). Therefore, the mice and rats in this study could have been ventilated at proportionately lower lung volumes at a given level of PEEP compared with other rodents, thus explaining the differences we found among species.

Nagase et al. (25, 26, 28, 29) used the alveolar capsule technique to partition lung resistance into its airway and tissue components in mice, rats, guinea pigs, and rabbits. They showed that lung tissue resistance increased significantly with PEEP. In rabbits this increase was compensated for by a decrease in Raw (29) so that total lung resistance was maintained. In mice, rats, and guinea pigs, total lung resistance increased with PEEP, despite a reduction in Raw (25, 26, 28). Other studies utilizing alveolar capsules in guinea pigs and rabbits confirm that lung tissue resistance increases substantially with lung volume (19, 35). Dogs also exhibit an increase in lung resistance as mean Paw increases, but the most striking increases in resistance occurred at levels of Paw below the relaxation volume (1). Dechman et al. (7) showed lung resistance in dogs to have a minimum at a PEEP of 3–4 hPa. They attributed the increase in resistance above this PEEP level to the nonlinear viscoelastic properties of lung tissue, whereas the increase in resistance at low PEEP levels was attributed to air space closure. The differences between our results and the previous ones by Nagase et al. (25, 26, 28, 29) in rodents are probably due to the considerably different volume amplitudes utilized for the assessment of respiratory mechanics.

Effects of PEEP on Hti. The dependence of respiratory system elastance on Hti was marked by a decline in NHti at lower levels of lung inflation in all species followed by an increase at 5 hPa, except in mice (Fig. 3). These results confirm a previous study in rats (17), in which Hti as a function of lung volume for both the lung and chest wall exhibited minima. Presumably the increasing values of NHti at low levels of PEEP reflect alveolar collapse and/or airway closure resulting from reduced airway-parenchymal interdependence forces, although nonlinear chest wall elastic properties may also have contributed to this phenomenon. The increase in NHti at higher levels of lung

\[
R = aBW^b \\
b = -0.75 \\
r^2 = 0.9712
\]

\[
Gti = aBW^b \\
a = 183.87 \\
b = 0.92 \\
r^2 = 0.9999
\]

\[
Hti = aBW^b \\
a = 1156.38 \\
b = -1.04 \\
r^2 = 0.9984
\]
inflation was probably due to the nonlinear elastic tissue properties of both chest wall and lungs. The absence of a clear minimum in the NHti curve for mice may reflect the fact that smaller animals with comparatively floppier chest walls have relatively lower lung volumes at a given PEEP. The range of PEEPs studied would then not have been sufficient to push the lungs and chest wall into the upper nonlinear portions of their respective pressure-volume curves. Another possibility is that an increase in NHti for the lung may have been compensated for by a decrease in NHti for the chest wall, because we know that in rats the minima in these two quantities occur at different inflation volumes (17). The lung volume dependence of pulmonary elastance has been previously studied in small rodents with the use of the alveolar capsule technique (19, 25, 26, 28, 29, 35), and in all animals a sharp increase in dynamic elastance with lung inflation has been reported. Nagase et al. (25, 26, 28, 29) studied lung mechanics at transpulmonary pressures as low as 3 hPa in mice, rats, guinea pigs, and rabbits but could not detect a fall in elastance at very low lung volumes, confirming the results of Shardonofsky et al. (35) in rabbits ventilated against PEEPs of 2–4.6 hPa. Most probably, the difference between our results and theirs is due to the fact that we used very-small-amplitude volume oscillations, whereas the alveolar capsule technique was performed during tidal ventilation.

**Tissue mechanics among species.** Leith (21) showed that chest wall compliance increases with BW to the 0.86 power, whereas lung compliance increases with BW to a power between 1.08 and 1.20. When Leith used respiratory system elastance in the equivalent of Eq. 4, he found a value for $b$ of –1.04, which is the exact value we found for Hti (Fig. 4). However, mice and rabbits had relatively more rigid respiratory systems at low PEEPs than did rats and guinea pigs (Fig. 3). This may have been due to differences in the relative compliances of the lung and chest wall among species. However, the chest wall contribution to respiratory system elastance is ~35% in mice (16) and 20% in rats (32). Therefore, it seems unlikely that a relatively increased chest wall elastance in rabbits would solely account for a higher NHti in rabbits than in rats or guinea pigs.

Alternatively, Haber et al. (11) showed that surface forces have a predominant influence on the elastic properties of the lung at volumes higher than functional residual capacity, which implicates alveolar size as the major determinant of specific pulmonary elastance for a constant number of alveoli. We used the data of Mercer et al. (24) to calculate lung volume in various species as the product of the number of alveoli per lung and the mean alveolar volume. We then assumed elastance to be inversely proportional to lung volume and calculated lung elastance normalized to BW relative to that of the mouse (Fig. 5). Although the normalized lung elastances decreased with size for most species, rabbits and mice had very similar pulmonary distensibilities because of the unusually small alveoli in the rabbit (24). We compared these values with estimates of NHti for the lung in mice, rats, and rabbits by assuming that the lung accounted for 65% of respiratory system NHti in the mouse, 55% in the rat, and 80% in the rabbit (16, 17, 30, 32). Figure 5 shows that our estimates of normalized pulmonary NHti agree well with the literature-derived values of lung elastance. It thus seems likely that mice and rabbits have relatively higher NHti compared with rats and guinea pigs because of proportionately smaller total air space volumes.

We found Gti to vary with BW to the $-1.02$ power, which is very similar to the relationship we found for Hti (Fig. 4). This means that Gti and Hti should have a constant ratio; therefore, $\eta$ should be independent of animal size. Although $\eta$ was essentially constant in mice over the PEEP range studied, rats, guinea pigs, and rabbits showed values of $\eta$ that varied with PEEP (Fig. 3). Hirai et al. (17) reported a modest variation in $\eta$ with lung volume for the respiratory system in rats that was due to only a slight variation in $\eta$ for the lung but a marked variation in $\eta$ for the chest wall. Lung $\eta$ has also been shown not to be affected by transpulmonary pressures between 3 and 11 hPa in mice (28) and between 2 and 4.6 hPa in rabbits (35), whereas hyper-inflated guinea pig lungs ventilated with normal tidal volume had reduced $\eta$ (19). This suggests that the observed PEEP dependence of respiratory system $\eta$ that we found was due to the chest wall.

Finally, we must consider some potential shortcomings of our study. In making a comparison among species, it is important to keep experimental conditions and protocols as similar as possible for the different animals. It is impossible to do this perfectly, especially when animals of different sizes are examined. In our
study, for example, we had to ventilate the different rodents with tidal volumes and frequencies pertaining to their respective breathing patterns. However, the actual measurements of respiratory mechanics were made by using the same volume perturbation waveform in each animal, scaled in amplitude according to the various animals’ tidal volumes. In this way, we hoped to avoid the confounding effects of frequency, amplitude, and PEEP that are known to affect the mechanical behavior of the respiratory system to a significant degree (1, 12–17, 30–32, 35). Another potential source of variability in our measurements was the fact that we did not use the same anesthetic and paralyzing agents in all species. Our experience is that different species are best treated with different drugs, especially in terms of the paralyzing agent used (complete paralysis is essential for the accurate determination of respiratory impedance). This raises the question as to whether our results could have been affected by these differences in drug treatment. We cannot know for sure. However, we suspect that the effects were negligible because the results we obtained in the different species scaled generally with animal size, with those departures being interpretable in terms of the previously reported differences in relative airway size between large and small animals.

In summary, we performed a comparative study of $Z_{rs}$ in mice, rats, guinea pigs, and rabbits using a computer-controlled SAV. We interpreted $Z_{rs}$ in terms of a constant-phase tissue model in series with a $R$ and $I$. We documented the PEEP dependences of airway and tissue properties in these animals and interpreted our observations in terms of various physiological phenomena, such as air space recruitment and airway-parenchymal interdependence. We also showed that $R$ is proportionately higher in larger animals, probably due to the relatively smaller increase in airway caliber as size increases. We also argued that a relatively smaller total air space volume could explain the higher values of $H_{ti}$ that we found in mice and rabbits. We thus conclude that a detailed, comparative study of respiratory system mechanics shows evidence of some structural differences among the lungs of various species, although, overall, the rodents that we studied had respiratory mechanics that scaled according to BW in a similar fashion to that reported in other species (21). This suggests that the lungs of the rodents that we studied differ from those of larger species essentially only in terms of scale, which supports their validity as general-purpose models of the human lung.

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