Broadband frequency dependence of respiratory impedance in rats

Cindy Thamrin,1 Peter D. Sly,1 and Zoltán Hantos1,2
1Division of Clinical Sciences, Telethon Institute for Child Health Research and Centre for Child Health Research, University of Western Australia, Perth, Australia; and 2Department of Medical Informatics and Engineering, University of Szeged, Szeged, Hungary
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Thamrin, Cindy, Peter D. Sly, and Zoltán Hantos. Broadband frequency dependence of respiratory impedance in rats. J Appl Physiol 99: 1364–1371, 2005. First published June 20, 2005; doi:10.1152/japplphysiol.00383.2005.—Past studies in humans and other species have revealed the presence of resonances and antiresonances, i.e., minima and maxima in respiratory system impedance (Zrs), at frequencies much higher than those commonly employed in clinical applications of the forced oscillation technique (FOT). To help understand the mechanisms behind the first occurrence of antiresonance in the Zrs spectrum, the frequency response of the rat was studied by using FOT at both low and high frequencies. We measured Zrs in both Wistar and PVG/c rats using the wave tube technique, with a FOT signal ranging from 2 to 900 Hz. We then compared the high-frequency parameters, i.e., the first antiresonant frequency (far,1) and the resistive part of Zrs at that frequency [Rrs(far,1)], with parameters obtained by fitting a modified constant-phase model to low-frequency Zrs spectra. The far,1 was 570 ± 43 (SD) Hz and 456 ± 16 Hz in Wistar and PVG/c rats, respectively, and it did not shift with respiratory gases of different densities (air, heliox, and a mixture of SF6). The far,1 and Rrs(far,1) were relatively independent of methacholine-induced bronchoconstriction but changed significantly with increasing transrespiratory pressures up to 20 cmH2O, in the same way as airway resistance but independently of changes to tissue parameters. These results suggest that, unlike the human subject, the first antiresonance in the rat is not primarily dependent on the acoustic dimensions of the respiratory system and can be explained by interactions between compliances and inertances localized to the airways, but this most likely does not include airway wall compliance.

antiresonance; forced oscillation; high frequency

MEASUREMENTS OF THE MECHANICAL properties of the respiratory system at frequencies other than the spontaneous breathing frequency have been used to infer functional and structural information in both health and disease (31). The respiratory impedance spectrum (Zrs) has been studied with the forced oscillation technique (FOT) most extensively at medium frequencies (e.g., between 4 and 40 Hz). This variant of the FOT has become a routine test in the adult and pediatric lung function laboratory (30). Recently, the extension of oscillation frequencies toward spontaneous breathing rate has provided valuable additional information about the partitioned mechanical properties of the airways and respiratory tissues, although the application of the low-frequency FOT is limited to apneic conditions, such as during mandatory mechanical ventilation (29), voluntary apnea (26), reflex apnea (38) in humans, and paralyzed experimental animals (14, 18, 33, 37).

Studies dating from the 1960s have elicited the frequency response of the lungs at higher frequencies up to around 3 kHz and revealed harmonic occurrences of minima and maxima in the magnitude of Zrs, i.e., points of resonance and antiresonance (9, 22, 41). More recently, there was interest generated in studying the first occurrence of antiresonance. In these studies, the Zrs maxima were defined to correspond to a peak in respiratory system resistance (Rrs), coupled with a zero-crossing in respiratory reactance (Xrs). Here the frequency at which this occurred was termed the first antiresonant frequency (far,1). The far,1 has been measured in dogs at 97 ± 13 Hz (24), in rabbits (12), and in human adults (2, 3, 6, 15, 23) and infants between 150 and 200 Hz (10, 11). Suki and colleagues (39) also studied antiresonance in excised calf tracheas. Human studies in particular have linked far,1 to the properties of the airway wall via changes with methacholine (MCh) constriction (10) and wheeze (11) in infants, as well as via correlation with chronic airflow limitation in adults (2). However, the exact physiological correspondence of antiresonance is still not well understood. The main question in determining this in any particular species is whether the first antiresonance point we see is purely due to the interactions between lumped properties of structures in the respiratory system, or is distorted by acoustic quarter-wave resonances arising out of the airways acting as a conduit for sound waves. The proposal has been made that, in smaller animals, the acoustic antiresonance would be shifted higher in the frequency spectrum owing to the shorter mean path length of wave propagation, thus possibly “exposing” antiresonances arising out of interactions between inertive and compliant components within the respiratory system (3). In either case, is the parameter far,1 useful in a physiological sense, or even in a clinical sense in humans? In cases in which the physiological information of interest can be deduced from the high-frequency Zrs spectrum alone, then the high-frequency oscillation technique would be preferable over the low- and medium-frequency methods, because it overcomes the practical issue of spontaneous breathing frequencies corrupting the low-frequency spectrum and imposing limitations on medium-frequency measurements.

The aim of this study is to look at antiresonance in the rat, to provide clues toward dissecting the mechanisms by which antiresonance occurs in the respiratory system while furthering understanding of its species dependence. Furthermore, we wish to compare antiresonance parameters with “conventional” medium-frequency estimation of airway properties. We hypothesize that because there is greater dominance of the airways over the impedance spectrum as frequency increases, the impedance...
measures at the antiresonance would correlate with the resistance of the airways as determined from the lower frequency spectrum. We chart the changes in antiresonance parameters at conditions in which airway caliber and lung stiffening are altered, i.e., at different lung volumes and during bronchoconstriction.

MATERIALS AND METHODS

Study 1: Effect of respiratory gas density. To determine whether the first antiresonance is predominantly acoustic in the rat, the effect of altering the density of the respiratory gas medium was studied. Twenty-four adult PVG/c rats (weight 276 ± 23 g) were prepared using a mixture of 10 mg/kg xylazine and 50 mg/kg ketamine. Once surgical anesthesia was established, the animals were tracheostomized, cannulated, and hyperventilated at 130 breaths/min in between measurements to induce apnea, by use of a Harvard ventilator with a tidal volume of 8 ml/kg.

Zrs spectra were acquired by using a slightly modified version of the wave tube setup (33), in which three transducers (model 8507C-2, Endevco, San Juan Capistrano, CA) were used for the simultaneous acquisition of low- and high-frequency spectra (Fig. 1). Low-frequency Zrs, on which parameter estimation was performed, was calculated as the load impedance on the longer wave tube segment between transducers P1 and P3 (length = 163 mm ID = 1.575 mm). High-frequency Zrs was obtained between transducers P2 and P3, over the shorter wave tube segment (length = 73 mm ID = 1.575 mm). This enabled the wave tube length limit imposed by the quarter-wave criterion to be satisfied for higher frequencies, whereas the longer segment offered a more accurate estimation of the low-frequency Zrs spectra and derived parameters.

A pseudorandom signal consisting of non-integer multiple frequency components ranging from 2 to 887 Hz was generated using a loudspeaker and delivered to the animal via the wave tube and endotracheal tube. The phase content of the signal was optimized to limit the peak-to-peak amplitude to 2 cmH2O. The signals of P1, P2, and P3 were low-pass filtered with Butterworth anti-aliasing filters at 900 Hz and sampled at 2 kHz. Measurements were made during 6-s pauses in room air ventilation, at end-expiratory transrespiratory pressures (Prs) of 0, 2, 5, 10, 15, and 20 cmH2O as measured via a water column. Zrs was then calculated as the load impedance at the end of the wave tube as described previously (20, 33). The procedure was repeated with the animals breathing either heliox (80% helium, 20% oxygen), neox (80% neon, 20% oxygen), or SF6-air mixture (20% SF6, 20% oxygen, balance nitrogen). Before the measurements with another resident gas, the animal was ventilated for 10 min with the corresponding gas, and the compliant bag in the loudspeaker box and the wave tube were flushed out with that gas. The physical properties for the gases used are found in Table 1. Measurements at Prs = 0 and 10 cmH2O were repeated after this with the animal breathing air again, to confirm that measured parameters are similar to those obtained before the introduction of the foreign gas. The animal handling and study protocol conformed to the guidelines of the Australian National Health and Medical Research Council and were approved by the Animal Ethics Committee of the Institute for Child Health Research.

Study 2: Bronchoconstriction and lung volume dependence. In a separate study, eight adult Wistar rats (weight 421 ± 38 g) were prepared by an intraperitoneal injection with a mixture of pentobarbital sodium (45 mg/ml) and pipercuronium bromide (0.2 mg/ml). The animals were tracheostomized, cannulated, and ventilated (75 breaths/min).

The standard wave tube technique was used in this part of the study (wave tube length = 73 mm, ID = 1.55 mm), with a FOT signal of a similar frequency range to that in study 1 (3–898 Hz). This was also a noninteger multiple signal, but with slightly different spacings between the frequency components. Signals were filtered and sampled as above. Measurements were made during a saline infusion, followed by a cumulative intravenous MCh challenge of 1, 2, 4, and 8 μg·kg⁻¹·min⁻¹, at Prs = 0 cmH2O. We also looked at the effect of changes in lung volume corresponding to Prs levels of 0, 2, 5, 10, 15, and 20 cmH2O. The animal handling and study protocol was approved by the Institutional Animal Care and Use Committees of the University of Szeged.

Data analysis. For all Zrs spectra acquired, the effect of experimental tubing and the endotracheal catheter was removed by treating

Fig. 1. Schematics of the experimental setup. The wave tube uses 3 transducers (P1, P2, and P3) to enable respiratory system impedance (Zrs) measurements at both low and high frequencies (see text). Two compliant bags containing the resident gas are used, one attached to the ventilator to supply gas during normal respiration and one attached to the wave tube to supply gas during Zrs measurement as well as to facilitate flushing of the gas in and out of the measurement circuit. The syringes and water columns are used to pressurize both the inside and outside of the compliant bag within the loudspeaker to the desired transrespiratory pressure. The diagonal lines indicate clamps that allow either the respirator or the measurement circuit to be connected to the animal. A/D, analog-to-digital.
Table 1. Physical parameters of respiratory gases used

<table>
<thead>
<tr>
<th>Gas</th>
<th>Composition</th>
<th>Dynamic Viscosity $\times 10^{-5}$ Pa/s</th>
<th>Density, kg/m$^3$</th>
<th>Ratio of Heats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>80% N$_2$, 20% O$_2$</td>
<td>1.76</td>
<td>1.198</td>
<td>1.4</td>
</tr>
<tr>
<td>Heliox</td>
<td>80% He, 20% O$_2$</td>
<td>1.94</td>
<td>0.399</td>
<td>1.6</td>
</tr>
<tr>
<td>Neox</td>
<td>80% Ne, 20% O$_2$</td>
<td>2.86</td>
<td>0.932</td>
<td>1.6</td>
</tr>
<tr>
<td>SF$_6$</td>
<td>20% SF$_6$, 20% O$_2$, balance N$_2$</td>
<td>1.71</td>
<td>2.180</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Each element as another wave tube in front of the lower respiratory system (20). Low-frequency analysis then consisted of fitting a model (18, 19) commonly applied to low-frequency Zrs data to obtain airway and constant-phase tissue parameters, modified by the incorporation of an empirical parameter $\beta$ (19) to account for the elevation of airway resistance $R$ with frequency ($\omega$) up to 79 Hz (7):

$$Z_{rs} = R(1 + \beta \omega^2) + j\omega I + \frac{G - jH}{\omega^2}$$

where $I$ corresponds to airway inertance, $G$ and $H$ quantify tissue damping and elastance, respectively, and $\alpha$ is determined by $G$ and $H$ as $\alpha = (2/\pi) \tan(\alpha G/H)$. The relative fitting criterion was used in the parameter estimation (17, 40). High-frequency analysis involved determining the position of far,1, and the magnitude of $R_{rs}$ at antiresonance, $R_{rs}(\text{far,1})$.

Statistical analysis. Unless indicated otherwise, all comparisons were made with one-way repeated-measures ANOVA (on ranks where the equal variance test was failed), where significance was indicated by $P < 0.05$. Post hoc tests were also performed, with significance indicated by $P < 0.05$, compared with the baseline measurement when appropriate.

RESULTS

Spectral characteristics of Zrs. In most of the Zrs spectra observed, the phase of the impedance was at a minimum but not equal to zero where maximum magnitude of the impedance ($|Z_{rs}|$) was found, and the first instance of local maximum in $R_{rs}$ did not correspond exactly with the definitive local maximum in $|Z_{rs}|$. We compared the two quantities in Wistar rats (study 2) and found that whereas far,1 obtained from peak $R_{rs}$ was significantly higher than that obtained from $|Z_{rs}|$ ($570 \pm 43$ (SD) Hz vs. $531 \pm 43$ Hz at 0 cmH$_2$O, paired $t$-test, alpha level $= 0.05$, $P < 0.001$), they were found to be strongly correlated to each other at all volumes ($r = 0.987$) and all MCh doses ($r = 0.995$), indicating a small systematic difference between the two quantities. Both showed similar trends with increasing lung volume and bronchoconstriction. Thus all far,1 values presented in this study were obtained from peak $R_{rs}$ as a surrogate for that obtained from peak $|Z_{rs}|$, to enable comparisons with the more recent antiresonance studies in the literature. In the PVG/c rats, the far,1 estimated from peak $R_{rs}$ was $456 \pm 16$ Hz at Prs of 0 cmH$_2$O.

Effect of gas density. Sample Zrs spectra taken from rats breathing air at Prs of 0 cmH$_2$O compared with heliox, neox, and SF$_6$ mixture, respectively, are shown in Fig. 2. In all cases, there were no significant differences in far,1 between air and heliox (paired $t$-test, alpha level $= 0.05$, $P = 0.792$), a statistically significant but small decrease with neox ($P = 0.006$), and again no significant differences with SF$_6$ ($P = 0.290$).

Figure 3 displays low-frequency sections of the Zrs data. To quantify the differences in the spectra, we compared the extent to which $R$ as obtained from model fitting was shifted for each gas compared with air. $R$ decreased by an average multiplicative factor of 0.63 $\pm 0.07$ with heliox (where the change was significant at $P < 0.001$), was not significantly altered by an average factor of 0.85 $\pm 0.30$ with neox ($P = 0.248$), and increased by an average factor of 1.25 $\pm 0.14$ with SF$_6$ ($P < 0.001$). $H$ remained unchanged in the case of neox ($P = 0.287$) and SF$_6$ ($P = 0.908$) and decreased by a statistically significant ($P = 0.044$) but small amount with heliox.

Effect of MCh. $R$ increased with the elevation of MCh dose (Fig. 4), although the change was not statistically significant compared with saline (denoted as 0 ml$^{-1}$) until the final MCh doses. MCh did not have a significant effect on $H$ and produced an increase in $G$ only at the highest dose (not shown).
Meanwhile, changes in far,1 with MCh were not significantly different until the highest dose was reached, whereas the increase in Rs(far,1) with bronchoconstriction was not significantly different until $4 \mu g \cdot kg^{-1} \cdot ml^{-1}$.

**Volume dependence of low- and high-frequency parameters.** At low frequencies, the volume-dependent decrease in $R$ estimated from the model fitting was significant at all pressures compared with baseline at 0 cmH$_2$O (Fig. 5). Changes in $H$ were significant at all pressures except for 10 cmH$_2$O compared with the data at Prs = 0 cmH$_2$O. Because of the nonmonotonic direction of change in $H$, observations at each Prs were compared with the previous pressure instead of with baseline, which was the case for the other parameters.

Both far,1 and Rs(far,1) were seen to decrease significantly with lung volume (Fig. 5), for all Prs levels in far,1, and from 10 cmH$_2$O onward in Rs(far,1). This pattern of change was also seen in the PVG/C rats (data not shown).

**DISCUSSION**

**Acoustic determinants of first antiresonance in rats.** When we consider a sound wave traveling in a rigid tube, the

![Fig. 3. Low-frequency portions of the impedance spectra showing Rs and Xrs from the same rats as in Fig. 2 at a transrespiratory pressure of 0 cmH$_2$O, breathing air followed by helix (left), air followed by neox (middle), and air followed by SF$_6$ (right), respectively. ●, Air; ○, relevant respiratory gas.](image1)

![Fig. 4. Pattern of change with methacholine of airway resistance (R), tissue elastance ($H$), the first antiresonant frequency (far,1), and respiratory resistance at first antiresonance [Rs(far,1)]. Shown are individual data in 7 Wistar rats. *One-way repeated-measures (RM) ANOVA $P < 0.05$ compared with baseline.](image2)
positions of the quarter-wave resonances depend on the acoustic properties of the tube: the mean path length traversed by the wave in the tube and the speed of wave propagation in the gas medium. The latter in turn depends on the gas inertance and compliance, as well as the diameter $d$ of the tube, for small diameters, where the limit for “small” is given by the approximation:

$$d \leq \left( \frac{\omega \rho}{\gamma \eta} \right)^{1/2}$$

where $\omega$ is the angular frequency, $\rho$ is density of air, $\gamma$ is ratio of specific heats, and $\eta$ is the dynamic viscosity of air (1, 23).

In a tube with nonrigid walls, the resonant properties of the tube wall structures can alter the speed of the propagating wave within the tube, thus potentially modifying the acoustic resonances and antiresonances in the $Z_{rs}$ spectrum. As a first approximation, if we describe a small segment of a conducting airway wall as a simple series resistance-inertance-compliance system, in parallel with gas compliance and thermal resistance, and in series with the gas inertance and viscous resistance (8, 39), the interaction between wall inertance and compliance would affect the position of the resonance points, whereas the wall resistance would modify the magnitude of the impedance at the resonance points.

Without the aid of computer modeling, it is difficult to surmise the effects of individual parameters on the $Z_{rs}$ spectrum when airways comprising many such elementary segments are arranged in a branching network, and where the parameters for each segment are dependent on the order of the airway which it comprises (8). It may be more intuitive to think of the airway tree as having many possible parallel paths, each path a serial combination of airways, each airway having its own mechanical wall resonance frequencies, and the overall combined resonance points as a result of the effective resonances of the dominant paths being reinforced or diminished by that of other paths. Many different parallel paths having the same resonant frequencies would produce clearly defined resonance maxima or minima, but paths having a heterogeneous mix of resonant frequencies would perhaps produce less pronounced, wider bands of maxima or minima. This neglects how the interactions between airways and terminal impedances that make up each path produce the effective resonances of that path but provides a first pass at how wall resonances can modify the acoustic quarter-wave resonances associated with the effective mean path length of the network.

The effect of using gases of different density ($\rho_{\text{gas}}$) than that of air ($\rho_{\text{air}}$) was studied to determine the nature of the first antiresonance in rats. If the antiresonance is predominantly acoustic in nature, then the frequency at which it occurs should shift with $\rho_{\text{gas}}$ by a multiplicative factor of $(\rho_{\text{air}}/\rho_{\text{gas}})^{0.5}$ compared with air (1.73 for heliox, 1.13 for neox, and 0.74 for the SF$_6$ mixture), via changes to the velocity of sound wave propagation $c$ (21):

$$c = \frac{\sqrt{\gamma P_0}}{\rho}$$

where $P_0$ is the mean static pressure, if the conditions in the lungs are isothermal such that the ratio of specific heats $\gamma = 1$. For adiabatic conditions, the factors for the three gases would be further scaled by $\lambda^{0.5}$ such that the gas-to-air ratio of velocities ($c_{\text{gas}}/c_{\text{air}}$) would be 2.19 for heliox, 1.43 for neox, and 0.88 for the SF$_6$ mixture, i.e., the directions of change would be preserved.

Because $\text{far,1}$ did not change significantly with gas density in heliox and SF$_6$, and decreased to a small extent in neox, opposite to the direction expected, we conclude that the first
occurrence of antiresonance in the rat is dominated by the resonant responses of respiratory structures independent of sound wave propagation. In this aspect, the first antiresonance in rats is similar to that in dogs, but different from the first antiresonance in humans for both adults (23) and infants (13), which were shown to be acoustic via lack of change in far,1 with the subjects breathing heliox compared with air. The work of Rotger et al. (34) also looked at changes in far,1 in adult humans with respiratory gases but eliminated the contribution of the extrathoracic upper airway shunt to the Zrs spectra. Whereas the far,1 values as well as the factors obtained for heliox and SF6 mixture compared with air were systematically different to those obtained from our spectra and those in the Jackson study (23), there was clearly a change in far,1 with gas density great enough to overcome the contribution of the upper airway, and which implicated sound wave propagation.

Interaction between Iti and Cg. Jackson and Lutchen (24) used the DuBois model (4) to lump inertive and compliant components in the respiratory system and predicted a value for antiresonance in dogs of 82 Hz, which was considered to correspond well to the measured value of 97 Hz. A cursory analysis of the DuBois model can show that the parameters that are primarily responsible for antiresonant behavior are the tissue inductance (Iti) and gas compliance (Cg) (3). However, it is known that Iti is a relatively small inductance component (36), which resides mostly in the chest wall (28) and which is difficult to estimate at an acceptable precision and in a model-independent manner (32). For comparison, DuBois model parameters obtained from a past FOT study in Sprague-Dawley rats of similar weights to our Wistar rats (25) were used to generate Zrs spectra up to 900 Hz. The simulation predicted an Iti-Cg antiresonance at 105 Hz. Similarly, using DuBois model parameters obtained from Zrs spectra at 0 cmH2O between 20 to 60 Hz from the Wistar rats in our study produced an expected antiresonance at 137 Hz. No antiresonances close to 100 Hz were observed in our measurements that would suggest the presence of an Iti-Cg antiresonance.

Although the DuBois model has been a powerful tool in understanding the oscillation mechanics of the respiratory system, it involves fundamental limitations that preclude us from making inferences on the basis of its parameters. These are derived from the fact that, first, all the resistances in the model are Newtonian, and, second, all the compliances are frequency independent, as they are in most classical models. In the first instance, we now know that lung tissue exhibits non-Newtonian, constant-phase resistance (18) even down to the level of single cells and up to very high frequencies (5), causing the quasi-hyperbolic decrease seen in Zrs at lower frequencies. (Although chest wall resistance does include a significant Newtonian component, we believe the potential for the chest wall to affect Zrs at antiresonance frequencies to be even smaller than that of the pulmonary tissue, because of its location in the periphery.) In the second instance, again from the constant-phase behavior of tissue, we know that tissue compliance does vary with frequency (18, 26, 33, 37). Meanwhile, gas compression compliance becomes increasingly adiabatic as the time constant of thermal exchange between the gas and the gas chamber wall becomes larger compared with the time period of oscillation (32), i.e., it is frequency dependent. However, there has been no experimental determination known to the authors of whether compressions in the alveoli are isothermal or adiabatic at the higher oscillation frequency regime relevant to this study. Finally, in the DuBois model, the increase in airway resistance generally seen with frequency is solely attributed to the airway compliance parameter Caw. This means that this parameter lumps the effects of gas compressibility, airway wall compliance, as well as inertial distortion of the velocity profile (7), and any inferences made on how it contributes to antiresonance will include all of the above factors. In this sense, Caw is similar in function to our empirical parameter β, although we have limited the use of β to the low-frequency spectrum solely with an aim toward improving our estimate of R, and we have not implied any physiological correspondence. Taking into consideration all the above factors, the DuBois six-element model provides for an unsatisfactory explanation of the occurrence of the first antiresonance in the rat.

Implications of the effect of bronchoconstriction and volume dependence. It was shown that increasing MCh dosage did not have a significant effect on far,1 and Rrs(far,1) until the highest doses were reached. Because of the intravenous delivery of MCh used in this study, the constriction of the airways at the periphery of the lungs would commence at an earlier dose than the larger airways (33). The increase in Rrs(far,1) at higher MCh dosage could therefore be explained by the characteristics of the dose-dependent increase in resistance of the higher-frequency dominated, larger airways. Thus the changes in Rrs at first antiresonance would be more reflective of events within the larger, more central airways than would resistance at lower frequencies. This is supported by the volume-dependent behavior of Rrs(far,1), as detailed below.

The volume dependence of all low-frequency parameters R, G, and H obtained from model fitting was consistent with previous observations (14, 37). At high frequencies, the volume dependence of Rrs(far,1) mirrors closely the pattern of airway resistance and appears to be unrelated to changes in the tissues, as reflected by H. This confirms that the first rat antiresonance does not arise out of interactions in the tissue compartment but is localized to the airways. As the lungs are subjected to a distending pressure, the larger airways are distended as well as the more peripheral ones. Thus, in the volume dependence data, the changes in the larger airways, as reflected by Rrs(far,1), follow those of the airway tree as a whole, which are reflected by changes in low-frequency R. There is a recent imaging study in excised rat lungs that charted the concurrent increase in diameter in both small (<30 μm diameter) and large airways as lung pressure increased from 0 to 27 cmH2O, even though the smaller airways showed greater distension than larger airways with pressure (35). It is also worth noting that past studies using a retrograde catheter in dogs show that at the resonant frequency of the lungs (in this case the first instance of resonance), the resistance of the central airways accounts for most of lung resistance compared with peripheral airways, and its role increases further as lung volume increases (27). At this frequency, Zrs reflects primarily the flow-resistive properties of the lungs, as is the case in antiresonance.

With respect to the position of antiresonance, we have seen that gas density and hence gas inductance have little effect on far,1 in the rat. The decreased compliance of the airway walls as they stiffen with increased lung volume would result in an upward shift in far,1, which is contrary to our observations in
this study. On the other hand, the direction of change of far,1 in our volume dependence data is consistent with lengthening of the airways as well as an increase in gas compliance as the airways expand. However, the degree of increase in airway length associated with lung volume would not account for such a pronounced change in far,1. On the other hand, the suppositions with regard to gas compliance are based on a simplistic picture of series resistance-interruption-compliance interactions in the airways and should be superseded by models that would both incorporate the acoustic properties of the airways and better reflect the distributed nature and the rheology of the inertial and elastic elements in the respiratory system as a whole, which is beyond the scope of the present study.

There has been evidence that antiresonance in the trachea can be attributed to the nonrigid tracheal wall displaying two-compartmental mechanical properties, where the two compartments represent the cartilaginous and the soft tissue segments of the trachea, respectively. This has been seen in excised calf (39) and dog (16) tracheas, as well as in vivo subglottal respiratory input impedance in humans (15). However, with respect to our study in rats, the tracheal properties were involved very little in the changes to the lungs (bronchoconstriction, increased Prs), especially because most of the trachea was cannulated, whereas significant changes occurred in antiresonance parameters.

In light of the above discussion, the first antiresonance in rats is not acoustic and furthermore is not related to interactions between inertances and compliances in the lung periphery. Thus it can most likely be attributed to changes in the inertive and/or compliant properties of structures within the airways, independently of their effects on wave propagation speed. Similarly, changes in Rs(far,1) would be related to changes to the resistance of the airways. The observations with MCH challenge and increased lung volume show that the phenomenon can be further localized to the larger airways. From the direction of change of far,1 with increased lung volume, it is likely that first antiresonance in the rat is less dependent on airway wall compliance than the compliance of gas in the airways as the lung expands.

The mechanisms behind the first antiresonance in rats are not those responsible for antiresonance in human adults and infants, hence making the rat an inappropriate model if one intends to investigate the value of antiresonance in clinical use. However, the idea that high-frequency spectral features such as antiresonance are a property of the larger airways is supported by the results of this study, and further investigations are required to confirm that this is the case in humans.

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