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Volume Dependence of High-Frequency Respiratory Mechanics in Healthy Adults

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Abstract—Respiratory system input impedance (Zrs) at low to medium frequencies below 100 Hz, and study of its volume dependence, have been used extensively to quantify airway and tissue mechanics. Zrs at high oscillation frequencies including the first antiresonant frequency (*f*ar,1) may contain important information about airway mechanics. Changes in high-frequency Zrs with lung volume have not been studied. The volume-dependent behavior of high-frequency Zrs, specifically *f*ar,1 and respiratory system resistance at first antiresonance (Rrs(*f*ar,1)), was characterized in 16 healthy adults. Zrs was measured with a forced oscillation signal (5–302.5 Hz) through a wavetube setup. To track Zrs, subjects performed slow deep inspiratory and expiratory maneuvers over 30-s measurements, during which average impedance was calculated over 0.4-s intervals, with successive overlapping estimates every 0.156 s. Flow was measured using a pneumotachometer and integrated to obtain volume. Transpulmonary pressure dependence (Ptp) of Zrs was separately determined in five subjects. Both *f*ar,1 and Rrs(*f*ar,1) decreased with increasing lung volume and Ptp, consistent with an increase in airway caliber and decreased airway wall compliance as volume increased. These characterizations provide insight into airway mechanics, and are furthermore a necessary first step toward determining whether volume dependence of the first antiresonance is altered in disease.

Keywords—Antiresonance, Forced oscillation, Respiratory input impedance.

INTRODUCTION

The frequency response of the respiratory system to forced oscillation[7] is determined by the structure and mechanics of the airways and lung tissue.[23,24] Current studies employing the forced oscillation technique (FOT) conventionally use low to medium frequencies under 40 Hz,[23] yielding either single-frequency values of respiratory system impedance (Zrs) or parameters from mathematical models of the multifrequency Zrs data and providing estimates of the resistive and reactive properties of the airways and lung tissue. In addition, the dependence of FOT parameters on changing lung volume has also been described at these frequencies in adults[1,3] and infants,[26] and has been suggested to be useful in the diagnosis of disease.[33]

Measurements of Zrs at high frequencies above 100 Hz have revealed harmonic occurrences of quarter-wave resonances in the Zrs spectrum, corresponding to minima (resonances) and maxima (antiresonances) in the magnitude of Zrs.[17,32] Zrs at higher frequencies is thought to reflect properties of the airways but not of the lung tissue or chest wall.[24] Subsequent studies concentrated on the frequency of the first occurrence of antiresonance (*f*ar,1) in the Zrs spectrum,[6,19] and provided evidence that sound wave propagation in the airways is responsible for the first antiresonance in humans.[18,28] Thus, airway wall properties could influence *f*ar,1, via the effect of the mechanical resonance of the compliant wall on the velocity of wave propagation. To date, the dependence of high-frequency impedance on lung volume has not yet been determined.

Measurements of Zrs are generally made by averaging impedance over several breathing cycles, i.e., over a measurement period including tidal changes in lung volume;[23] or by tracking single-frequency Zrs during breathing[25] or deep inhalation maneuvers.[21] While multiple-frequency Zrs tracking has been possible since the first application of a composite driving signal,[22] it is only in recent years that more studies have been reported in which multiple-frequency Zrs is measured continuously during changing lung volume,[15] deep inhalation,[20] or following bolus injection of methacholine.[30] Thus, the aims of this study were to characterize the lung volume dependence of the first

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antiresonance in health, and to determine the feasibility of making continuous multiple-frequency Zrs measurements at antiresonance frequencies. The first antiresonance was quantified using two parameters: *f*ar,1 and the value of the resistive component of Zrs at *f*ar,1 (Rrs(*f*ar,1)). We compared these parameters with resistance simultaneously obtained from the medium frequency range of FOT between 7.5 and 35 Hz.[23]

MATERIAL AND METHODS

Study Population

Sixteen healthy adult volunteers (eight males, eight females); median age 41 years (range 24–69 years); height 171 cm (range 151–183 cm); and weight 73.7 kg (45.0–103.4 kg); were studied. All subjects had normal forced expiratory volume in 1 s and total lung capacity (TLC) values, i.e., within two standard deviations of the predicted mean.[2,5,14]

Measurement of Zrs

A schematic of the measurement setup is shown in Fig. 1. The pseudorandom forced oscillatory signal was generated with a loudspeaker and consisted of 39 frequency components ranging from 5 to 302.5 Hz, which were non-integer multiples of the fundamental 2.5 Hz; the signal period was 0.4 s. The signals were low pass filtered using eighth-order Butterworth filters at 250 Hz and sampled at 640 Hz. The attenuation of the filter was −17 dB at the highest frequency, and the obtained Zrs spectra were reliable and had repeatable coherence values. Zrs was estimated using the wavetube technique[9,31] (internal diameter = 12.7 mm, length = 245 mm), with lateral pressure transducers P1 and P2 (ICS 33NA002D, Miltipas, CA, USA). The length was chosen to be less than the characteristic quarter-wavelength of the wavetube so as to prevent the setting up of standing waves within the tube that would obscure the measured antiresonance. Zrs measurements were corrected for the cylindrical mouthpiece by treating the latter as another wavetube segment.[16] Volume change was obtained by integrating flow obtained from a pneumotachometer P3 (Hans Rudolph, MO, USA). Two types of FOT measurements were made with the subjects in the sitting position:

Steady-state measurements were made during a 10-s apnea at functional residual capacity (FRC) and at TLC. Subjects supported their cheeks, and nose clips were avoided to prevent reflex opening of the velum.[4] Reproducibility was assessed by comparing the initial measurements with those made one day later (Day 2), and once again between Days 5–8. The following measurements were also made at FRC: (1) after breathing heliox (80% helium, 20% oxygen; density 0.399 kg m^{-3} and viscosity 1.94×10^{-5} Pa s^{-1}) for >5 breaths, (2) wearing a nose clip, (3) without cheek support, and (4) extending the neck.

Continuous FOT measurements were made over 30 s during each breathing maneuver. Zrs was computed by moving sample-by-sample along the recording[15] such that an average impedance was obtained over 0.4-s intervals, with successive overlapping estimates obtained every 0.156 s. Subjects were instructed to breathe tidally at FRC followed by either inspiration to TLC and then expiration to residual capacity (RV), and or by expiration to RV and then inspiration to TLC.

Data Analysis

From each Zrs spectra, *f*ar,1 and Rrs(*f*ar,1) were determined using polynomial fitting and a peak-detection algorithm (Matlab, The Mathworks Inc,

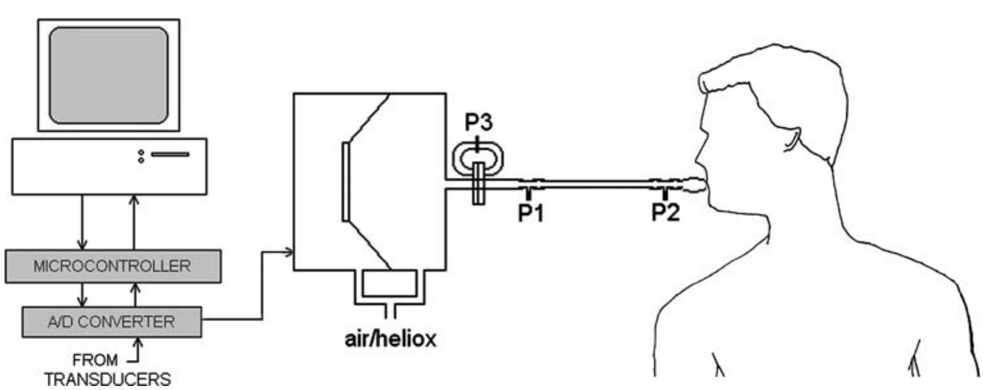

FIGURE 1. Schematic of forced oscillation setup. The transducers P1 and P2 are used in the measurement of load impedance at the end of the wavetube, while P3 is used in the pneumatachometer to determine flow.

MA, USA): an initial estimate for maximum Rrs was first determined from the measured data points. To improve the estimation of both the peak and the frequency, quadratic interpolation with resolution 0.1 Hz was applied to the five data points centered on the initial estimate of maximum Rrs. The final estimate of maximum Rrs was then determined from the interpolated data set. This value, and the frequency corresponding to it, were taken to be Rrs($f$ar,1) and $f$ar,1, respectively. The average value of Rrs between 7.5 and 35 Hz, i.e., in the medium FOT frequency range (Rrs(7.5–35)) was also calculated.

Measurement of Transpulmonary Pressure

In a separate study, the effect of distending pressure on high-frequency impedance parameters was studied in five of the subjects. Continuous measurements were made simultaneously with an oesophageal balloon placed within the lower two-thirds of the oesophagus providing an estimate of pleural pressure. Balloon pressure was measured with a differential pressure transducer (Statham PM131TC, Oxnard, CA, USA) referenced to airway opening pressure from the wave-tube setup to obtain transpulmonary pressure (Ptp). The signal was amplified and filtered at 50 Hz (Grass low-level DC amplifier (model 7P122G)). Subjects breathed tidally at FRC followed by inspiration to TLC and then expiration to FRC, and additionally inspiration and expiration flows were varied and recorded.

All protocols were approved by the Human Research Ethics Committee at Princess Margaret and Sir Charles Gairdner Hospitals. Written consent was obtained from all participants. All statistical tests (paired and unpaired t-tests, and the corresponding tests on ranks where normality and/or equal variance tests failed) were performed using SigmaStat (v.2.03, SPSS Inc., Chicago, IL) with $\alpha = 0.05$, with significance indicated by $p < 0.05$. Similarly, Pearson product moment correlations with $p < 0.05$ were reported as significant.

RESULTS

Study 1: Characterization of Antiresonance in Health

Influence of Measurement Conditions

Sample spectra from steady-state measurements under the different measurement conditions are shown for one individual in Fig. 2. In some but not all subjects, wearing a nose clip caused a change in the Zrs spectrum, shifting the $f$ar,1 lower and sometimes splitting the single antiresonance into two (Fig. 2). Wearing a nose clip significantly altered $f$ar,1 and Rrs($f$ar,1) ($p < 0.05$). In contrast, withdrawing cheek support and extending the neck did not change either of the antiresonance parameters significantly (Fig. 3).

Gas Density

$f$ar,1 obtained from the steady-state Zrs spectra at FRC had a median value of 209.4 Hz (range 191.1–257.4 Hz). Following heliox breathing at FRC, $f$ar,1 increased to a median value of 252.2 Hz (range 195.3–281.4 Hz, $p < 0.001$). Rrs($f$ar,1) was 21.0 cm

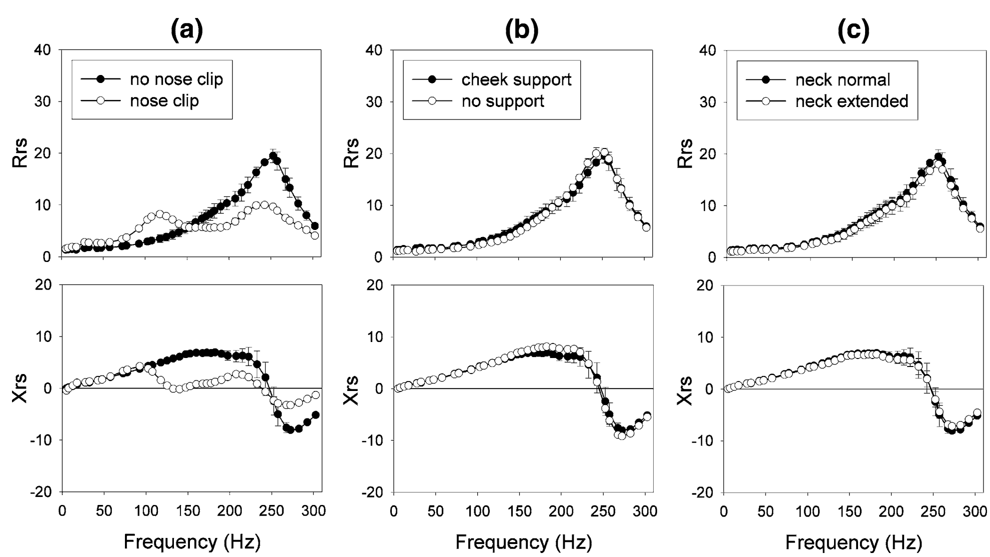

FIGURE 2. Sample respiratory system resistance (Rrs) and reactance (Xrs) from steady-state measurements in a healthy subject, showing the effects of (a) wearing a nose clip, (b) cheek support, and (c) neck position on the first antiresonance.

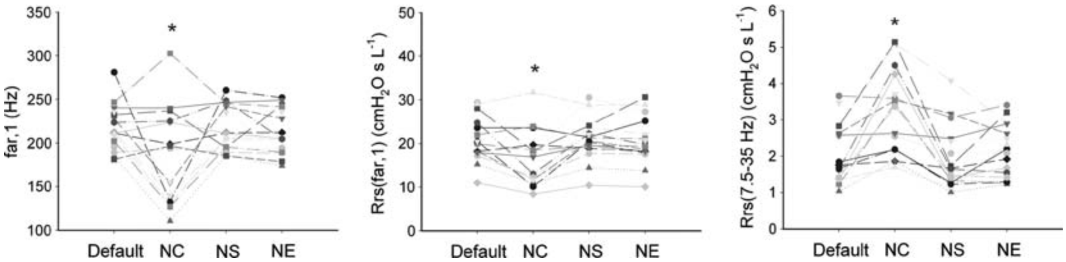

FIGURE 3. Effect of wearing a nose clip (NC), lack of cheek support (NS), and neck extension (NE) on the first antiresonant frequency (*f*ar,1), magnitude of respiratory system resistance (Rrs) at antiresonance (Rrs(*f*ar,1)), and average resistance at low frequencies (Rrs(7.5–35)). ****p* **< 0.05.**

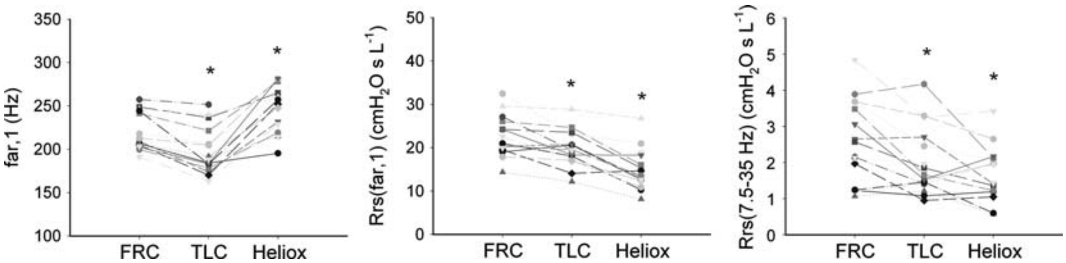

FIGURE 4. Effect of lung volume (TLC vs. FRC) and gas density (heliox vs. air, measurement at FRC) on the first antiresonant frequency (*f*ar,1), magnitude of Rrs at antiresonance (Rrs(*f*ar,1)), and average resistance at low frequencies (Rrs(7.5–35 Hz)). ****p* **< 0.05. All comparisons were made with breathing air at FRC.**

H_2O s L^{-1} (14.3–32.5 cmH_2O s L^{-1}) and decreased to 13.6 cmH_2O s L^{-1} (8.1–26.7 cmH_2O s L^{-1}) with heliox ($p < 0.001$) (Fig. 4).

Antiresonance at FRC vs. TLC

*f*ar,1 decreased with inhalation to TLC to 189.8 Hz (163.4–251.6 Hz, $p < 0.001$) while Rrs(*f*ar,1) decreased to 19.4 cmH_2O s L^{-1} (12.2–28.8 cmH_2O s L^{-1}, p = 0.005) (Fig. 4).

Reproducibility

*f*ar,1 and Rrs(*f*ar,1) were reproducible over the number of days studied, with no systematic differences between the three sets of measurements at either FRC or TLC (one-way repeated measures ANOVA, $p > 0.05$). Figure 5 shows Bland-Altman plots for Day 1 vs. Day 2, revealing that any differences between days were unrelated to the magnitude of the measured values, i.e., no systematic bias was seen in the measurements. Similar plots were obtained for Day 1 vs. Day 5–8 (not shown).

In all conditions, the medium-frequency spectra were noisier, in that greater relative variability was observed in Rrs between 7.5 and 35 than at frequencies around first antiresonance. There was no correlation between Rrs(7.5–35) and Rrs(*f*ar,1). However, the changes in Rrs(7.5–35) were in the same direction and of the same significance as Rrs(*f*ar,1), when comparing the effects of nose clip, cheek support and neck extension, as well as heliox, lung volume, and short-term variability.

Volume Dependence

In the continuous breathing maneuvers in healthy subjects, *f*ar,1 and Rrs(*f*ar,1) decreased as lung volume increased during inhalation from FRC to TLC, and increased during exhalation from TLC to RV. However, many subjects had difficulty maintaining an open glottis during exhalation, especially toward RV. Thus, for the rest of the study we focused a large part of our analysis on data during inspiration between FRC and TLC.

To facilitate comparison between subjects, lung volume was first expressed as percentage of predicted TLC. The volume dependence of *f*ar,1 (VD*f*ar,1), of Rrs(*f*ar,1) (VDRrs(*f*ar,1)), and of Rrs(7.5–35) (VDRrs(7.5–35)) were then defined as the slopes of linear fits to the plots, standardized to between 25% and 75% of the inspiratory capacity (IC), as subjects tended to narrow their glottis near FRC (40% of subjects) and near TLC (30% of subjects) causing large fluctuations in estimates of *f*ar,1 and Rrs(*f*ar,1). The narrowing was apparent from the sudden increase in the amplitude of pressure oscillations. A representative linear fit was obtained for each subject by averaging the slopes and intercepts obtained from each measurement

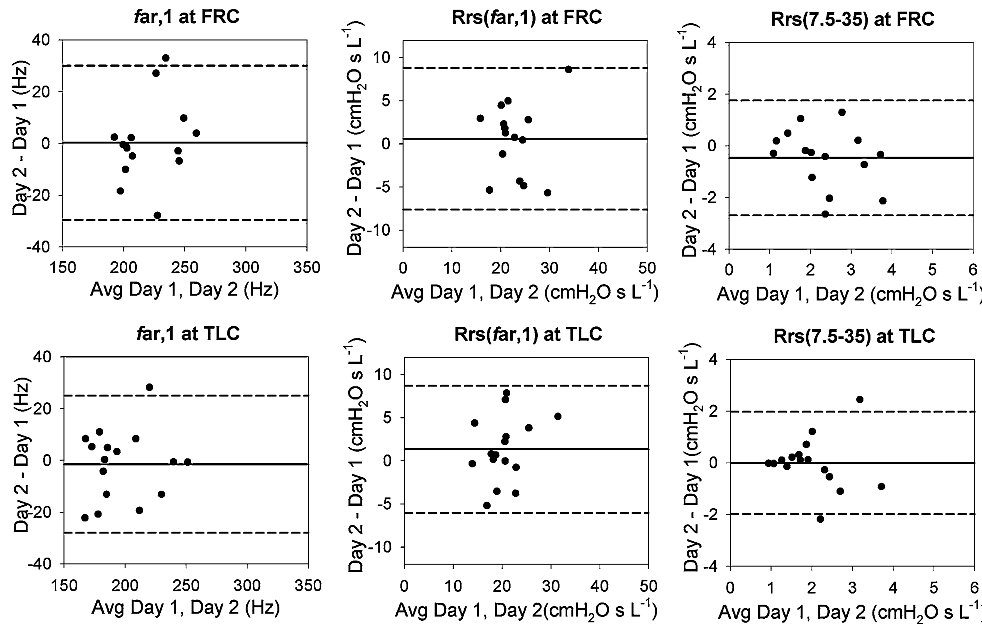

FIGURE 5. Bland-Altman plots showing reproducibility of the first antiresonant frequency (*f*ar,1), magnitude of respiratory system resistance Rrs at antiresonance (Rrs(*f*ar,1)), and average resistance at low frequencies (Rrs(7.5–35)) between days 1 and 2, at FRC (*top panels*) and TLC (*bottom panels*).

for that subject (Fig. 6). The group mean VD*f*ar,1 and VDRrs(*f*ar,1) were –0.43 (SD 0.35) Hz $(\%\text{predTLC})^{-1}$ and –0.075 (SD 0.066) cmH_2O s L^{-1} $(\%\text{predTLC})^{-1}$, respectively.

Study 2: Dependence on Transpulmonary Pressure

When the antiresonance parameters were plotted against Ptp linearity was preserved within 25% and 75% IC (mean r^2 for the fits was 0.63 (SD 0.28) for *f*ar,1 vs. Ptp, and 0.56 (SD 0.29) for Rrs(*f*ar,1) vs. Ptp). Strong correlation was found between slopes obtained from plots against lung volume and those against Ptp (regression coefficient = 0.44, $p < 0.001$ with $r = 0.87$, $p < 0.0001$ for *f*ar,1, and regression coefficient = 0.37, $p < 0.001$ with $r = 0.94$, $p < 0.0001$ for Rrs(*f*ar,1)).

Over the volume excursion range used for fitting, VD*f*ar,1 exhibited a slight positive dependence ($p = 0.001$ for the regression) on the mean inspiratory flow ($r = 0.44$, $p = 0.0014$), but there was no significant relationship between VDRrs(*f*ar,1) or VDRrs (7.5–35) and flow over this volume range.

With complete inspiratory–expiratory measurements, a hysteresis was observed between the inspiratory and expiratory limbs in the volume- and pressure-dependent behavior of both *f*ar,1 and Rrs(*f*ar,1) (Fig. 7). For any given lung volume or Ptp, the expiratory value of either antiresonance parameter was systematically lower than that during inspiration. To allow comparison between subjects, hysteresis was normalized to the area of the loop formed by the inspiratory and expiratory limbs. Table 1 shows the average hysteresis values for both *f*ar,1 and Rrs(*f*ar,1) plotted against Ptp.

DISCUSSION

Characterization of Antiresonance in Healthy Humans

Although the frequency response of the respiratory system exhibits characteristic patterns at high frequencies, its physiologic interpretation is complex. The first antiresonance in humans is not adequately described by the classical DuBois 6-parameter model,[6,8] and is attributed to the acoustic properties of the airways.[18] The mixture of heliox used in these studies was three times less dense than air, and would predict an increase of *f*ar,1 by a multiplicative factor of 1.73 greater than the 1.2 we see in our studies; however, this prediction assumes propagation in a rigid and not compliant tube. We can instead confirm that the increase in *f*ar,1 is due to the increase in the velocity of sound wave propagation in that the increase was to an extent greater than the effect of gas compression alone (5%), according to previous investigators.[18] The values for *f*ar,1 in healthy adults obtained from steady-state measurements both at FRC and TLC were higher than previously published values of *f*ar,1,[4,6] although, the latter were obtained from spectra averaged during tidal breathing, a period of changing lung volume, whereas

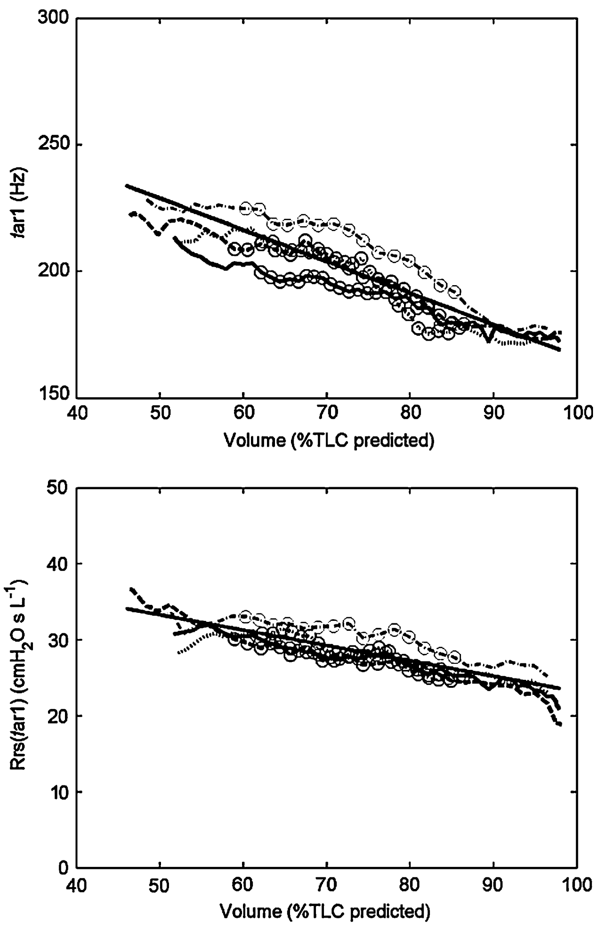

FIGURE 6. Sample linear fits to graphs of first antiresonant frequency (*f*ar,1, *top*) and magnitude of Rrs at antiresonance (Rrs(*f*ar,1), *bottom*) vs. lung volume. Repeated measurements are shown for each subject. The circles on each measurement denote regions of the linear fit, defined as between 25 and 75% of the volume excursion for that measurement.

our measurements were obtained with constant lung volumes during breathholding. We have also found that baseline values of *f*ar,1 are also strongly influenced by the type of the mouthpieces and the location of the P2 lateral pressure sampling (data not shown), since any piece of tubing or apparatus joining P2 with the airway opening has the potential to add a significant inertial component to the antiresonance spectrum, and thus needs to be corrected for these as done in this study.

The effect of wearing a nose clip at high perturbation frequencies is well-documented to be due to the reflex opening of the velum while the nose clip is on, as opposed to reflex velum closure when subjects are asked to breathe exclusively through their mouth without a nose clip.[4,10] We also found that cheek support resulted in little change to the antiresonance spectrum in healthy subjects, possibly because the inertia of the cheeks makes these upper airway wall structures fairly rigid at high frequencies. However, all subjects were asked to support their cheeks during measurements, due to the simultaneous measurement of medium frequency FOT,[23] and to facilitate future comparison with possible increased influence of upper airway compliance in subjects with lung disease and/or increased lower airway resistance. Using a head generator setup, Farré et al.[8] observed that cheek support per se made little difference, when compared to the effect of the upper airway as a whole. Their finding with regards to the upper airway is subject to the frequency response limitations of the pneumotachometer at higher frequencies (which in our study is used only to calculate lower frequency resistance). In any case, in our studies the configuration of the upper airway would have changed little between consecutive measurements, between subjects, between different gas densities and lung volumes. Rotger and colleagues have shown that the same changes to antiresonance with gas density occur when the contribution of the upper airway is taken into account.[28] Additionally, neck extension did not make a significant difference to the spectra we measured. Taken together, these findings show that high-frequency impedance measurements demand less cooperation by the subjects and less standardization of the measurement conditions than those required by most lung function techniques including even the medium-frequency FOT between 7.5 and 35 Hz.[23]

Volume Dependence of Antiresonance Parameters

We compared *f*ar,1 at different lung volumes in healthy humans, i.e., at FRC and TLC. To our knowledge, such measurements have only been made in excised dog lungs, where the first two antiresonance peaks shifted to lower frequencies as Ptp was incremented from 5 to 30 cmH_2O.[27] More importantly, we have tracked high-frequency Zrs continuously with changes in lung volume. Measurement of multiple-frequency Zrs continuously over time has only been reported in mice at relatively low frequencies, where the mechanics of the lung periphery dominates,[15,30] and in dogs.[13] We have seen that both *f*ar,1 and Rrs(*f*ar,1) decrease with increasing lung volume in a manner that can be approximated by linear regression within the mid-region of lung volume.

A decrease in *f*ar,1 is consistent with an increased mean path length for wave propagation within the airway tree as the lung expands, and with a decrease in propagation velocity which in turn has a complex dependence on wall compliance. At the same time, the frequency at which wall resonance occurs depends on airway wall compliance and inertance. Thus, the change in *f*ar,1 with volume could be attributed to

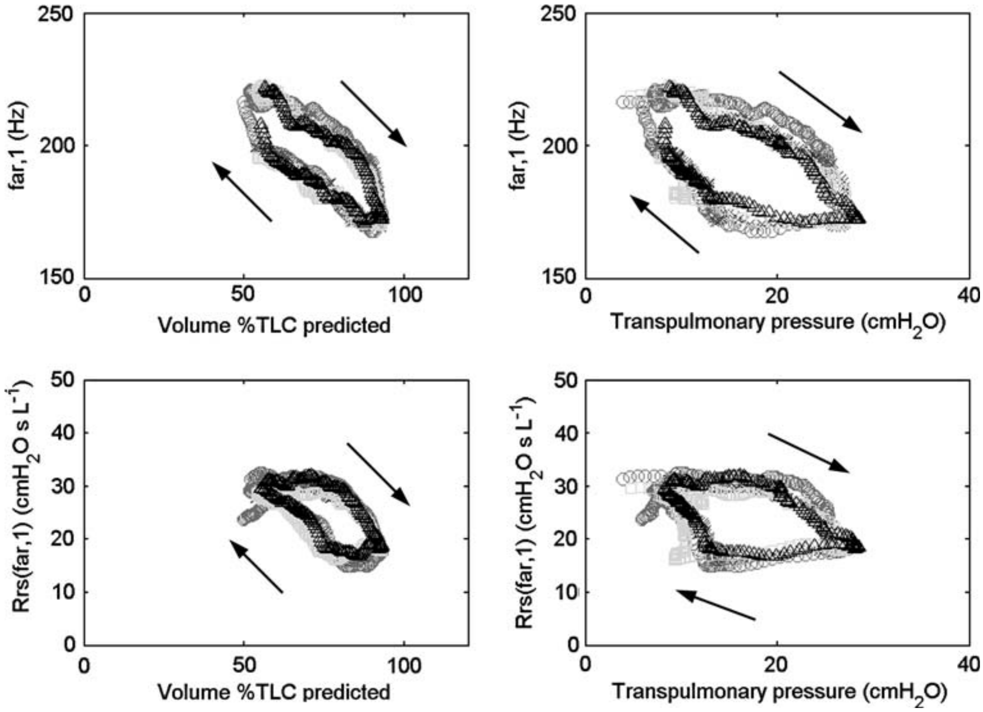

FIGURE 7. Plots of antiresonance parameters *f*ar,1 (*top*) and Rrs(*f*ar,1) (*bottom*) vs. lung volume (*left panels*) and vs. transpulmonary pressure (*right panels*), showing hysteresis between the inspiration and expiration limbs in a healthy subject. Repeated measurements are shown for the subject. Arrows show the direction of the maneuver during the measurement.

TABLE 1. Hysteresis seen in antiresonance parameters *f*ar,1 and Rrs(*f*ar,1) vs. transpulmonary pressure Ptp.

Subject	*f*ar,1 vs. Ptp hysteresis, Hz	*f*ar,1 vs. Ptp hysteresis, normalized, cmH_2O^{-1}	Rrs(*f*ar,1) vs. Ptp hysteresis, $cmH_2O\ s\ L^{-1}$	Rrs(*f*ar,1) vs. Ptp hysteresis, normalized, cmH_2O^{-1}
1	–27.0 (7.9)	–0.044 (0.014)	–4.93 (1.00)	–0.037 (0.013)
2	–27.7 (12.9)	–0.050 (0.021)	–5.87 (5.51)	–0.055 (0.025)
3	–44.9 (7.0)	–0.043 (0.021)	–16.67 (1.67)	–0.041 (0.015)
4	–32.9 (13.1)	–0.080 (0.023)	–9.30 (4.28)	–0.070 (0.014)
5	–33.6 (8.1)	–0.057 (0.017)	–12.45 (2.78)	–0.059 (0.009)
Mean (SD)	–33.2 (7.2)	–0.055 (0.015)	–9.84 (4.84)	–0.052 (0.013)

Mean (SD) values are shown for each subject in whom both inhalation and exhalation were recorded, and the means are averaged for the five subjects. Hysteresis is defined as the parameter value on the expiratory limb minus the parameter value on the inspiratory limb. Normalization is done by dividing the hysteresis by the area of the loop formed by the two limbs.

decrease in wall compliance owing to tissue stiffening,[29] wall inertance, increased mean path length, or a combination of the above. However, it must be noted that these relationships are deduced from single tube mechanics, and while network models have been used to dissect mechanisms responsible for *f*ar,1,[12] its interpretation remains complex.

The volume-dependent decrease in Rrs(*f*ar,1) seen in this study may primarily reflect decreasing airway resistance as airway diameter increases with lung expansion. The changes in Rrs(7.5–35) were consistent with the known behavior of low-frequency airway resistance with increasing lung volume.[3] However, the lack of correlation between medium- and high-frequency Rrs perhaps suggests that the two may reflect the average resistance over different parts of the airway tree, with medium-frequency Rrs less likely to be influenced by the properties of the airway wall, at least in subjects without obstructive lung disease.

Validation of Volume Dependence Measurements

Since our interpretations of the continuous measurements are expressed in terms of changes in airway dimensions, it is perhaps more appropriate to consider the pressure distending the airways rather than lung volume. Based on the correlation between slopes obtained from plots against lung volume and Ptp, we deduced that during inspiration in our region of interest between FRC to TLC, it was valid to use inspiratory slopes against lung volume as a surrogate of transpulmonary pressure to describe changes in airway caliber; making the high-frequency oscillation measurements much easier to perform. Also, our studies showed that flow nonlinearities appear to have minor influence on the high-frequency mechanics compared with those in the medium frequency range used here. The hysteresis observed in both *f*ar,1 and Rrs(*f*ar,1) between inspiration and expiration imply that mean path length and/or wall compliance (as reflected by *f*ar,1) and airway caliber (as reflected by Rrs(*f*ar,1)) is greater at expiration compared to inspiration. While either path length or wall compliance (the latter being more likely) may be greater during expiration than inspiration, the observation that expiratory Rrs(*f*ar,1) is lower than inspiratory Rrs(*f*ar,1) is at first surprising, as it is the opposite of that expected of resistance in general. It is, however, in accord with increased shunting of oscillations to the airway wall on expiration, which is in turn consistent with an increased airway wall compliance on expiration. Again this suggests that Rrs(*f*ar,1) does not simply reflect airway caliber, but is indirectly affected by airway wall properties as well.

In summary, we have been able to characterize the volume dependence of antiresonance in a group of healthy subjects with a range of ages and sizes, using continuous measurement of Zrs with lung volume. Measurement of VD*f*ar,1 and VDRrs(*f*ar,1) is simple and quick to perform, is minimally impacted by cheek support and head position and it is more reproducible than medium-frequency Rrs. These characterizations have provided further insight into airway mechanics at higher frequencies, although interpretation of the changes in antiresonance parameters remains complex. We propose that it may be more practical to compare these new volume-dependence parameters with known clinical measures of disease, and make interpretations based on knowledge of the pathologies involved. In the past, *f*ar,1 has been shown to be significantly higher in adults with chronic airflow obstruction when compared to matched controls,[4] and changed with methacholine in infants with wheezy disorders,[11] both consistent with an alteration in airway wall mechanics. A parameter that can be shown to be easy to measure and consistently related to airway wall compliance would be of great benefit in clinical disease monitoring. Thus, the next step for further study would be to examine whether volume dependence of *f*ar,1 parameters is also altered in disease.

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