Tracking variations in airway caliber by using total respiratory vs. airway resistance in healthy and asthmatic subjects


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WE RECENTLY SHOWED that asthmatic subjects have a diminished capacity to maximally dilate their airways with a deep inspiration (DI) (11). This finding employed a technique to track airway resistance (Raw) with high time resolution, as an index of airway caliber. This technique is based on the concept that lung tissue is purely viscoelastic without a Newtonian component. Hence, by 8 Hz, the contribution of lung tissue resistance to overall lung resistance (RL) is nil (12, 13, 15, 17). Likewise, although heterogeneous constriction increases RL at low frequencies, the impact is complete by 8 Hz. Hence, measurement of RL at 8 Hz is equivalent to the measurement of Raw. This particular method allowed us to track Raw with a 1/8-s resolution. Raw then provides real-time tracking of an index of airway caliber during tidal breathing or before, during, and after a DI. Unfortunately the measurement of Raw requires the placement of an esophageal balloon. Use of the total respiratory system resistance (Rrs) rather than RL at 8 Hz would not require an esophageal balloon. However, measurements of Rrs would include the resistance of the chest wall (Rcw). Studies that have measured Rcw at low frequencies report that, unlike for parenchymal tissue, there is a finite Newtonian component of chest wall tissue (1–3, 7, 10). Measurements of the time course of Rcw during tidal breathing and a DI have not yet been reported, nor has the dependence of Rcw on lung volume for a range from functional residual capacity (FRC) to total lung capacity (TLC). The goals of this study were to establish whether Rrs rather than Raw could be used to track airway caliber in healthy and asthmatic subjects, both before and after a methacholine challenge, and, in particular, to assess the impact of Rcw on this approach as a function of lung volume.

METHODS

Subjects. Measurements were made on seven asthmatic (3 men and 4 women) and seven healthy (5 men and 2 women) subjects, all nonsmokers, before and after a methacholine challenge. Subjects ranged from 19 to 45 yr of age (mean of 26 ± 8 yr for the healthy subject group and 28 ± 7 yr for the asthmatic subject group). Table 1 gives the demographics for the subjects. All asthmatic subjects had been previously diagnosed by a physician according to American Thoracic Society (ATS) guidelines and were presently taking inhaled

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bronchodilators. Of the seven asthmatic subjects, five used only short-acting β₂-agonist (albuterol), and two were on a combination of albuterol and inhaled corticosteroids. Airway hyperreactivity was assessed before the day of the study by interpolating the methacholine dose-response curves to the concentration that causes a 20% decrease from the subjects’ baseline forced expiratory volume in 1 s (PC₂₀) (18). Subjects were instructed not to take albuterol or any form of caffeine 8 h before the study. We also asked each subject to refrain from taking other medications as directed by the ATS guidelines for methacholine challenges (6). Our institutional research committees approved the study, with informed consent from each subject required.

**Tracking airway caliber.** At any given frequency, the lung can be modeled as a single resistance and elastance in series (often called the single-compartment model). This model has the governing equation

\[ Ptp = Rt_\text{L} Qao + EL Qao + k \]  

(1)

where Ptp is transpulmonary pressure, Qao is flow at the airway opening, EL is lung elastance, and k is the Ptp when flow and volume are zero. For Rrs, the same system is used, except it is applied to airway opening pressure (Pao) rather than to Ptp, i.e.,

\[ Pao = Rrs Qao + Ers Qao + k \]  

(2)

where Ers is the respiratory system elastance.

Now, Rrs = Raw + RtL + Rw, where RtL is the resistance of the parenchymal tissue of the lung. For an 8-Hz Qao the RtL is considered to be essentially zero (12, 13, 15, 17). The application of Eq. 2 presumes that we ignore all shunt impedances, including gas compression and airway wall shunting, so that Rrs = Raw + Rw. Here, Rw is not necessarily zero, and our study will quantify RcW at FRC and during a DI to TLC.

**Experimental measurements.** The experimental setup has been previously described in detail elsewhere (11). Briefly, we use a computer-controlled pump to deliver 8-Hz oscillations with an amplitude of 0.9 l/s, which are superimposed on the subjects’ normal breathing. Qao is measured by a pneumotachograph (Fleisch no. 2) connected to a differential pressure transducer (±2 cmH₂O model LCVR, Celesco). Ptp is recorded with a differential pressure transducer (±50 cmH₂O model LCVR, Celesco) with one tap measuring esophageal pressure (Pes) via a 10-cm latex balloon catheter inserted into the esophagus transnasally and the other tap measuring Pao. A separate differential pressure transducer (±50 cmH₂O model LCVR, Celesco) records transrespiratory pressure (Prs) with one tap measuring Pao and the other measuring atmospheric pressure.

During 8-Hz DI maneuvers, there is a three-way valve that is opened to allow the subject to breathe to atmosphere through a high-inertance tube. The high-inertance tubing (~212 ml dead space) behaves as a low-pass filter, allowing the patient to breathe to atmosphere while the energy from the superimposed 8-Hz oscillations goes into the subject. The 8-Hz signal is generated by a computer board (Data Translation, DT-2811 analog-to-digital/digital-to-analog board) at a sampling rate of 100 Hz. The pressure and flow signals are stored digitally on the computer by the same board at a sampling rate of 100 Hz.

**Protocol.** All subjects first underwent baseline spirometry. A balloon catheter was then placed in the esophagus transnasally. The initial positioning of the balloon was verified with an occlusion test. After a brief training period (5–10 min) on the system, each subject was asked to make a tight seal around the mouthpiece with their mouth and firmly support their cheeks. Once set, they were asked to breathe tidally for 5–10 breaths, take a steady DI to TLC followed by a passive expiration to FRC, and then continue breathing tidally for another 5–10 breaths. This maneuver was done at baseline and after a methacholine challenge. The methacholine was administered by using a Rosenthal New Standard Dosimeter (Pulmonary Data Services) according to the five-breath dosimeter protocol set forth by ATS. The methacholine dose sequence was 0.078, 0.156, 0.3125, 0.625, 1.25, 2.5, 5, 10, and 25 mg/ml. Healthy subjects were given a modified methacholine challenge. The modified challenge is a methacholine challenge in which DIs are prohibited. This type of challenge has been shown to amplify healthy subjects’ airway

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Table 1. **Subject demographics**

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Healthy subjects

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Asthmatic subjects

FEV₁, forced expiratory volume in 1 s; PC₂₀, concentration of methacholine causing a 20% drop in FEV₁; M, male; F, female; MCh, methacholine; %Pred, percent predicted.
hyperreactivity to a given dose of methacholine (16). In asthmatic subjects, however, the prohibition of Dls has only a minor impact on airway hyperreactivity (5). Thus asthmatic subjects performed a standard methacholine challenge in which basic spirometry was carried out after each dose, and the challenge continued until they reached their PC20 dose.

Data analysis. All recorded pressure and flow signals were separately low- and high-pass filtered at a cutoff frequency of 4 Hz (4 Pole Butterworth digital filter) to isolate the 8-Hz from the low-frequency tidal volume changes. The 8-Hz pressure and flow data were sent through the recursive least squares algorithm (RLS), and the resulting resistance vs. time data was compensated for both the filter and the algorithm’s phase response (11). Lung volume changes were calculated by integration of the low-frequency flow data. The overall result was resistance vs. lung volume for all subjects, pre- and post-methacholine challenge. Specifically, if we used Ptp and Qao, the RLS algorithm’s output was Raw. If instead the input was Pao and Qao, then the resulting output was Rrs at 8 Hz. Rcw at 8 Hz was estimated as the difference between Rrs at 8 Hz and Raw (Rcw = Rrs − Raw). We examined three key features in the resistance vs. lung volume data (Rrs and Raw): the minimum resistance achieved during a DI to TLC, the mean pre-DI resistance, and the mean post-DI resistance.

Two separate transducers were used to measure Ptp and Prs, and each had different connection tubing configurations. We evaluated the common mode rejection ratio of each transducer at 8 Hz as a function of input pressure amplitude and used these data to ensure that both transducers were matched (9). For each transducer, Ptrue = Pmeasured − PCM offset, where Ptrue is the true pressure, PCM offset is the common mode offset pressure, and Pmeasured is the pressure that would be measured by the transducer in the single-ended transducer configuration. To calculate Ptrue, the PCM offset must be expressed as a function of the measured pressure amplitude. By linear regression, we found that at 8 Hz

\[ P_{CM\ offset} = -0.003 + 0.23 \cdot Prs \]
\[ P_{CM\ offset} = 0.0002 + 0.039 \cdot Prs \]

for the Ptp and Prs transducers (Ptp-CM offset and Ppr-CM offset, respectively). Note the elevated PCM offset for the Ptp transducer. This value of PCM offset became the correction factor needed to adjust Pmeasured to obtain Ptrue for each transducer separately.

The Raw or Rrs data were also converted to effective diameter variations as used by Jensen et al. (11). Here, we assume that resistance is related to airway diameter through the fully developed Poiseuille flow

\[ R = \frac{128 \cdot \mu \cdot l}{\pi \cdot d^4} \]

where \( \mu \) is the fluid viscosity, \( l \) is the length of the airway, \( R \) is the resistance, and \( d \) is airway diameter. The baseline diameter is defined to be equal to 1 for a healthy individual at FRC. Hence, the effective diameter as a function of time can be written as

\[ d_e(t) = \left( \frac{R_{H}}{R(t)} \right)^{1/4} \]

where \( d_e(t) \) is the effective diameter (based on resistance) as a function of time, \( R_{H} \) is the 8-Hz resistance of a healthy individual at FRC, and \( R(t) \) is either Raw or Rrs at 8 Hz.

RESULTS

Figure 1 compares typical tracking results for Raw, Rrs, and Rcw for both healthy and asthmatic subject types before and after a methacholine challenge. Generally, during tidal breathing, the minimum of the Raw occur at end inspiration and the maximum at end exhalation. This is not always the case, because glottal

Fig. 1. Airway resistance (Raw), respiratory system resistance (Rrs), and chest wall resistance (Rcw) at 8 Hz data for a healthy subject (subject 7) at baseline (A) and postmethacholine challenge (B) and for an asthmatic subject (subject 10) at baseline (C) and postmethacholine challenge (D). The line types are the same for all panels, as described in A. Note that the volume scale is on the right of each plot, whereas the resistance scale is on the left of each plot.
artifacts can impose distortions in Raw, particularly at end exhalations. Raw decreases during a DI until the subject reaches TLC, at which point the resistance is minimum. At baseline, the pre-DI mean Raw for this healthy subject was 1.6 ± 0.22 cmH2O·l⁻¹·s and the minimum Raw was 0.95 cmH2O·l⁻¹·s. The pre-DI Rrs tracking results vary similarly to Raw but with increased magnitude. Specifically, the pre-DI mean Rrs was 2.13 ± 0.30 cmH2O·l⁻¹·s. However, the minimum Rrs at the end of a DI was 0.92 cmH2O·l⁻¹·s, which was very similar to the minimum Raw. Rcw is estimated as the difference between these two measurements. The Rcw oscillates between 0.5 and 1 cmH2O·l⁻¹·s during tidal breathing but decreases to near zero at TLC during the DI. Thus Rcw was volume dependent. This same behavior occurred for the healthy subject postmethacholine challenge, as well as the asthmatic subject at baseline and postchallenge. Also, we see that the estimated Rcw does not appear to be affected much by a methacholine challenge.

Pooling the data for all subjects (Fig. 2), we see that, at FRC, Rrs is greater than Raw in all cases by 0.5–1.0 cmH2O·l⁻¹·s, which is in agreement with the single subject data shown in Fig. 1. The difference between Rrs and Raw during tidal breathing (pre-DI) was significant (P < 0.0004) in healthy and asthmatic subject groups. However, at TLC, there was no statistical difference between minimum Raw and minimum Rrs for healthy subjects pre- or postmethacholine challenge conditions. Thus, in healthy subjects, estimated Rcw at 8 Hz is essentially zero at TLC and minimum Rrs reflects minimum Raw. Figure 3 isolates the estimate of Rcw at FRC and at TLC for all healthy and asthmatic subjects, both at baseline and after a methacholine challenge. Likewise, in asthmatic subjects, even though the difference between the minimum Rrs and the minimum Raw was statistically significant at baseline (P = 0.034) and postchallenge (P = 0.0007), the absolute value of the difference is small. Again, the estimation of Rcw at 8 Hz is nearly zero, and Rrs reflects primarily Raw.

The postchallenge Rcw at FRC is slightly higher both for the healthy and asthmatic subjects (Fig. 3). The slight increase was not significant for either group. After a methacholine challenge, Rcw at TLC increased for both the healthy subject group and the asthmatic subject group. The difference in Rcw at TLC from baseline to challenge was significant for asthmatic subjects but not for healthy subjects.

Using Eq. 5, we calculated the increase in an effective diameter associated with a DI as inferred by either Raw or by Rrs (Fig. 4). Using Raw, one would infer that healthy subjects could increase their effective airway diameters by 28.1% at baseline and 29.5% postchallenge when inhaling to TLC. In contrast, using Rrs, one would infer a 38.3% increase in the healthy subject group’s effective diameter at baseline and a 32.4% increase postchallenge. Likewise, using Raw in asthmatic subjects, one would infer a 21.4% increase at baseline and a 21.4% increase postchallenge. When Rrs is used, these values become 25.0 and 21.3%, respectively. Generally, use of Rrs at 8 Hz overestimates the
change in diameter during a DI, but the overestimation is less important as baseline Raw increases. This is because Rcw is essentially the same for all conditions, but in healthy subjects postchallenge or asthmatic subjects pre- or postchallenge, Raw increases and the ratio of Rcw to Rrs decreases. Thus Rcw is a smaller artifact on effective diameter reduction.

**DISCUSSION**

The primary goal of this study was to determine whether Rrs could be a reliable substitute for Raw in tracking airway caliber modulation. If so, an esophageal balloon would not be needed when tracking airway caliber (static and dynamic) in vivo. Our concern was that, unlike lung tissue, chest wall tissue would have a non-zero Newtonian component at 8 Hz. Although values of this Newtonian component have been reported in the literature (1–3, 7, 10), its dependence on lung volume from FRC to TLC has not been previously reported. Indeed, we found that at FRC our estimation of Rcw at 8 Hz was between 0.5 and 1.0 cmH2O·l−1·s. We also found that our estimation of Rcw, estimated from the simple additive model (i.e., where we assume chest wall flow = Qao), decreases to nearly zero at TLC.

Jensen et al. (11) reported that minimum Raw in healthy subjects was nearly the same after a methacholine challenge as it was at baseline, i.e., healthy subjects retained the ability to maximally dilate their airways postchallenge. Our results show that Rrs displays this trend as well (Fig. 2). Jensen et al. also reported that asthmatic subjects have a decreased capacity to maximally dilate their airways at baseline and that this defect is further amplified after a methacholine challenge. This trend is still evident in minimum Rrs. At baseline, the minimum Rrs in asthmatic subjects is elevated above the level of healthy subjects, and it is even further elevated postchallenge.

One important consequence of using Rrs vs. Raw is the overestimation associated with the calculation of the increase in effective diameter with a DI. Our results show that because Rcw decreases from a finite value at FRC to zero at TLC, the Rrs would significantly overestimate the change in effective diameter during a DI for healthy subjects, both pre- and post-methacholine challenge. This difference is minimal in asthmatic subjects because they already have an elevated Raw, and so the constant Newtonian component due to Rcw is a smaller fraction of the measured Rrs.

Another goal of our study was to study the sensitivity of Rcw to changes in lung volume. Barnas et al. (2) proposed that total Rcw contains contributions from two major components: 1) a frequency-dependent plastic dissipation that is consistent with measurements on both lung tissue and upper airways, and 2) a frequency-independent Newtonian resistance. They
showed that the Newtonian component of the total Rcw (essentially the value of Rcw at 8 Hz) in four healthy subjects at FRC varied between 0.5 and 1.25 cmH2O·l−1·s−1 (1). At FRC, we found Rcw at 8 Hz to be between 0.5 and 1.0 cmH2O·l−1·s−1 (Fig. 3). This range of values is also consistent with the data reported by D’Angelo et al. (7) using the interrupter technique. They found that the interrupter Rcw in anesthetized, paralyzed humans ranged between 0.3 and 0.6 cmH2O·l−1·s−1. Although these values are slightly smaller than those we report here, it may be argued that the resistance measured by D’Angelo et al. does not include the resistive components associated with the activated chest wall that are present during spontaneous tidal breathing. Also, all methods, including ours, estimate Rcw as Rs – Rl. Thus the assumption is that there is negligible gas compression and airway wall shunting impacting the Ptp, Pao, and Qcw data.

Barnas et al. (3) reported that when measurements of Rcw were made with oscillations of a volume of ~1.1 liters greater than a subject’s FRC, there was a decrease in total Rcw between 0.5 and 4 Hz. Although these results imply an inverse dependence of Rcw on lung volume, we could not find a previous study that reported on the change in Rcw with lung volume during a DI from FRC to TLC. In this study, we found that the estimated Rcw changed significantly with an increase in lung volume from FRC to TLC (Fig. 3) for both healthy and asthmatic subjects, pre- and post-methacholine challenge. Our results show that the estimated Rcw decreases to around zero at TLC in the healthy subject both pre- and post-methacholine challenge (Fig. 3) and close to zero in the asthmatic subject, especially at baseline conditions.

Rcw vs. lung volume. Why would our estimation of the Newtonian component of Rcw decrease from a finite value to nearly zero at TLC? We first address methodological issues. Initially, we considered potential artifacts from the esophageal balloon method. For example, although the balloon position relative to the nasal passage could not have changed (it was taped in place), with increasing lung volume its position relative to the contents of the thoracic cage could be different. If the pleural pressure variations are not uniform around the lung, then the balloon could be picking up a different form of the fluctuations in pleural pressure for FRC vs. TLC, depending on its position relative to the lungs. Although we did not perform the occlusion test at different lung volumes in all subjects (only to check the initial position of the balloon at FRC), we did perform it in one subject. In that subject, we found that the ratio of change in Pes to change in Pao (ΔPes/ΔPao) during the test was essentially unity even up to 3 liters above FRC. Also, Baydur et al. (4) showed that even at 80% of vital capacity, the change in Pes was only slightly larger than the change in Pao during occlusion tests. Moreover, an overestimation of Pes would lead to an increase in Rcw, not to a decrease. Peslin et al. (14) also showed that the amplitude ratio of Pes to Ppl was <10% from unity for oscillations from 2 to 32 Hz. It is also possible that the esophageal wall does not transmit the pressure identically at FRC vs. TLC. There is some evidence in the literature that the greater the tone in the esophageal wall the smaller the pressure difference picked up by the balloon because some of the pressure is not transmitted across the esophageal wall (8). But it is unlikely that the pressure variations transmitted to the balloon would decease to essentially zero, such that the estimation of Rcw becomes zero.

A far more likely methodological candidate for why our estimate of Rcw decreases during a DI derives from our assumption that Qao equals the flow (rate of change in volume) of the chest wall (Qcw). This is true so long as there are no shunt flow pathways between the mouth and chest wall. But, in concept, there could be shunting into the airway walls and into alveolar gas compression. In fact, Hantos et al. (10) showed that when they neglected shunt pathway impedances in the model used to fit their forced oscillatory impedance
data of the respiratory system there was an underestimation of $R_{cw}$ of $\sim 20–30\%$ at higher frequencies. We created a simple lumped model to estimate the potential impact of shunting into gas compression. The model topology is shown in Fig. 5. Here, an airway resistance compartment leads to a gas compression compliance, $C_g$, in parallel with the lung and chest wall tissues. The tissue compartment has separate properties for the lung and chest wall tissues. Specifically, $R_{LT}$ and $C_{LT}$ are the resistance and compliance of the lung tissue, respectively, and $C_{cw}$ is the compliance of the chest wall. We simulated a DI and calculated the ratio of $R_{cw}$ that would be estimated on the basis of airflow opening data only (i.e., applying the assumption that $Q_{ao} = Q_{cw}$ vs. the true $R_{cw}$ that was assigned at FRC (Fig. 6). Specifically, we set Raw to 2.0 cmH$_2$O·$l^{-1}$·s$^{-1}$. $R_{LT}$ to zero (i.e., no Newtonian component to parenchymal tissues), and $R_{cw}$ to 1.0 cmH$_2$O·$l^{-1}$·s$^{-1}$. Assuming an FRC of 3.0 liters, we set $C_g$ to 0.003 l/cmH$_2$O. Likewise, at FRC, we set $C_{LT} = C_{cw} = 0.2$ l/cmH$_2$O. To simulate a DI, we let lung volume vary from an FRC of 3.0 liters to a TLC of 7.0 liters by increasing $C_g$. As volume increased, Raw decreased linearly from 2.0 to 1.0 cmH$_2$O·$l^{-1}$·s$^{-1}$ (as would occur for a healthy subject). Also, $C_{LT}$ and $C_{cw}$ were either held constant or allowed to decrease. The decrease in compliances during the DI occurred either linearly by a designated percentage or according to the slope of a sigmoidal curve fit to the quasistatic pressure-volume curve from a typical healthy subject at baseline. The key point is that as volume approaches TLC, lung and chest wall tissues become very stiff while the increase in alveolar gas provides for an increased shunt compliance.

Figure 6 shows that the estimate of $R_{cw}$ based on $Q_{ao}$ will be within 10% of the true value at FRC, but then decreases during a DI. The underestimation in $R_{cw}$ is substantial for when the tissue compliances at TLC experience a 95% decrease from their values at FRC. Finally, although not shown, we also expanded the simulation study to include a shunt compliance for the airway walls, and the effect was small but in the direction of further underestimation of the true $R_{cw}$.

These simulation results largely implicate that the reported decrease in $R_{cw}$ at TLC from the value at FRC (Fig. 3) derives from a breakdown in the assumptions that $Q_{ao}$ and $Q_{cw}$ are identical at all lung volumes. In fact, Fig. 2 showed that $R_{cw}$ is elevated postchallenge and/or does not decrease at TLC from FRC as much in asthmatic subjects. This may reflect that such subjects simply cannot reach a point on the pressure-volume curve for which large decreases in tissue compliances occur (i.e., they stay to the left of Fig. 6 even at TLC). The net effect is a false apparent increase in the $R_{cw}$ at TLC from its value prechallenge. As the pressure needed to generate an increase in lung volume to TLC becomes larger postchallenge, the subject would need a corresponding increase in chest wall muscle activation to overcome this. Such activation could further decrease $C_{cw}$, which would reduce the true $Q_{cw}$ and therefore increase $R_{cw}$. Consequently, the increase in $C_{cw}$ would also amplify the bias due to shunting as lung volume increased above FRC as per our simulations (Fig. 6).

Also, constriction can lead to some hyperinflation, and, according to our data, increases in lung volume result in a corresponding decrease in our estimation of $R_{cw}$. Unfortunately, we did not look at absolute volumes before and after the methacholine challenge in this study. Measurements of absolute lung volume may have given us more insight into the effects of hyperinflation on the $R_{cw}$ at FRC and TLC.

In conclusion, measured with this approach, $R_{cw}$ appears volume dependent, having a magnitude of 0.5–1.0 cmH$_2$O·$l^{-1}$·s$^{-1}$ during tidal breathing and decreasing to zero at TLC. The decrease in apparent $R_{cw}$ during a DI is likely a consequence of $Q_{ao}$ underestimating $Q_{cw}$ at increased lung volume. Hence, although this technique would overestimate the net decrease in $R_{ao}$ and net increase in effective diameter during a DI, the general trends in the DI response shown by Jensen et al. (11) with $R_{ao}$ tracking are still present in $R_{ao}$ tracking. Therefore, we conclude that $R_{ao}$ can be used as an effective index to quantify maximum airway caliber achievable. That is, estimates of $R_{ao}$ at TLC obtained by using $R_{rs}$ would be nearly identical to the estimate obtained with $R_{ao}$.

DISCLOSURES

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