Modeling airway resistance dynamics after tidal and deep inspirations

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Thorpe, C. William, Cheryl M. Salome, Norbert Berend, and Gregory G. King. Modeling airway resistance dynamics after tidal and deep inspirations. J Appl Physiol 97: 1643–1653, 2004. First published July 16, 2004; doi:10.1152/japplphysiol.01300.2003.—Using the forced oscillation technique, we tracked airway resistance continuously during quiet breathing (QB) and deep inspiration (DI), thus observing fluctuations in resistance that may reflect mechanisms of airway stretch and renarrowing. After DI, however, the resistance may be depressed for a period not related to volume changes. We hypothesized that this gradual increase in resistance after DI-induced dilation was determined by a simple time constant. Furthermore, to the extent that this effect reflects dynamic characteristics of airway renarrowing, the resistance change after each tidal inspiration should also be constrained by this temporal limit. A model relating resistance fluctuations to the breathing pattern, including both instantaneous and delayed effects, was developed and applied to data from 14 nonasthmatic and 17 asthmatic subjects (forced expiratory volume in 1 s = 103 ± 13 and 83 ± 12%, respectively, means ± SD) after methacholine challenge (dose 145 ± 80 and 3.0 ± 3.4 μmol, respectively) that resulted in respective forced expiratory volume in 1 s reductions of 16 ± 7 and 24 ± 6% from baseline. Resistance was measured continuously for 1 min of QB, a DI, followed by a further minute of QB. Resistance values at end expiration (Ree) and end inspiration were calculated. We found that the sequence of Ree after DI was best modeled by a power-law function of time rather than an exponential decay ($r^2 = 0.82 ± 0.18$ compared with $0.63 ± 0.16$; $P < 0.01$). Furthermore, the coefficient characterizing this “renarrowing function” was close to equal to the coefficient characterizing the equivalent function of resistance change between each resistance value at end inspiration and subsequent Ree during QB, particularly in the nonasthmatic subjects for whom the intraclass correlation was 0.66. This suggests that the same time-dependent factors determine renarrowing after both large and small breaths.

respiratory resistance; airway caliber; power law; velocity of shortening

THE FORCED OSCILLATION TECHNIQUE allows airway resistance at the mouth to be measured continuously by means of superimposed oscillations applied to the breathing flow. This provides a method for observing the dynamic characteristics of the respiratory system during normal breathing and in response to interventions such as deep inspirations (DI) or applied bronchoconstriction. It has long been observed that the measured impedance fluctuates in line with the breathing cycle (18), with this variation arising from both volume-related (26, 27, 31, 34) and flow-related (1, 7, 23) effects.

In addition to the phasic variations in resistance related to the breath cycle, reductions in resistance caused by DI can persist for some time after the volume has returned to normal levels (11). To the extent that the measured resistance reflects airway caliber, this gradual increase in resistance may be said to represent delayed “renarrowing” of the airways after DI-induced stretch.1 Jensen et al. (19) suggest that the delayed renarrowing effect seen in some normal subjects, particularly after challenge, may be due to the temporal dynamics of airway smooth muscle (ASM). They propose that in asthmatic airways the ASM is in a “latch state” (15), which cannot be broken by the DI compared with normal airways where the stretch is able to break the actin-myosin cross bridges in the ASM, which then take some time to reform. In other experiments, Stephens and coworkers (10, 32) have shown that the velocity of shortening of ASM is comparable to the breathing rate and may be altered under certain conditions. Delayed renarrowing in some subjects after DI-induced stretch may therefore be a direct consequence of reduced ASM velocity of shortening restricting the ability of the airways to renarrow, and this could also be a determinant in the amount of shortening that occurs after tidal stretches (30). Indeed, in a recent study (29), our laboratory showed that the magnitude of the delayed renarrowing effect after DI was correlated with baseline tidal fluctuations in resistance, suggesting that similar mechanisms may underlie both effects.

The present study extends the work of both Salome et al. (29) and Jensen et al. (19) by modeling the time course of resistance change after DI and tidal inspirations by an explicit function of time. The underlying hypothesis is that the pattern of renarrowing is determined by a time-related constant that is the same for both small and large stretch. Provided that the slope of the renarrowing function is smaller than the equivalent rate of volume decrease during expiration, the delayed renarrowing effect will be the limiting factor in the corresponding resistance fluctuations. To test this hypothesis, the model was applied to recordings of resistance during tidal breathing and after DI obtained from normal and asthmatic subjects after methacholine challenge. The results show that the coefficient characterizing the post-DI recovery function is directly related to the equivalent coefficient representing resistance changes after each tidal inspiration. The mechanisms that determine the

1 In our description of resistance change after inspiration, it is convenient to assume that there is a direct relationship between the measured resistance and the underlying airway caliber through an inverse fourth power. Thus the decrease in resistance associated with inspiration may be termed “stretch,” and the subsequent increase, whether during a single expiration or, in the case of gradual increase following DI, may be said to represent “renarrowing” of the airway caliber. Although we have chosen to present the data in terms of resistance, the description will, where necessary, make use of this terminology, which makes implicit assumptions about the relationship between measured resistance and the underlying airway caliber.
recovery from DI are therefore likely to be the same as those operating during quiet breathing and possibly directly related to dynamic properties of ASM such as its velocity of shortening.

**MATERIALS AND METHODS**

**Subjects and protocol.** Nonasthmatic subjects, with no history of respiratory symptoms and without airway hyperresponsiveness [pro-vocative dose that causes 20% decline in forced expiratory volume in 1 s (FEV1) of >12.2 μmol], were included in this study. Asthmatic subjects having a clinical diagnosis were included if they exhibited airway hyperresponsiveness. Baseline spirometry was assessed (Spirocard, QRS Diagnostics) as the best of at least two recordings in which the FEV1 and forced vital capacity were reproducible to within 5%. Predicted values were those of the European Community for Steel and Coal (28). Baseline mean resistance (Rms, mean) was calculated as the average resistance computed over the first minute only of quiet breathing after exclusion of outlying values as described below. Resistance was in all cases measured before spirometry. The protocol was approved by the Human Ethics Committee of the University of Sydney (no. 00/11/19), and informed consent was obtained from all subjects. Methacholine challenge was performed using a modification of the method of Chai et al. (3, 5). Methacholine chloride was administered in doubling, cumulative doses ranging from 0.15 to 1.20 μmol via a DeVilbiss no. 646 nebulizer attached to oxygen at 138 kPa (20 psi). Nebulization during inspiration from just below functional residual capacity (FRC) to approximately midway between FRC and total lung capacity was controlled by a nebulization dosimeter (Rosenthal French, Baltimore, MD) at a setting of 0.6 s per inhalation. Resistance and then spirometry were measured 30–60 s after each inhalation, and the next dose was given immediately. The challenge was stopped when FEV1 fell by more than 20% from baseline or the maximum dose had been administered. Dose response ratio, a continuous measure of airway responsiveness, was calculated as % fall FEV1/dose in μmol, and a threshold of 2.5 (24) was used to define airway hyperresponsiveness.

Postmethacholine resistance was recorded during 1 min of quiet breathing, followed by a single, slow DI to total lung capacity followed by passive expiration to FRC, and a subsequent further minute of quiet breathing. Subjects were seated, supporting their cheeks with their hands, and wore nose clips.

**Resistance calculation.** We measured respiratory system impedance at 6 Hz using an in-house-developed device that followed the general design of earlier forced oscillation systems where the subject can breathe through a resistive exhaust port while the oscillations are applied. Flow was determined by means of a 50-mm-diameter Fleisch pneumotach with the differential pressure drop measured by a ± 2.5 cmH2O silicon transducer (Sursense DCAL-4, Honeywell Sensing & Control). Mouth pressure was measured by a similar transducer, with a range of ±12.5 cmH2O. The resistance of the apparatus itself was ~1 cmH2O·l−1·s−1. The mouth pressure and flow signals were low-pass filtered at 25 Hz and sampled at 300 Hz with a 16-bit analog-to-digital converter (DT-9805, Data Translation). All subsequent filtering and processing was performed digitally by custom software written in the Matlab (The Mathworks) digital signal processing environment. The pressure and flow signals were filtered by a band-pass filter centered on the oscillation frequency (6 Hz) to produce oscillation-frequency pressure [P osc(t)] and flow [V osc(t)], respectively. The bandwidth of this filter determines the temporal smoothing that is imposed on the flow and pressure signals and, hence, the ability to detect rapid changes in resistance. For the results presented here, a bandwidth of 2 Hz was used. The raw flow signal was separately low-pass filtered with a cutoff of 2 Hz to provide an estimate of the breathing flow signal [V res(t)]. The phase responses of the band-pass and low-pass filters were matched to preserve the temporal relationship between V osc(t) and V res(t). The breathing volume signal [Vb(t)] was obtained by integration of V res(t). Drift correction was applied by subtracting from Vb(t) a straight-line fit through all the FRC points in the recording.

Following the approach previously described by Horowitz et al. (17), the time-varying respiratory impedance was computed from P osc(t) and V osc(t) by division in the frequency domain of segments equal in length to the period of the oscillation signal (1/6 s). The impedance was calculated at a rate of 12 times/s by overlapping the segments. To provide an estimate of confidence in the impedance values, the coherence [γ2(t)] was also computed from three overlapping segments of P osc(t) and V osc(t). Values of the time-varying respiratory impedance for which γ2(t) was <0.95 were flagged as unreliable impedance estimates (12). For the analyses presented here, we retained only the resistance corresponding to the real part of the impedance.

The end-expiratory instants were automatically identified by locating the zero-crossings (t0) in the flow signal Vb(t) for which the volume Vb(t0) was at local minima. To exclude possible false detection of breaths (i.e., zero flow points other than at breath end points), those zero crossings associated with volume excursions of less than one-eighth of the median tidal breath volume during the recording were excluded from the set of end-expiratory instants. The end-inspiratory instants were then defined at the points of local maxima in volume Vb(t) between every adjacent pair of end expirations.

**Resistance model.** Following previous studies on volume and flow effects on airway resistance (27), we modeled the instantaneous intrabreath variations in resistance (see Fig. 1) by linear coefficients on breathing flow and volume

\[ R(t) = K_0 + K_d[V_t(t)] + K_{I/R}[V_{b}(t)] - K_{V_t}(t) \]  

where the term K0 represents the resistance when both Vb(t0) and Vb(t) are zero, Kd and Kd represent flow-related nonlinearities for inspiratory (Vb) and expiratory flow (Vb), respectively, and Kv represents the volume-related decrease in resistance between end expiration and end inspiration.

The delayed effect of renarrowing on resistance change after DI (see Fig. 2) was modeled by including a time-dependent memory term in the resistance model so that the DI-induced resistance decrement corresponding to the volume stretch increased only slowly with respect to the subsequent breath pattern. In other words, the stretch-related resistance [Rosc(t)] is composed of both an instantaneous component [K, Vb(t)] and a residual effect [F RN(t)] carried forward from a previous stretch. To the extent that the memory effect masks the instantaneous component (for instance, if the previous stretch is large), we can approximate the total stretch-related contribution by a “peak-decay” type of nonlinearity

\[ R_{osc}(t) = \max[K, Vb(t), F_{RN}(t - t_{eq})] \]  

where a large stretch is applied at the end-inspiratory instant (t0). The functional form chosen for the renarrowing memory term FRN(t) then determines the overall pattern and slope of the post-DI resistance recovery. We propose a power-law function to determine the persistence of airway dilatation after a DI

\[ F_{RN}(t) = \frac{K_{DI}}{b_0 + t} \]  

where \(K_{DI}\) is the amount of “stretch” occurring at the DI (\(t = 0\)), and \(K_{RN}\) is the renarrowing constant. The factor \(b_0\) is the time intercept of the log-log relation [i.e., \(F_{RN}(t) = K_{RN}\)]. Partly because there is some uncertainty in the actual time at which the DI occurs (i.e., due to sampling interval and finite breath pause at DI), the value of \(b_0\) may vary from subject to subject. It is important to note that this relationship can be equivalently applied to either the resistance or to the equivalent airway caliber (i.e., if it is assumed that caliber is simply related to airway resistance by an inverse fourth power, the coefficient \(K_{RN}\) is 4 times smaller and of opposite sign for caliber).
The coefficients describing the renarrowing relationship $F_{RN}(t)$ were obtained from the pattern of resistance recovery post-DI. To exclude interactions with instantaneous flow and volume effects, we fit $F_{RN}(t)$ to the sequence of the end-expiratory (i.e., where breathing flow and volume both equal zero) resistance values $Ree$ following the DI up to the point at which $Ree$ exceeded the median of the pre-DI values of $Ree$. The initial stretch $K_{DI}$ was defined as the resistance at the instant of DI $R(t_{DI})$. The values of $t_0$ and $K_{RN}$ were then obtained by a least squares fit to these values in the log-log domain. For comparative purposes, we also attempted a fit of the post-DI data to exponential and linear functions of time. The degree of fit for each alternative model was compared using a two-tailed paired $t$-test.

Because the DI and subsequent renarrowing effects alter the direct relationship between resistance and volume, the coefficients for the instantaneous model were obtained from the breathing signal only up to and including the inspiratory portion of the DI.

Although we have defined the renarrowing function in terms of the slow increase in resistance often observed after a DI, an equivalent reasoning can be applied to the increase in resistance occurring after every breath (30) during tidal breathing. The implication of this reasoning is that the change in resistance from each end inspiration to the following end expiration, after the effects of flow nonlinearities are excluded, is primarily by a function of time rather than being determined by the change in volume. We therefore define a tidal renarrowing coefficient [$K_{RN}(QB)$] based on the (non-flow related) resistance changes during expiration in tidal breathing. We calculated $K_{RN}(QB)$ by a least squares fit (in the log-log domain) of Eq. 3 to the resistance change during each individual expiration before the DI, after removing the expiratory flow effect $K_{fe}$ described in Eq. 1. The values of $K_{RN}(QB)$ so obtained were compared with the equivalent values of $K_{RN}$ obtained from the post-DI data by calculating the intraclass correlation.

**RESULTS**

**Lung function.** A total of 14 nonasthmatic and 17 asthmatic subjects were included in the study. These subjects comprised a subset of the data in Ref. 29, for whom there was a reasonable duration (∼60 s) of post-DI data. Anthropometric data and lung function at baseline and after methacholine challenge are shown in Table 1. The asthmatic and nonasthmatic groups had
similar anthropometric characteristics, except that there were more men in the asthmatic group (9:8 compared with 3:11). No subjects were current smokers, and only two asthmatic subjects had a significant smoking history (>10 pack-yr). Spirometric function was normal in the nonasthmatic subjects but significantly reduced (FEV\textsubscript{1} = 82.9 ± 11.7% predicted) in the asthmatic subjects. None of the nonasthmatic subjects had a history of respiratory symptoms or regular respiratory medication use, whereas all asthmatic subjects had a history of symptoms and were receiving medication for their asthma.

Baseline R\textsubscript{os,mean} was within the normal range for all except 4 of the nonasthmatic subjects, whereas 8 (of 17) of the asthmatic subjects had a baseline R\textsubscript{os,mean} outside the normal range. The changes in mean resistance and FEV\textsubscript{1} at the end of the methacholine challenges were (mean ± SD) 83 ± 66 and −16 ± 7%, respectively, for the nonasthmatic subjects, and 69 ± 46 and −24 ± 6%, respectively, for the asthmatic subjects. However, none of the nonasthmatic subjects could be classified as hyperresponsive to methacholine challenge, with the smallest provocative dose that causes 20% decline in FEV\textsubscript{1} being 13.5 μmol and dose response ratio ranging from 0.024 to 1.3% fall in FEV\textsubscript{1} per micromole. By contrast, all asthmatic subjects exhibited hyperresponsiveness to methacholine challenge, with the provocative dose that causes 20% decline in FEV\textsubscript{1} ranging from 0.1 to 10.4 μmol, and corresponding dose response ratio of between 1.8 and 156% fall in FEV\textsubscript{1} per micromole.

**Instantaneous model fit.** Figure 1 shows an example of resistance recorded over a period of 1 min of quiet breathing, indicating the variability that typically occurs in conjunction
with tidal breathing flow and volume. In this example, breath volume and resistance are shown as functions of time in Fig. 1, A and B, respectively, with Fig. 1, C and D, showing resistance as a function of breathing flow and volume, respectively. The instantaneous model represents these flow- and volume-related variations in resistance, indicated by the slopes of the straight lines drawn in Fig. 1, C and D. The coefficient values obtained at baseline and after methacholine challenge are detailed in Table 2. As indicated in Fig. 1C, the slope of the resistance nonlinearity differs between positive and negative flow ($P < 0.01$ at baseline and $P < 0.001$ post-methacholine challenge). The values of $K_0$ and $K_8$ both increased significantly after methacholine challenge for both the nonasthmatic ($P < 0.0001$) and asthmatic ($P < 0.005$) groups. The change in $K_8$ after methacholine challenge was also significant ($P < 0.01$) for the nonasthmatic group after normalization by $K_0$. The volume coefficient $K_v$ (see Fig. 1D) increased slightly after methacholine challenge, but this was only significant in the asthmatic group ($P < 0.001$). The resistance predicted by this model is shown by the dotted line in Fig. 1B. On average, across the 14 nonasthmatic subjects, the instantaneous model accounted for $61 \pm 21\%$ of the variability in the resistance through each breath cycle during tidal breathing at baseline and $65 \pm 17\%$ of the variability after methacholine challenge. In the asthmatic subjects, the model accounted for $69 \pm 14\%$ of the variance at baseline and $68 \pm 18\%$ after methacholine challenge. There was a slightly worse fit ($50 \pm 8\%$) for the four nonasthmatic subjects with a $R_{\text{os,mean}}$ of $>140\%$ predicted. Compared with the subjects with normal resistance, these subjects exhibited greater expiratory flow and volume effects, which contributed to the high mean resistance. For the asthmatic subjects, however, there was no difference in how well the model fit the subjects with low or high mean resistance.

Between the asthmatic and nonasthmatic groups, the only model coefficient to differ significantly was $K_d$ at baseline ($P < 0.05$). However, when subjects with poor fit to the model (<50%) were excluded, then all coefficients were significantly greater ($P < 0.05$) for the asthmatic group than in the nonasthmatic group at baseline but not after methacholine challenge.

Delayed renarrowing post-DI. Figure 2 shows an example of delayed renarrowing after DI-induced stretch in one of the subjects after inhalation of 100 μmol of methacholine. As indicated in Fig. 2A, the volume returned to the pre-DI levels within two breaths, but the resistance, shown in Fig. 2B, only gradually recovered over a period of about seven breaths and so no longer followed a simple volume and flow relationship, as indicated in Fig. 2, C and D. In addition, there appears to be a reduction of the intrabreath fluctuation in resistance during the recovery phase. This delayed renarrowing effect was modeled by including a time-dependent memory term in the resistance model so that the DI-induced resistance decrement corresponding to the volume stretch increases only slowly with respect to the subsequent breath pattern. The functional form of the renarrowing memory term then determines the overall pattern and slope of the post-DI resistance recovery. In Fig. 3, the resistance at each end-expiratory instant after the DI is shown on linear, log-linear, and log-log graphs with respect to the time after DI. As these three graphs indicate, the time course of resistance change after DI in this individual appeared to follow a power-law (log-time vs. log-amplitude) rather than an exponential (log-amplitude vs. linear-time) or linear relationship. Examples of the log-log fit for other subjects are shown in Figs. 4 and 5 for the nonasthmatic and asthmatic groups, respectively.

In four of the nonasthmatic subjects, Ree exceeded the pre-DI level after only one or two breaths, as in the examples shown in Fig. 4, E and I, which meant that it was not possible to fit the log-log $FR_{\text{RN}}(t)$ to these subjects’ data without making an a priori assumption about the value of the intercept term $t_0$. The average number of breaths post-DI over which the line was

Table 1. Demographic characteristics and effects of methacholine challenge

<table>
<thead>
<tr>
<th></th>
<th>Nonasthmatic Subjects</th>
<th>Asthmatic Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Male:female</td>
<td>3:11</td>
<td>9:8</td>
</tr>
<tr>
<td>Age, yr</td>
<td>34.4±1.14</td>
<td>41.3±12.6</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170.9±7.5</td>
<td>171.4±7.9</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.3±4.1</td>
<td>25.7±3.3</td>
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<tr>
<td>FEV₁, %predicted</td>
<td>102.9±13.2</td>
<td>82.9±11.7</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>86.6±6.2</td>
<td>76.4±5.7</td>
</tr>
<tr>
<td>$R_{\text{os,mean}}$, %predicted</td>
<td>124±58</td>
<td>138±39</td>
</tr>
<tr>
<td>Methacholine dose, μmol</td>
<td>141±80</td>
<td>3.0±3.4</td>
</tr>
<tr>
<td>DRR, %fall FEV₁/μmol*</td>
<td>0.13 (0.02–1.3)</td>
<td>15.8 (1.8–156)*</td>
</tr>
<tr>
<td>FEV₁, %fall</td>
<td>15.8±6.6</td>
<td>23.7±5.5</td>
</tr>
<tr>
<td>$R_{\text{os,mean}}$, %increase</td>
<td>83±66</td>
<td>69±46</td>
</tr>
</tbody>
</table>

Values are means ± SD, except *, which is geometric means and ranges. BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; $R_{\text{os,mean}}$, mean oscillatory resistance during quiet breathing; DRR, dose-response ratio.

Table 2.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonasthmatic</th>
<th>Asthmatic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post-MCh</td>
</tr>
<tr>
<td>$K_0$, cmH₂O⁻¹·s⁻¹</td>
<td>4.1±2.3</td>
<td>6.5±2.3</td>
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<td>$K_8$, cmH₂O⁻¹·s⁻²</td>
<td>0.3±1.8</td>
<td>2.4±2.3</td>
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<tr>
<td>$K_v$, cmH₂O⁻¹·s⁻¹</td>
<td>4.1±4.7</td>
<td>4.0±2.6</td>
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<tr>
<td>$K_{RN}$ (post-DI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_0$ (post-DI)</td>
<td>(n = 10)</td>
<td>0.20±0.10</td>
</tr>
<tr>
<td>$K_{RN}$ (fix $t_0$) (post-DI)</td>
<td>(n = 0.09)</td>
<td>0.21±0.09</td>
</tr>
<tr>
<td>$K_{RN}$ (QB)</td>
<td>0.21±0.14</td>
<td>0.17±0.04</td>
</tr>
<tr>
<td>$t_0$ (QB)*</td>
<td>0.21 (0.08–44)</td>
<td></td>
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</table>

Values are means ± SD, except *, which is geometric mean and range. Instantaneous model coefficients: $K_0$, constant term; $K_8$, inspiratory flow effect; $K_v$, expiratory flow effect; $K_v$, volume effect. Renarrowing model coefficients: $K_{RN}$, power exponent; $t_0$, time intercept term. MCh, methacholine challenge.
fitted for the remaining 10 subjects was 10 ± 5 (range 3–18). There was a good fit of the power-law renarrowing model to the time-dependent change in resistance post-DI after methacholine challenge (see examples in Fig. 4), with an average $r^2$ value of 0.78 ± 0.23 (range 0.19–0.97) and a mean square error (normalized to resistance at DI) of 0.04 ± 0.06 over the Ree points post-DI that were included in the fit. The exponential renarrowing model did not provide the same level of fit to the data, with a significantly lower average $r^2$ value of 0.62 ± 0.17 ($P < 0.01$, degrees of freedom = 9) and higher mean square error of 0.23 ± 0.27 ($P < 0.05$). Note that this fit included the resistance at DI. All subjects had a lower mean square error, and only one subject had a lower $r^2$ for the power-law model compared with the exponential model. Likewise, the fit of the linear model resulted in an average $r^2$ value of only 0.59 ± 0.16, which was significantly less than the fit for the power law function ($P < 0.01$), and a mean square error of 0.29 ± 0.36, which again was higher for each of the individual subjects. The power-law model was also better than the other models for the asthmatic data (see below), and over both groups the average $r^2$ value was 0.82 ± 0.18 compared with 0.63 ± 0.16 for the exponential model and 0.58 ± 0.18 for the linear model.

The mean value of $K_{RN}$ over the 10 subjects was 0.20 ± 0.10, and the intercept term $t_0$ had an average value of 0.28 ± 0.42 s, but with a wide range from 0.004 to 1.3 s and a median of 0.09 s. For the four subjects in whom Ree returned to its pre-DI value within one or two breaths only, a renarrowing coefficient was computed by fixing the intercept $t_0$ at 0.09 s, which was the geometric mean and median value of $t_0$ for the other 10 subjects. The inclusion of these subjects changed the average value of $K_{RN}$ to 0.23 ± 0.11. There is a high correlation between $K_{RN}$ and log $t_0$ ($r^2 = 0.74$), but if $t_0$ is fixed at 0.09 s for all 14 subjects the average value of $K_{RN}$ changed only slightly to 0.21 ± 0.09. The mean square error of fits (in effect including the DI value) was 0.06 ± 0.06, which was lower than the equivalent exponential model for all except one subject, and despite the wide range this difference is also significant ($P < 0.05$).

In the asthmatic subjects, the post-DI renarrowing coefficient $K_{RN}$ was 0.17 ± 0.011 in the 12 subjects for whom the post-DI renarrowing took more than two breaths (average 5.6 ± 2 breaths) until Ree reached its pre-DI level. However, due to apparent noise in the post-DI resistance estimates, some of these fits were poor, with an average $r^2$ value of only 0.50 ± 0.29. By excluding outliers from the post-DI sequence of Ree, we were able to improve the fit of the model such that the average $r^2$ value became 0.88 ± 0.11 over an average of 4.9 ± 2 breaths post-DI in 12 subjects. The average $K_{RN}$ was then 0.24 ± 0.08 with $t_0 = 0.59 ± 0.93$ s (median 0.13 s, range 0.001–3.2 s). These values were not, however, significantly different from corresponding values for nonasthmatic subjects.

Renarrowing during tidal breathing. Figure 6B shows an example of the resistance time course during tidal breathing, as indicated in Fig. 6A, with the flow effect (i.e., second 2 terms in Eq. 1) removed. In Fig. 6C, all end-inspiratory to end-expiratory increments are overlaid together with the renarrowing function obtained from the post-DI resistance, as defined in Eq. 3. In this example, it is clear that the time course of renarrowing after each tidal inspiration is quite similar to the time course after the DI, albeit with some degree of interbreath

Fig. 3. Pattern of resistance change post-DI ($R/R_{DI}$) of the example shown in Fig. 2. End-expiratory (circles) and end-inspiratory (diamonds) instants are shown on linear time vs. linear resistance (A), linear time vs. logarithmic resistance (B), and logarithmic time vs. logarithmic resistance (C) scales. The straight line is a least squares fit to the end-expiratory points.
variability. The mean value of the tidal renarrowing quiet breathing coefficients $K_{RN}(QB)$ over all nonasthmatic subjects was 0.21 $\pm$ 0.14, with a range of 0.07–0.50. The corresponding quiet breathing values of $t_0$ [$t_0(QB)$] had a mean of 0.23 $\pm$ 0.10 s, with a range of 0.08–0.44 s. In the asthmatic subjects, the mean value of $K_{RN}(QB)$ was 0.17 $\pm$ 0.04, with corresponding values of $t_0(QB)$ being 0.22 $\pm$ 0.14 s and a range of 0.008–0.47 s.

Figure 7 shows the relationship between the renarrowing coefficient calculated from the post-DI changes in resistance and those obtained from the tidal breathing before DI in the nonasthmatic subjects. There is a reasonable correlation (intraclass correlation $= 0.66$) between $K_{RN}$ (post-DI) and $K_{RN}(QB)$ and a close association with the line of identity. There was no correlation between the values of $t_0$ computed from the tidal breathing data and the values obtained from the post-DI renarrowing. By fixing the intercept $t_0$ to the same value ($t_0 = 0.09$ s) for both the DI and the quiet breathing renarrowing function, the agreement between $K_{RN}$ (post-DI) and $K_{RN}(QB)$ improved with an intraclass correlation of 0.81, as shown in Fig. 7B. In the asthmatic data, however, there was no correlation between $K_{RN}$ (post-DI) and $K_{RN}(QB)$.

**DISCUSSION**

The temporal pattern of variation in oscillation resistance exhibits periodic effects that are strongly correlated with the breathing signals $V_b(t)$ and $V_b(t)$. Previous studies have shown that much of the periodic variation can be associated with breathing-related effects such as nonlinear flow resistance (1, 4, 7, 23), phasic changes in upper airway caliber between inspiration and expiration (8, 20), and the effects of volume stretch on the airway caliber (2, 6, 22). The model of flow and volume effects presented here explained a large proportion of the variation in oscillation resistance. However, such instantaneous effects cannot explain the slow increase over several breaths that can often be observed after DI, particularly in nonasthmatic subjects after a high-dose challenge (19). We modeled this delayed effect by a simple function of time and showed that the recovery followed a power-law (log time) rather than an exponential (linear time) type of decay. This result has important implications with respect to the possible mechanisms determining this slow renarrowing after stretch.

Several explanations for the delayed effect of volume stretch have been proposed (35), including changes in the nature of the

![Fig. 4. Post-DI power-law renarrowing function fits to examples of the nonasthmatic subjects. A–I: readings from 9 different nonasthmatic subjects. The time origin is taken to be the instant of maximum DI, and the abscissa is normalized to the resistance at DI (R_{DI}). The horizontal dashed line indicates the pre-DI median of end-inspiratory resistance, and the solid line indicates the pre-DI median of end-expiratory resistance. # End-expiratory resistance value post-DI; $\diamond$, end-inspiratory resistance values post-DI. The dashed lines in E and I indicate fits obtained by setting time intercept ($t_0$) to 0.09 s as described in the text.](http://jap.physiology.org/)
bridge dynamics in ASM after a larger than normal stretch (13) and the possibility that the velocity of shortening of the ASM may be slow enough in some cases that it takes several breaths for the muscle to shorten after a stretch (30, 32). In the perturbed equilibrium model (13), the force that the ASM is able to generate during cyclic stretching is greatly reduced from the maximum static force because a proportion of the actin-myosin cross bridges becomes detached by the applied stretches. Furthermore, after particularly large stretches, the generated force remains depressed for some time (13). Jensen et al. (19) suggest that, after a DI, the actin-myosin cross bridges that are detached by the stretch take some time to reattach, thus providing a reduced force on the airways and explaining the prolonged reduction in resistance after DI in normal subjects. In asthmatic subjects, however, the ASM is hypothesized to be in a “latch-bridge” state with stronger actin-myosin bonds, implying both that the ASM is stiffer and so not able to be stretched as much by the DI and also that the bonds are less easily broken, so that after the DI is complete, the airway returns immediately to its pre-DI state.

A power-law function implies that there is not a single time constant but rather that the response is produced by the combined effect of a multitude of interacting elements with a wide range of time constants. In the lung, such a mechanism could occur at several scales, ranging from interaction within the cytoskeleton of constituent cells (9), actin-myosin interactions within the ASM (14), hysteresis in the parenchymal forces acting on the airways (16), stress adaptation in lung tissue after a step-length change (25), or even heterogeneity in the airway tree arising from airway closure and reopening (33). The dynamics of ASM may be well modeled by power-law functions because the active elements of the muscle effectively consist of loosely coupled molecular chains. The overall time course of narrowing is therefore determined by the combined effect of each of the individual molecular links, which can be modeled as probabilistic processes. It turns out that a combination of many such loosely coupled interacting elements gives rise to power-law behavior (9) in which there is no single time constant. Indeed, although our data are at a different level of structure in the organism, the value of our power-law coefficient $K_{RN} = 0.2$ is quite similar to the equivalent coefficient $(x - 1 = 0.2)$ obtained by Fabry et al. (9) in their observations of the dynamic characteristics of cytoskeletal mechanics in human ASM cells. Peslin et al. (25) also obtained a similar power-law coefficient of 0.17 in their analysis of pressure change after a step increase in lung volume.

We did not find any significant differences in the renarrowing coefficients obtained from asthmatic and nonasthmatic subjects. Symbols and lines have the same meanings as in Fig. 4.

![Fig. 5. Post-DI power-law renarrowing function fits to examples of the asthmatic subjects. A–I: readings from 9 different asthmatic subjects.](image-url)
ASM behavior but also of other factors, such as stress adaptation in passive lung tissue (25). Indeed, Fabry et al. (9) found power-law renarrowing behavior in a wide range of different cell types.

Renarrowing during quiet breathing. Although the delayed effects of slow renarrowing are most easily seen after DI, our results show that the change in resistance (after accounting for nonlinear flow effects) after tidal inspirations is also well represented by the same coefficient that determines the post-DI shape. Several authors [e.g., Stephens et al. (32) and Solway and Fredberg (30)] have proposed that the finite velocity of shortening of activated ASM may limit the rate at which airways can narrow during tidal breathing. Indeed, measurements of the velocity of shortening in vitro suggest that it is roughly of the same time scale as breathing frequencies (32).

Fig. 6. Time course of volume during tidal breathing (A) and volume-related resistance changes (i.e., with flow effects removed; B) highlighting renarrowing during expiration. C: resistance changes after removal of flow effects during expiratory phases, shown in relation to the resistance at each end-inspiratory instant (Rei). The dark line is the function $F_{RN}(t)$ as obtained from the post-DI renarrowing for the same subject. $t_{EI}$, end-inspiratory instant; see Eq. 2.

Fig. 7. A: relationship between renarrowing coefficient during DI [$K_{RN(DI)}$] calculated from post-DI data and the quiet breathing coefficient [$K_{RN(QB)}$] computed from expiratory changes during tidal breathing before DI (both data are post-methacholine challenge). O, 4 subjects in whom the post-DI renarrowing $K_{RN(DI)}$ was calculated with an assumed $t_0$ of 0.09 s. B: relationship between $K_{RN(DI)}$ and $K_{RN(QB)}$ computed with an a priori fixed value of $t_0 = 0.09$ s for all subjects post-DI and during quiet breathing.
According to this hypothesis, the same mechanism would operate after both small and large stretches, with the rate of subsequent renarrowing determined by the speed at which the ASM can shorten (if this is slower than the rate at which the applied volume stretch is removed). This suggests that tidal fluctuations in airway caliber may be limited by the magnitude of the velocity of shortening (30) in the same way that the recovery after a DI is limited at a relatively slow rate in some subjects. In other words, if the velocity of shortening is slower than the breathing rate, then the ASM does not have enough time to fully renarrow during the expiratory phase of the breathing cycle, and the tidal fluctuations are reduced from what they would be if there were no limit on the rate of renarrowing. Our results, at least in the nonasthmatic subjects, tend to support this hypothesis, because the rate at which the resistance increased after each tidal stretch could be well modeled by a time-dependent renarrowing function that was almost the same as the renarrowing that could be observed after a DI. Also, there was no correlation between the renarrowing coefficient $K_{RN}$ and the volume stretch coefficient $K_{v}$, implying that the renarrowing during expiration was unrelated to the volume-induced stretch during tidal inspiration.

In the asthmatic subjects, the renarrowing coefficient obtained during quiet breathing was not correlated to that after DI and was smaller (although not significantly so) than that obtained for the nonasthmatic subjects. This result does not seem to support the hypothesis that $K_{RN}$ is a measure of velocity of shortening, particularly if we expect that to be greater in asthmatic subjects (30). However, it is possible that our model of time-dependent narrowing during quiet breathing does not fit the asthmatic subjects so well. In particular, our calculation of $K_{RN}(QB)$ assumes that the immediate volume effect $K_{v}V_0(t)$ in Eq. 1 does not affect the expiratory time course of resistance change. However, this is only true if volume decreases relatively fast after the inspiration (relative to the time over which we can measure the renarrowing). During a DI, this assumption is met, but during quiet breathing the time course of expiration is comparable to the time course over which we are trying to calculate $K_{RN}(QB)$. There is thus an upper limit on the value of $K_{RN}(QB)$, which we can measure, related to the rate of expiration. It may be necessary to measure the tidal renarrowing during artificially constrained breathing patterns, e.g., a short expiration followed by a pause.

Conclusions. In summary, we have presented a model that quantifies the time course of changes in airway resistance during periodic stretch applied to the airways during normal breathing as well as the change that occurs after a large-amplitude stretch due to DI. We have shown that the time course of slow renarrowing (over several breaths) after a DI can be well modeled by a power-law function of time and, furthermore, that the time course by which airways narrow after each tidal inspiration is similar (at least in nonasthmatic subjects) to the time course of narrowing after a DI. The analysis extends the earlier work presented by Salome et al. (29), who compared the relative changes in resistance between the DI and the subsequent breath to the tidal fluctuations during quiet breathing at baseline and found a high degree of correlation in both normal and asthmatic subjects.

The analysis and results presented here provide some evidence that the mechanism of delayed recovery after stretch is similar for both large and small inspirations, with a close similarity in the shape and time course of the renarrowing functions computed after DI and during quiet breathing. The results support the supposition of Solway and Fredberg (30) that temporal dynamics of airway mechanisms are important in maintaining airway caliber during breathing in normal subjects. They also suggest that it may be possible to make measurements in vivo of the temporal behavior of ASM. Such measurements could be made during quiet breathing and after DI, as in our data here, or by following a specific breathing pattern designed to better separate the instantaneous and temporal effects. Furthermore, it would be very worthwhile to utilize multiple-frequency forced oscillation technique to see whether there is any frequency dependence in the effect that could be associated with variations in airway tree heterogeneity (21).

GRANTS

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REFERENCES