Airway remodeling in asthma amplifies heterogeneities in smooth muscle shortening causing hyperresponsiveness

HEATHER L. GILLIS AND KENNETH R. LUTCHEN
Department of Biomedical Engineering, Boston University, Boston, Massachusetts 02215

Gillis, Heather L., and Kenneth R. Lutchen. Airway remodeling in asthma amplifies heterogeneities in smooth muscle shortening causing hyperresponsiveness. J. Appl. Physiol. 86(6): 2001–2012, 1999.—Although airway remodeling and inflammation in asthma can amplify the constriction response of a single airway, their influence on the structural changes in the whole airway network is unknown. We present a morphometric model of the human lung that incorporates cross-sectional wall areas corresponding to the adventitia, airway smooth muscle (ASM), and mucosa for healthy and mildly and severely asthmatic airways and the influence of parenchymal tethering. A heterogeneous ASM percent shortening stimulus is imposed, causing distinct constriction patterns for healthy and asthmatic airways. We calculate lung resistance and elastance from 0.1 to 5 Hz. We show that, for a given ASM stimulus, the distribution of wall area in asthmatic subjects will amplify not only the mean but the heterogeneity of constriction in the lung periphery. Moreover, heterogeneous ASM shortening that would produce only mild changes in the healthy lung can cause hyperresponsive changes in lung resistance and elastance at typical breathing rates in the asthmatic lung, even with relatively small increases in airway resistance. This condition arises when airway closures occur randomly in the lung periphery. We suggest that heterogeneity is a crucial determinant of hyperresponsiveness in asthma and that the acute asthma is more of a consequence of extensive airway wall inflammation and remodeling, predisposing the lung to produce an acute pattern of heterogeneous constriction.

inhomogeneous; lung mechanics; lung resistance; lung elastance; impedance

IN ASTHMA, long-standing airway inflammation can lead to airway remodeling. Hence, asthmatic patients have increased airway wall area, the degree of which depends on disease severity (12). Asthma is characterized by hyperresponsiveness to nonspecific stimuli. This means that for asthmatic patients the dose-response curve will display both a leftward and upward shift. One possible mechanism for this hyperresponsiveness is that, for a given degree of airway smooth muscle (ASM) shortening, an airway with increased wall area will have exaggerated luminal constriction (24). Also, the thickened airway walls can uncouple the ASM from the parenchyma and cause a decrease in the elastic load opposing ASM shortening (19). These mechanisms describe how a single airway can be hyperresponsive. The focus of this study is the role these mechanisms have in establishing the pattern of constriction throughout the airway tree. Specifically, we hypothesize that the heterogeneity, rather than the mean level of constriction, may be a crucial determinant of hyperresponsiveness in asthma and that the airway remodeling modulates the pattern of constriction.

It is well established that the same dose of a bronchodilator will cause a greater increase in dynamic lung resistance \( (R_L) \) and elastance \( (E_L) \) in the asthmatic subject than in the healthy one (25). Moreover, there is direct and indirect evidence that the primary location causing the amplified response is in the lung periphery (22, 26). The role that inflammation and airway wall remodeling have in establishing the pattern of bronchoconstriction is unclear. In our previous modeling studies (4, 15), constriction was applied by directly reducing the lumen, and there was no airway wall remodeling consistent with asthma. Nevertheless, we showed that the pattern of constriction is a very important determinant of the net change in \( R_L \) and \( E_L \) at typical breathing rates. In fact, heterogenous constriction that includes random peripheral airway closure can cause dynamic \( R_L \) and \( E_L \) to become highly elevated at typical breathing frequencies \(<0.5 \text{ Hz})\, even without an excessive increase in airway resistance.

In this study, we have taken a more physiological approach as in the paper by Thorpe and Bates (21). The model input is heterogeneous or homogeneous ASM shortening, and the resulting distribution of constricted luminal diameters is dependent on the airway geometries and wall areas. Wall areas for healthy and mildly and severely asthmatic human airways, as established by postmortem histological studies (12), were incorporated as well as parenchymal tethering (14). In all cases, the \( R_L \) and \( E_L \) levels from 0.1 to 5.0 Hz were simulated. We established how airway wall areas govern the pattern of peripheral constriction for a given ASM stimulus and, hence, the net effect on the mechanical properties of the human lung.

MODEL

We use an asymmetric airway tree structure that conforms to the morphometry of the human lung, as described by Horsfield et al. (8). Terminal airways are attached to viscoelastic alveolar tissue elements (7). Airway walls are nonrigid, account for gas compression, and include rheological and geometric properties. Each airway impedance is calculated by an acoustic transmission line model.

Airway wall remodeling consistent with asthma (i.e., thickened airway walls) is incorporated as follows.¹ For

¹ Note that our terminology follows the anatomic guidelines set forth by Bai et al. (1) rather than that used by Kuwano et al. (12) and Lambert and Paré (13). Our model closely follows these latter works, and the only distinction is that what they previously labeled as "submucosa" we now label "mucosa."
each order, the airway wall is subdivided into the adventitia, ASM, and mucosa (Fig. 1A). Kuwano et al. (12) made histological measurements on human postmortem lungs and empirically identified a linear relationship between basement membrane perimeter and the square root of wall area. The coefficients of these relations were reported for each of the three airway layers, and the coefficients differ for the healthy and mildly and severely asthmatic patients (Table 1). The perimeter of the basement membrane is computed by assuming that the airway conforms to a perfect circle at total lung capacity (TLC), with a diameter corresponding to the Horsfield diameter at TLC ($d_{TLC}$). The combined wall area of the mucosa and the ASM for the three cases as a function of luminal diameter at functional residual capacity ($d_{FRC}$) is shown in Fig. 1B, and the corresponding relative increase in wall areas for mild and severe asthma is shown in Fig. 1C. The severe asthma case has at least a threefold increase from the healthy case in airways with diameter $1.5$ mm. Most importantly, the percent wall (PW) area internal to the outer layer of the ASM occupied by the mucosa and ASM is greatest in the peripheral airways for all three health conditions (Fig. 1D) and greater for all generations with severely asthmatic airways.

Airway constriction: geometric equations. The model shortens the ASM, and the corresponding luminal diameter is computed. The computation assumes that airway walls are incompressible and that the airway lumen remains circular (i.e., wall areas for each order are constant and there is no mucosal folding). The equations relating ASM shortening and luminal constriction are given by Moreno et al. (20). At a given relaxed (i.e., reference) luminal radius ($r$), the outer

### Table 1. Coefficients used to determine wall areas

<table>
<thead>
<tr>
<th>Layer</th>
<th>Healthy</th>
<th>Mild Asthma</th>
<th>Severe Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adventitia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>0.079</td>
<td>0.116</td>
<td>0.167</td>
</tr>
<tr>
<td>I</td>
<td>0.116</td>
<td>0.047</td>
<td>0.070</td>
</tr>
<tr>
<td>Airway smooth muscle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>0.020</td>
<td>0.044</td>
<td>0.068</td>
</tr>
<tr>
<td>I</td>
<td>0.056</td>
<td>0.026</td>
<td>0.005</td>
</tr>
<tr>
<td>Mucosa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>0.052</td>
<td>0.092</td>
<td>0.106</td>
</tr>
<tr>
<td>I</td>
<td>0.067</td>
<td>$-0.004$</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Airway wall can be divided into adventitia, airway smooth muscle, and mucosa. Square root of airway wall area ($WA$; in mm$^2$) for each layer is linearly related to perimeter of basement membrane ($P_{bm}$; in mm) (=luminal perimeter). Coefficients are from Kuwano et al. (12) and are distinct for healthy lung and mild and severe asthma airways, with mucosa used here, instead of submucosa, as originally stated. $\sqrt{WA} = P_{bm}S + I$, where $S$ is slope and $I$ is intercept.

Fig. 1. Properties and schematic of airway wall areas. Wall areas are determined empirically from luminal airway diameter at total lung capacity and are from histological data from healthy and mildly and severely asthmatic airways (12). A: schematic of a relaxed reference airway wall has 3 layers: mucosa, airway smooth muscle (ASM), and adventitia. During asthma, these individual layers have increased wall areas. Shown are radii to the lumen ($r$) and the outer layers of mucosa ($r_{muc}$), ASM ($r_{sm}$), and adventitia ($r_a$). B: combined wall area of mucosa and ASM for healthy (solid line), mild asthma (dashed line), and severe asthma (dotted line) wall areas vs. diameter at functional residual capacity (FRC) ($d_{FRC}$). Also shown are Horsfield order 21 (largest peripheral airway, $d_{FRC} = 2.2$ mm) and order 31 (largest order constricted, $d_{FRC} = 6.9$ mm). Airway wall area increases as airway order increases and with the severity of asthma. C: ratio of total wall area in mild (dashed line) and severe asthma (dotted line) to healthy total wall area vs. airway order. D: percent wall (PW) area circumscribed by outer layer of ASM occupied by mucosa and ASM (see Eq. 4). Note that peripheral airways have increased PW and that PW is greater with severe asthma.
ASM radius \( r_{sm} \) is given by

\[
r_{sm} = \sqrt{r^2 + \frac{W_{muc} + W_{sm}}{\pi}}
\]

(1)

where \( W_{muc} \) is the mucosal wall area and \( W_{sm} \) is the ASM wall area. The percent ASM shortening (PS) is specified, and the constricted ASM radius \( r_{smc} \) is given by

\[
r_{smc} = r_{sm}(1 - PS(1 - c))
\]

(2)

where \( c \) is the fraction of cartilage in the airway wall (5).

Whether the cartilage content can modulate the degree of constriction below the trachea and main-stem bronchi is not certain. Our discussion will point out that this assumption is not an important contributor to our primary conclusion. The corresponding constricted internal (luminal) radius \( r_c \) is

\[
r_c = \sqrt{r^2 + \frac{W_{muc} + W_{sm}}{\pi}}
\]

(3)

\[
= r_{smc} \sqrt{1 - [1 - PS(1 - c)]^2 - PW}
\]

where \( PW \) is the fractional area bound by the outer ASM occupied by the airway wall in the preconstricted state. That is

\[
PW = \frac{W_{muc} + W_{sm}}{\pi r_{smc}^2}
\]

(4)

Note that peripheral airways have a higher PW than central airways, and for a given airway size the severe asthma case has a higher PW than does the healthy case (Fig. 1D). The percent luminal diameter reduction from relaxed to constricted state (PLC) is

\[
PLC = \left(1 - \frac{r_c}{r}\right) 100
\]

(5)

The distending pressure is

\[
P_{in} = P_L + \Delta P
\]

(8)

where \( P_L \) is the lung recoil pressure and \( \Delta P \) is the additional stress transmitted to the airway by the lung parenchyma. The additional stress imparted by the parenchyma is

\[
\Delta P(PS) = \frac{2S r_{atLC} - r_a(PS)}{r_{atLC}}
\]

(9)

where \( S = 0.7P_L \) is the elastic shear modulus of the lung parenchyma (cf. Ref. 13), and \( r_{atLC} \) and \( r_a(PS) \) are the radii to the outer border of the adventitia at TLC and the constricted state, respectively.

The \( P_{out} \) is calculated as in Thorpe and Bates (21)

\[
P_{out}(PS) = P_{TLC} \left(\frac{r_c r_{TLC} - \alpha_0}{1 - \alpha_0}\right)^3
\]

(10)

where \( P_{TLC} = 30 \) cmH\(_2\)O is the transpulmonary pressure at TLC, \( r_{TLC} \) is the luminal radius at TLC, and \( \alpha_0 \) is the ratio of the radius at a zero transpulmonary pressure to the radius at TLC. Equation 10 describes the pressure-area characteristics of the airway and is consistent with Gunst and Stropp (5). Thorpe and Bates (21) reported a linear relation between Horsfield’s orders for the dog (k) and \( \alpha_0 \)

\[
\alpha_0 = 0.2 + 0.011k
\]

(11)

To incorporate this equation for the human lungs, we modified the relation to one between k and \( d_{TLC} \) such that

\[
30.2 + 20.1 \log(d_{TLC}) \quad d_{TLC} < 0.14 \text{ cm}
\]

(12)

\[43.6 + 6.1 \log(d_{TLC}) \quad d_{TLC} \geq 0.16 \text{ cm}
\]

where \( d_{TLC} \) is in cm.

In summary, the amount of tension developed in the ASM is order dependent and is determined as follows.

1) Specify percent ASM shortening PS.
2) Calculate constricted radii \( r_c \) (Eqs. 1–4) and \( r_{muc} \) (Eq. 7).
3) Calculate \( P_{in} \) (Eqs. 8–9) and \( P_{out} \) (Eqs. 10–12).
4) Calculate T (Eq. 6).

The tension required to achieve the constriction is then compared with the maximum tension \( T_{max} \) that can be developed at the muscle’s constricted length (Lc).

If \( T > T_{max} \) at \( L_c \), then the PS is reduced until \( T = T_{max} \) (see APPENDIX).

Before simulations, the maximum percent ASM shortening (PS\(_{max}\)) for each airway order was determined by finding either the PS that developed an active tension equal to \( T_{max} \) or the PS at which the airways closed. Figure 2 shows the maximum percent diameter reduction (i.e., diameter reduction for \( PS = PS_{max} \)) as a function of diameter at FRC for the healthy lung and asthma cases. A 100% diameter reduction indicates \( PS_{max} = PS_{close} \). Several important distinctions occur.
First, for a given case, peripheral airways can undergo more constriction. Second, for a given airway size, the severe asthma case can undergo the most constriction. In the healthy lung, $T_{\text{max}}$ prevents central airways (i.e., $d_{\text{FRC}} > 2.1 \text{ mm}$) from undergoing $20\%$ diameter reductions, and only airways with $d_{\text{FRC}}, 0.4 \text{ mm}$ can close. In contrast, the severely asthmatic lung airways with $d_{\text{FRC}}, 5 \text{ mm}$ can have diameter reductions from $80$ to $100\%$, and central airways can constrict up to $50\%$.

Heterogeneity. The input to our model is $PS$. Heterogeneities are introduced by having $PS$ follow a Gaussian distribution defined by a mean $PS$ ($\mu_{PS}$) and standard deviation $PS$ ($SD_{PS}$). Theoretically, a random draw on this Gaussian distribution can produce negative $PS$ values, which represent dilation and are permitted. Similarly, the random $PS$ value can be $\geq PS_{\text{max}}$. Random draws that produce a $PS > PS_{\text{max}}$ are set to $PS_{\text{max}}$.

SIMULATIONS

The simulations were aimed at answering the following questions. First, how does homogeneous ASM shortening affect $RL$ and $EL$ during airway remodeling? Second, how do heterogeneities in ASM shortening alter $RL$ and $EL$, and are asthmatic patients more sensitive to these heterogeneities? Third, what are the relative contributions of the peripheral and central airways, and do these contributions differ in the healthy and asthmatic lung?

Simulations were performed at FRC. Baseline Horsfield lengths were all scaled equally, and the diameters at TLC were scaled to FRC by an order-dependent sigmoidal scaling function (6). This scaling function allows peripheral airways to narrow more than the central ones in a manner consistent with experimental data and their relatively higher wall compliance (6). All ASM shortening was referenced to the ASM length at FRC and $PL = 5 \text{ cmH}_2\text{O}$. The $RL$ and $EL$ were calculated for the frequencies of 0.1–5 Hz for $\mu_{PS} = 0–30\%$ and $SD_{PS} = 0–15\%$. The PS distribution was applied to all airways excluding orders 32–35. These orders have the largest diameter and have a total of six airways. Each shortening condition was simulated for three different wall area cases that corresponded to healthy lungs and to mild and severe asthma (Table 1). The above simulations were compared with simulations where only peripheral ASM shortened to determine the effect of peripheral constriction. In this model, peripheral airways correspond to orders 1–21 (i.e., $d_{\text{FRC}} < 2.1 \text{ mm}$).

RESULTS

Homogeneous ASM shortening. The dynamic $RL$ and $EL$ values for homogeneous ($SD_{PS} = 0\%$) ASM shortening in orders 1–31 for the healthy lungs and mild and severe asthma cases are shown in Fig. 3. The nonconstricted baseline conditions are nearly identical for the three cases. This indicates that an increase in wall area alone will not alter $RL$ and $EL$. From 0.1 to 0.5 Hz, the $RL$ showed a small frequency-dependent drop due to the viscoelastic tissue. At higher frequencies, tissue resistance was negligible, so that the $RL$ at 5.0 Hz represents mean airway resistance (Raw) (16, 17). This $Raw = 0.7 \text{ cmH}_2\text{O} \cdot l^{-1} \cdot s^{-1}$. Baseline $EL$ increased...
slightly at low frequencies (due to tissue viscoelasticity) and then began to decrease due to airway inertia. A homogeneous 20% ASM shortening uniformly elevated RL and had negligible impact on EL for all three cases (dashed-and-dotted lines in Fig. 3). The increase in RL was similar for the healthy and mild asthma cases, but it was bigger in the severe asthma case. The Raw for the healthy, mild, and severe cases increased to 2.1, 2.3, and 3.0 cmH₂O·l⁻¹·s⁻¹, respectively. Note that, although the input signal (PS) was identical for all constricted orders, the resulting luminal constriction for each order differed because of the order-dependent nature of the airway wall areas.

A homogeneous 30% ASM shortening again increased RL uniformly, but the increase with severe asthma was far greater than in the other cases. The Raw were 5.1 (healthy), 5.8 (mild asthma), and 15.5 (severe asthma) cmH₂O·l⁻¹·s⁻¹. Again, none of the cases showed an increase in the EL at typical breathing frequencies (<1 Hz). However, all cases showed an increase in EL at frequencies >1 Hz. In fact, the severe asthma case exhibited a large and monotonic increase from 1 to 5 Hz. This monotonic increase represents flow shunting into the compliant central airway walls as the downstream airway resistance increases (15, 16). This increase in EL would not occur if the airways were modeled with rigid walls.

In summary, homogeneous PS uniformly elevated RL and could cause EL to increase at frequencies >1 Hz. The degree to which both occur is amplified in the severe asthma case, particularly as μps increased. The hyperresponsiveness of RL to ASM shortening in the severe asthma model is consistent with the homogeneous constriction reported by Wiggs et al. (22, 24). The effect that heterogeneity in ASM shortening has on lung mechanics is discussed next and is perhaps more provocative in understanding how airway wall remodeling can compromise lung function during acute asthma.

Heterogeneous ASM shortening. Recall that the homogeneous ASM shortening simulations of Fig. 3, applying μps = 20%, produced a relatively minor effect on RL and EL for healthy, mild, and even severe asthma. In Fig. 4, the μps = 20% is repeated but now at two levels of heterogeneities, SDps = 10% (dashed-and-dotted lines) and 15% (dotted lines). The RL and EL values are shown for the healthy, mild asthma, and severe asthma. Baseline curves correspond to no constriction. For each μps and SDps, the corresponding changes in RL and EL were amplified as the severity of asthma increased. For any single health condition, an increase in the heterogeneity of ASM shortening increased the frequency dependence and level of RL and EL, with the greatest difference occurring below 1 Hz. These increases were slight in the healthy case but became extremely exaggerated for the severe asthma case. For example, when SDps = 15%, the RL at 0.2 Hz increased by only 4:1 and 5:1 in the healthy and mild asthma cases, respectively, but it increased by 12:1 in severe asthma. Moreover, the increase in RL at 0.2 Hz was greater than that of the homogeneous case with the same mean ASM shortening (Fig. 3). Specifically, for severe asthma, RL increased from 1.6 to 3.9 cmH₂O·l⁻¹·s⁻¹ with homogeneous shortening but to 18.3 cmH₂O·l⁻¹·s⁻¹ for heterogeneous shortening. The Raw (i.e., RL at 0.5 Hz) was 3.0 cmH₂O·l⁻¹·s⁻¹ for the homogeneous shortening condition and 7.8 cmH₂O·l⁻¹·s⁻¹ for the heterogeneous shortening condition.

There were no features in EL indicative of airway wall shunting (i.e., rising dynamic EL beginning above 1 Hz as in Fig. 3). However, there are features indicative of airway closure occurring randomly throughout the periphery. These closures caused loss of communication to a large percentage of the terminal tissue elements. Hence, there was an increase in the apparent (static) tissue elastance as measured from the airway opening, causing an increase in EL at 0.1 Hz (despite no...
real change in tissue properties). For a given level of heterogeneity, the severe asthma case had more closed airways, indicated by a greater increase in $E_L$ at 0.1 Hz. The heterogeneous constriction pattern caused by the heterogeneous ASM shortening results in a very disparate distribution of parallel mechanical time constants. This phenomenon increased the frequency dependence of dynamic $E_L$, but, unlike airway wall shunting (Fig. 3), the increase in Fig. 4 occurs primarily between 0.1 and 2 Hz. The amount of frequency-dependent increase was far greater in the severe asthma case. Thus, in contrast to homogeneous ASM shortening, the net change in $E_L$ at 0.2 Hz was substantially greater as the severity of asthma increased.

In summary, the same heterogeneous ASM shortening stimulus caused a more extreme heterogeneous pattern of airway constriction (with more randomly occurring peripheral airway closures) with increased severity of asthma. The net effect had far worse consequences on the net increase in RL and $E_L$ at typical breathing rates than in homogeneous shortening.

ASM shortening in periphery alone. So far, the input signal $PS$ has been applied to both central and peripheral airways. However, because of airway wall geometry and cartilage content, peripheral airways have a greater luminal reduction for a given $PS$ (see DISCUSSION). To determine the sensitivity to location of ASM shortening, the shortening conditions $\mu_{PS} = 30\%$ with a $SD_{PS} = 0\%$ (dotted line) and $\mu_{PS} = 20\%$ with a $SD_{PS} = 15\%$ (dashed line) were repeated, with shortening applied only to the peripheral ASM ($\bullet$; Fig. 5). Conditions were compared with the corresponding cases where the $PS$ was applied to both central and peripheral airways (lines, no symbol). These simulations predicted that the majority of change in the RL and $E_L$ during constriction arose from the periphery (d $<$ 2 mm) in the healthy lung and mild and severe asthma cases. There was slightly more airway wall shunting when the periphery alone was constricted. This is because constricting the central airways also stiffens the airway walls, which will mitigate the net amount of shunting. During heterogeneous shortening, there was negligible difference in both RL and $E_L$ when only the peripheral ASM was shortened, compared with when both peripheral and central ASM were shortened. These results suggest that the lung is designed to have peripheral airways dominate the RL and $E_L$ constriction response, even when the stimulus is applied throughout the entire airway tree.

**DISCUSSION**

We have reemphasized that the pattern of constriction is a crucial determinant of the changes in $RL$ and $E_L$ at the breathing rate. The most important result of our modeling study is that, for a given distribution of ASM shortening, airway wall remodeling that occurs in asthma predisposes the lung to a more heterogeneous pattern of peripheral airway constriction and consequent increased hyperresponsiveness. Specifically, more extensive remodeling increases the likelihood of random airway closure or near closure, a constriction pattern for which the net increase in RL and $E_L$ near typical breathing rates is much greater than the change in Raw.

Previous models. Several previous models have investigated how airway wall geometry influences airway constriction and causes hyperresponsiveness (10, 13, 14, 18, 20–24). Equations relating ASM shortening to decreased luminal diameter that accounted for cartilage content in the airway wall were reported by Moreno et al. (20). Their equations elucidate how decreased cartilage content results in a greater amount of luminal constriction. Furthermore, for a given change in ASM length, luminal diameter is reduced more when the airway wall is thicker (increased PW). These equations were employed by James et al. (9, 10), who made histological measurements of airways. The epithelium and mucosa wall areas in airways of postmortem asthmatic and nonasthmatic humans were measured

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**Fig. 5.** Comparison of applying ASM shortening to peripheral airways only (diameter $<$ 2.2 mm; $\bullet$) and applying ASM shortening in both peripheral and central airways (no symbol). ASM shortening included $\mu_{PS} = 30\%$ with a $SD_{PS} = 0\%$ (dotted line) and $\mu_{PS} = 20\%$ with a $SD_{PS} = 15\%$ (dashed line). Baseline is the solid line. A: healthy lung; B: mild asthma; C: severe asthma.
and used to predict the ASM shortening required to close an airway and the relative change in airway resistance. Measurements confirmed thickened wall areas in asthmatic patients, and calculations showed that the thickening was sufficient to cause hyperresponsive luminal narrowing. These studies calculated airway resistances for individual airways, but no attempt was made to calculate the change in airway resistance for the entire lung. We point out that perhaps more important than the change in a single airway, or even in airway resistance of the lung, are the changes in $R_L$ and $E_L$ values at typical breathing rates.

Wiggs et al. (24) were the first to apply Moreno et al.’s (20) equations to the branching airway structure. These studies used a symmetric human lung model, with airway dimensions and connectivity described by Weibel to study how changes in the airway resistance of the whole lung were sensitive to changes in ASM shortening and thickened airway walls. Baseline mucosa and ASM wall areas were calculated from empirical equations relating luminal airway perimeter to wall areas (9). Cartilage content was assumed to be zero, except in the trachea, main-stem bronchi, and lobar bronchi. Changes in wall areas corresponding to asthma and chronic obstructive pulmonary disease were included (9). These studies arbitrarily set maximum ASM shortening to 40% and applied the same amount of shortening throughout the airway tree. They showed that the amount and peripheral vs. central location of airway wall thickening were major determinants of airway hyperresponsiveness.

Lambert et al. (14) modified Wiggs’ previous model (24) to calculate, rather than arbitrarily assign, maximum ASM shortening. The maximum shortening was determined by calculating the maximum tension that could develop and accounted for the elastic forces the ASM must overcome. Wall areas of the mucosa, ASM, and adventitia were incorporated according to histological data (12), and the elastic loads considered were the recoil of the lung, parenchyma-airway interdependence, and passive pressure in the airway wall. A study by Macklem (18) also applied the use of elastic loads to determine maximum shortening in a single 0.88-mm luminal diameter dog airway. Lambert et al. (14) concluded that decreased parenchymal interdependence caused by an increase in adventitial wall area decreased the elastic load and increased the amount of luminal constriction. In agreement with previous studies, they confirmed that mucosa’s thickness increased luminal constriction for a given amount of ASM shortening. In a subsequent study, Lambert et al. (13) determined the sensitivity of ASM shortening to changes in the parenchymal shear modulus and changes in lung recoil pressure. The sensitivity of total airway resistance to shear modulus was significant only at low lung recoil pressures.

New models. The focus of all of the above studies showed the relationship between total airway resistance and changes in airway wall geometry. However, all lacked alveolar tissue elements, and none permitted heterogeneities in ASM shortening. Thorpe and Bates (21) recently simulated dog lung impedance for different amounts of ASM shortening. The Horsfield ordering system for a dog lung was used, and heterogeneities were introduced by assigning maximum ASM shortening to follow a Gaussian distribution. In accordance with other studies, the peripheral airways were constricted proportionately more than the central airways. However, these studies did not examine human models and did not systematically examine the relationship between heterogeneous ASM shortening, wall area, parenchymal tethering, and $R_L$ and $E_L$ over typical breathing rates.

Luchten and colleagues (15, 16) have also imposed heterogeneous constriction on models with realistic airway morphometry and which account for alveolar tissues. Our investigations directly (4, 15) constricted the airway lumen without regard to the physiological mechanism responsible. In the present model, the input is ASM shortening, and by incorporating wall areas consistent with asthma we can investigate how the pattern of constriction and, consequently, $R_L$ and $E_L$ are altered when airway remodeling occurs. Furthermore, the sensitivity to heterogeneities in ASM shortening during airway remodeling can be investigated. It is highly unlikely that ASM shortening will be identical everywhere in the lung when the lung is exposed to a bronchoconstrictor. Although our heterogeneities exist at the level of ASM shortening, this could actually reflect a number of factors, including heterogeneity of agonist delivery, receptor density, distribution of ASM, and inherent physiological variability.

In this study, we have developed a model of asthmatic and healthy lungs to simulate lung impedance during bronchoconstriction that is governed by ASM shortening. By accounting for wall areas and determining the maximum tension that can be developed, the model reflects physiology more realistically. Our results show how the airway wall geometries and wall areas predispose the lung to have changes in $R_L$ and $E_L$ dominated by peripheral constriction. In addition, the peripheral airways and asthma cases are more sensitive to heterogeneities. Whereas these results are not surprising and are consistent with previous studies, we now have a model that simulates lung impedance by specifying an input that has a more physiological basis.

How increased wall areas predispose the lung to increases in heterogeneous constriction. The healthy airways and asthma models have different wall areas but the same baseline luminal diameter (i.e., no luminal encroachment). Hence, imposition of the same PS stimulus will not produce the same pattern of constriction. For example, the resulting means and SDs of luminal diameter reduction for the $\mu_{PS} = 20\%$ and $SD_{PS} = 15\%$ shortening condition in Fig. 4 are shown in Fig. 6. First, regardless of whether the lung had asthmatic wall areas, the means and the SDs in diameter reduction were greatest for the peripheral airways. Second, for any given order, the severe asthma airway had not only a greater mean but a greater SD of airway constriction. The increase in SD during severe asthma caused a constriction distribution that...
resulted in random peripheral airway closure and acute increases in $R_L$ and $E_L$. These increases were more than suggested by increases in Raw alone.

What conditions facilitate the “hyper” heterogeneous state? For the three airway wall cases, the relative amount of wall area occupying the total area enclosed by the ASM (PW) was shown as a function of airway $d_{FRC}$ (Fig. 1D). Airway wall areas were calculated from airway $d_{TLC}$ and are assumed incompressible. Choosing the abscissa as the $d_{FRC}$ was done to show the sensitivity to ASM shortening with respect to FRC values. In all three cases, peripheral airways ($d_{FRC} \leq 2.1$ mm) have a substantially higher PW than do the central airways and, generally, the healthy case has the least PW. All airways have an increased PW in the severe asthma case.

For a given PS, the constricted luminal diameter is a function of PW and PS (Eq. 3). Neglecting cartilage, the PLC can be expressed as

$$PLC = \left(1 - \frac{\rho}{r}\right) \times 100$$

$$= [1 - \sqrt{1/(1 - PW)} \sqrt{(1 - PS)^2 - PW}] \times 100$$

The sensitivity of PLC to ASM shortening can be calculated as the derivative of the Eq. 13 and is

$$\frac{d(PLC)}{dPS} = \frac{(1 - PS) \sqrt{1/(1 - PW)}}{\sqrt{(1 - PS)^2 - PW}}$$

To demonstrate how increased wall areas predispose the lung to heterogeneous constriction containing airway closure, we show the PLC and $d(PLC)/dPS$ as a function of PS for PW ranging from 0 to 50% (Fig. 7). This corresponds to the PW range found at FRC in the airways of all cases (Fig. 1D). For a given PW, an increase in PS increases the percent diameter reduction (Fig. 7A). Furthermore, for a given PW, there is a range of PS for which the luminal reduction becomes particularly sensitive, as indicated by the sharp knees in the curves (Fig. 7B). Conversely, for a given PS, the resulting percent luminal constriction increases with increasing PW. For example, a 20% ASM shortening in an airway with a PW = 50% will have twice the percent diameter reduction as that of an airway with PW = 10%. Now consider a $\mu_{PS} = 20\%$ but with small heterogeneities ($SD_{PS} = 10\%$). These small variations in PS can cause closure in many airways with a PW = 50% but not in airways with a PW < 30%.

The higher PW in the peripheral airways supports the hypothesis that peripheral airway narrowing will dominate the RL and EL spectra. Furthermore, the increased PW in the asthma models supports the hypothesis that asthmatic patients will have an increased response for a given level of shortening. Figure 7 illustrates how airway constriction becomes sensitive to heterogeneities when ASM shortening increases to the value at the bend in the curve. Heterogeneities will

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Fig. 6. Resulting mean and SD luminal diameter reduction in healthy (solid line), mild asthma (dashed line), and severe asthma (dotted line) lungs when input ASM shortening PS had a $\mu_{PS}$ of 20% and SD$_{PS}$ of 15% (shortening condition in Fig. 4).

Fig. 7. Sensitivity of airway constriction to wall areas and percent ASM shortening PS. A: percent luminal constriction (PLC; Eq. 13) as a function of PS is shown for different PW areas. B: slope (Eq. 14) of curves in A.
be particularly important in 1) peripheral airways of all cases and 2) all airways of the asthma cases.

When does maximum tension limit become important? The maximum ASM shortening is the lesser of the PS that causes airway closure or the PS causing maximum tension limit to be reached. The corresponding maximum diameter reduction is order dependent (Fig. 2). Diameter reductions of 100% indicate airway closure. The tension limit prevents airway closure in most airways of the healthy case. The maximum shortening that can occur in central healthy airways causes a luminal diameter reduction of ~20% with respect to FRC. Peripheral healthy airways can narrow more, but only orders 7–10 (0.2 ≤ dFRC ≤ 0.4 mm) can close.

To evaluate the importance of limiting PS, simulations from Fig. 4 were repeated with no maximum tension limit (i.e., PSmax = PSclose). The RL did not change in the severe asthma case and increased <20% in the mild asthma case. However, the RL increased ~35% in the healthy lung. Thus, in the healthy lung, the airway wall geometry prevented stimulated muscle from producing excessive airway narrowing because the tension required to produce the shortening was greater than the active tension the ASM could develop.

Because narrowing is limited, the acute form of heterogeneity that produced the RL and EL during severe asthma simply cannot occur. The T max limit is important in preventing highly constricted or nearly closed airways. This limit will have the most effect in healthy airways with a dFRC > 0.4 mm. Clearly, this mechanism may contribute to prevention of hyperresponsiveness in healthy subjects.

All of the behavior above is a consequence of the specific length-tension curve we imposed for governing smooth muscle (cf. Ref. 14 and APPENDIX). Such curves have been established from in vitro studies, and we imposed them in vivo. However, there is evidence that such an assumption is not fully valid. A recent paper by Brown and Mitzner (2) provides remarkable evidence in a healthy canine that, with a sufficiently localized and concentrated stimulation, the in vivo smooth muscle is, in fact, capable of generating sufficient tension to close even larger airways. This means that the elastic load in concert with healthy wall area does not prevent such closure. This suggests that our model might be underestimating the in vivo T max for human ASM. This does not mean that our conclusions are qualitatively altered. Namely, it still holds that increased wall area for a given heterogeneous smooth muscle shortening will tend to amplify the resulting heterogeneity of constriction and make random airway closure more likely.

Nevertheless, the work of Brown and Mitzner (2) begs the question of why asthmatic patients are hyper-responsive or even what is the phenotype of hyperresponsiveness? We submit that their study implies that asthmatic ASM is inherently more sensitive, in that, for the same stimulus in vivo, ASM during spontaneous asthma may be inherently capable of generating more tension than ASM in healthy lungs. This may be a consequence of a transition to a latch state facilitated by a reduction in the dynamic periodic stretching of the muscle (3), which could occur with increased wall inflammation and thickening. Based on our model, the increase in muscle contractility combined with the increase in WA (as in severe asthma) sets up an unusual high tendency to develop a dangerous heterogeneous pattern of peripheral airway constriction, in which random airway closures are more likely then in the airways of healthy subjects (for the same stimulus).

Elastic shear modulus S. The tension developed by the ASM depends on the S (Eq. 9). An increase in S indicates an increased coupling to the parenchyma, whereas a decrease indicates a reduction in the force opposing airway narrowing. It has been shown that ASM resistance is sensitive to S at low lung volumes (i.e., PL = 2 cmH2O) (13). We repeated simulations at FRC (PL = 5 cmH2O), with an S ranging from 0 to 25, and found no significant sensitivity to the S, except in the healthy and mild asthma cases when µ PS = 20% and SDPS = 15%.

Additional modeling limitations. Our model assumes that the cartilage attenuates ASM shortening (Eq. 2), that there is no luminal encroachment of the airway wall at FRC, and that the ASM throughout the tree is equally sensitive to the given stimulus. Generally, these assumptions provide a “best case” RL and EL response in that relaxation of them would only increase the differences in the healthy vs. asthmatic RL and EL during heterogeneous constriction.

The amount of cartilage present in the human airways decreases with airway size and is absent in peripheral airways. It is unclear as to the mechanical role of cartilage in attenuating ASM shortening. Recent data suggest that cartilage does not limit ASM shortening (2). However, these data were obtained by using suprastimulated airways, and it is doubtful whether this level of stimulation could occur in vivo. We reexamined the simulated RL and EL without allowing cartilage to attenuate the PS by setting c = 0 in Eq. 2 (not shown). The net increases in the RL and EL were minor and did not change the essential findings and conclusions as to the potential role for increased wall area to exacerbate the heterogeneity of constriction. The insensitivity of the PS to cartilage content can be explained by considering which airways were constricted. We constricted all airway orders <32. Orders 1–13 have no cartilage, orders 14–25 have <5% cartilage, and orders 26–31 have <11% cartilage content. Thus the degree to which cartilage could mitigate shortening is small. In addition, the minimum diameter that an airway can obtain (due to T max limit being reached) is unaltered. The amount of cartilage simply determines what PS will cause this minimum diameter to be reached. That is, PSmax is influenced by cartilage, but the minimum diameter is not. We note that the other role of cartilage content is its contribution to the net airway wall impedance. The more rigid the airway walls, the less airway shunting that can occur.
The luminal diameter in our model is the same for the normal and asthmatic models. That is, we do not model luminal encroachment. If luminal encroachment were incorporated, the RL and EL values at baseline for the asthmatic conditions would be greater than those for the normal subjects (because of decreased airway diameter). Constriction would further amplify the difference.

Mucosal folding patterns are not accounted for, and this may be distinct for asthmatic and healthy airways. Specifically, Wiggs et al. (23) recently showed that, as the airways thicken, fewer folds and more luminal encroachment is likely. Inclusion of the details of the folding pattern throughout the entire airway tree was beyond the scope of this study.

Not all the causes of asthma are well understood. We have taken an approach whereby we apply the same input to a normal and asthmatic model. The only parameters that are different between the normal and asthmatic model are the airway wall areas. Another possibility would be to model (as alluded to above) the asthmatic ASM as having increased sensitivity. Whereas we have not included this aspect of asthma in our model, to do so would again further increase the asthmatic RL and EL responses shown.

Finally, we point out that the Horsfield structure, while mimicking the morphometry of the tree in a computationally stylized manner, is not a one-to-one mapping of a human airway tree. Similarly, the model remains essentially a serial depiction of airways connected to tissue. Thus we express some caution in overly interpreting the anatomic locations (i.e., peripheral airway sizes) that dominate the constriction response in a real lung.

Conclusions. We have an anatomically realistic human lung model that accounts for airway wall remodeling consistent with asthma. The input to the model is ASM shortening, which then imposes a pattern of constriction that depends on the airway wall geometry and degree of parenchymal tethering. The outputs are RL and EL. This model has been used to determine the effects that airway wall remodeling have on RL and EL during heterogeneous ASM shortening.

The peripheral constriction (airways <2 mm) dominates the response, even when the stimulus is applied to the entire lung. Airway remodeling and inflammation can act in concert with heterogeneous ASM shortening to amplify the lung's mean mechanical response as well as the heterogeneity of it. The maximum tension permitted, based on previous in vitro studies, would prevent excessive airway narrowing in the healthy lung but not in the severe asthmatic lung. More recent studies suggest that this may not be the case in situ. Airway remodeling and inflammation are important factors in airway hyperresponsiveness, because amplification of the heterogeneities in ASM shortening can cause dangerous patterns of constriction; i.e., ones that include random peripheral airway closure.

APPENDIX

Lambert et al. (14) defined the $T_{\text{max}}$ as the maximal stress-length relationship for an elastic loaded airway. They also defined $P_{\text{max}}$ as the transmural pressure at which maximum stress ($\sigma_{\text{max}}$) can be developed, and for each airway $L_{\text{max}}$ is the corresponding ASM length at $P_{\text{max}}$. The $L_{\text{max}}$ is calculated by solving for $r_c$ in Eq. 10. The $T_{\text{max}}$ is calculated as
where $h_{\text{ASM}}(L_{c})$ (cm) is the thickness of the ASM at $L_{\text{max}}$ and $\% \sigma_{\text{max}}$ is the percent of maximum stress that can be developed at a given ASM length. The $h_{\text{ASM}}$ is

$$h_{\text{ASM}}(L_{\text{max}}) = \frac{L_{\text{max}}}{2\pi} - \sqrt{\frac{L_{\text{max}}^{2} - WA_{\text{ASM}}}{4\pi}}$$

We fit a sigmoidal equation to the $\% \sigma_{\text{max}}$ reported in Ref. 14 and use

$$\% \sigma_{\text{max}} = y_0 + \frac{a_1}{1 + e^{-A(x-o)/s}}$$

where $L_{c}$ is the constricted length of the ASM, $a_1 = 130.91$, $a_2 = 0.27$, $a_3 = 3.91$, $x_0 = 0.33$, and $y_0 = 0.15$. The $T_{\text{max}}$ developed at any $L_{c}$ is found by combining Eqs. A1-A3. We assume that $\sigma_{\text{max}} = 1.5$ kg/cm² and is developed at $P_{\text{max}} = 10$ cmH₂O (14). At this pressure, luminal diameters ranged from 80 to 90% of the diameter at TLC.

We can now perform an analysis similar to that of Lambert et al. (13, 14), in which the $T_{\text{max}}$ that can be developed at a given length is calculated from Eq. A1 and then shown as a percent of $T_{\text{max}}$ in Fig. 8 (dotted lines). For each airway order, the length at which maximum tension can be developed and is always greater than zero. In contrast, the $P_{\text{out}}$ term can contribute to forces constricting the airway, whereas negative $P_{\text{out}}$ values represent airway wall tension and is always greater than zero.

REFERENCES


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Address for reprint requests and other correspondence: H. L. Gillis or K. R. Lutchen, Dept. Biomedical Engineering, Boston Univ., 44 Cummingston St., Boston, MA 02215 (E-mail: hgillis@enga.bu.edu; or klutch@enga.bu.edu).

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