Airway narrowing and internal structural constraints

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Seow, Chun Y., Lu Wang, and Peter D. Pare. Airway narrowing and internal structural constraints. J. Appl. Physiol. 88: 527–533, 2000.—A computer model has been developed to simulate the movement restriction in the lamina propria-submucosa (L-S) layer (sandwiched by the basement membrane and the muscle layer) in a cartilage-free airway due to constriction of the smooth muscle layer. It is assumed that the basement membrane is inextensible; therefore, in the two-dimensional simulation, the perimeter outlining the membrane is a constant whether the airway is constricted or dilated. The cross-sectional area of the L-S layer is also assumed to be constant during the simulated airway narrowing. Folding of the mucosal membrane in constricted airways is assumed to be a consequence of the L-S area conservation and also due to tethering between the basement membrane and the muscle layer. The number of tethers determines the number of folds. The simulation indicates that the pressure in the L-S layer resulting from movement restriction can be a major force opposing muscle contraction and that the maximum shortening of the muscle layer is inversely proportional to the number of tethers (or folds) and the L-S layer thickness.

THE MECHANISM THAT PREVENTS noncartilaginous airways from collapsing due to airway smooth muscle (ASM) contraction is still not completely understood. It has been suggested that mechanical loading from lung parenchyma and within the airway wall may attenuate the shortening of the smooth muscle in normal subjects and that a decrease in the loads may explain the exaggerated airway narrowing observed in diseases such as asthma. ASM in vitro can shorten to <25% of its resting length under zero load (15). With this amount of shortening, ASM would certainly close all airways in the lung if there is no resisting force to counteract the force generated by the muscle (9, 11). There are at least two sources of resistive force that have been considered. One is the tethering of the ASM wall to lung parenchyma (12); the elastic parenchyma provides a radial force through the tethers of alveolar attachments and counteracts the force generated by the constricting muscle. Another possible source of resistive force is from the folding of basement membrane (7, 8, 18). The elastic load provided by the parenchyma was found to be insufficient to explain the observed limitation of shortening of the ASM (2, 12, 13). Estimation of the resistive force provided by the folding basement membrane depends on knowledge of flexural rigidity of the membrane, which is still an unknown. Calculation of the flexural rigidity of the basement membrane from its tensile strength involves an assumption that the membrane material is homogeneous and isotropic, which is certainly not valid. Although bending of the basement membrane and deformation of the lamina propria may create resisting force, the magnitude of the force has yet to be shown to be physiologically significant. Our observation in rabbit bronchial sections indicates that there is an abundance of collagen fibers within the lamina propria-submucosal (L-S) layer (Fig. 1A); a close examination reveals that the orientation of the collagen fibers is, in general, perpendicular to the muscle layer. These fibers appear to be responsible for anchoring the folding basement membrane to the muscle wall (Fig. 1B). In the following theoretical analysis, we present an alternative model based on this structural evidence, in which force generated by the ASM is counteracted by the geometric and kinematic restrictions in the L-S layer sandwiched between the relatively inextensible basement membrane and the muscle layer itself. Tethers are assumed to connect the basement membrane and the muscle wall to enhance the effectiveness of the membrane to withstand pressure and confine the movement of L-S material between the membrane and the muscle wall. Although mechanical pressure is not simulated in this model, it is expected to exist due to the confinement of the L-S layer and muscle contraction. The pressure in the L-S layer acts on both the membrane and the muscle wall and therefore provides resistance to muscle shortening. In this model, high tensile strength of the basement membrane is crucial in confining the L-S material and generating pressure. To simplify the model, forces associated with the bending of the membrane and the L-S layer, as well as tethering to the parenchyma, are assumed to be negligible and are ignored in the analysis. This, however, does not preclude their existence.

ANALYSIS

Folding of the bronchial mucosal layer such as the one shown in Fig. 1 is assumed in our model to be due to tethering between the basement membrane and the wall of the muscle layer. The critical structural components of the airway wall (Fig. 2) for this model consist of the outer L-S layer attached to the smooth muscle layer (with a radius $R_m$), the basement membrane (with a radius $R_b$ when fully extended), and the...
L-S layer. Four major assumptions are made in the mathematical simulation of airway constriction.

1) The L-S material behaves like a liquid; that is, it is deformable and yet incompressible. Its volume (or area in a two-dimensional model) is conserved during bronchoconstriction.

2) The basement membrane is inextensible, and therefore its surface (or perimeter in a two-dimensional model) is conserved during bronchoconstriction.

3) Tethers that anchor points on the basement membrane to the muscle wall are inextensible; therefore, the radial distance between the point of anchor on the basement membrane and muscle wall is constant during bronchoconstriction.

4) The tethers are equally spaced along the perimeter of the airway ring. Consequently, the folding pattern of the basement membrane is symmetrical. In addition, there are several minor assumptions. These minor assumptions are of no consequence as far as the conclusions reached in the analysis are concerned, but they greatly simplify the simulation.

1) The angular slope \( \frac{dR}{d\theta} \) (Fig. 2) of the basement membrane is zero at the point of tethering due to a finite value of flexural rigidity of the membrane.

2) The angular slope of the basement membrane is zero at the midpoint between two tethers, a result of minimization of local radii along the perimeter of the basement membrane.

3) When the airway ring is fully dilated, the...
basement membrane perimeter is perfectly circular. 4) The length of all tethers is the same, and it equals the thickness of the L-S layer (t, Fig. 2) in the relaxed or fully dilated state.

The simulation starts with calculation of the L-S area (A) in the relaxed state (Fig. 2)

\[ A_{L-S} = \pi(R_o^2 - R_i^2) \]  

(1)

Basement membrane perimeter (P_{bm}) is then calculated (Fig. 2, thick inner circle)

\[ P_{bm} = 2\pi R_i \]  

(2)

\[ R_o \text{ and } R_i \text{ represent values of radii when the airway is fully dilated. We use } r_o \text{ and } r_i \text{ to designate the corresponding values of radii during bronchoconstriction (Fig. 3). As the outer perimeter (2\pi r_o) of the L-S layer shortens (due to muscle contraction), it causes constriction of an imaginary circle (with radius } r_i \text{) that connects the points where the tethers anchor to the basement membrane (with a circumference } 2\pi r_i, \text{ as shown in Fig. 3, dotted circle). The relationship between } r_o \text{ and } r_i \text{ is} \]

\[ r_i = r_o - t \]  

(3)

where t is the length of the tether, which also equals the thickness of the L-S layer in a fully relaxed airway; t remains constant throughout constriction.

As the airway constricts, the area contained in \( \pi(r_o^2 - r_i^2) \) becomes smaller and smaller compared with the area \( \pi(R_o^2 - R_i^2) \), which is assumed to be conserved during constriction. The area difference \( \pi(R_o^2 - R_i^2) - \pi(r_o^2 - r_i^2) \) therefore must equal the area bounded by the folded perimeter of the basement membrane (Fig. 3, thick curve) and the circle with radius \( r_i \) (Fig. 3, dotted circle). Theoretically, there are infinite ways to fill up an area bounded by a fold with no definite shape. The computer is instructed to fill the given area, with constraints that the L-S area and \( P_{bm} \) length must be conserved, and also it is instructed to set the angular slopes at the points of tether attachment to basement membrane and at midpoint between two tethers on the membrane to zero (as illustrated in Fig. 3). To speed up the simulation, the initial shape of a half-fold is assumed to be sigmoidal (in polar coordinates). The initial condition, however, does not limit the final outcome. The final shape of the curve (mathematically speaking) is not known. An exhaustive searching method is used to determine the contour of \( P_{bm} \), until all constraints are met within 0.1% tolerance. The choice of 0.1% tolerance is arbitrary; we do find that the shape of the curve changes slightly with different levels of tolerance. When the simulation reaches a point at which further decreases in the value of \( r_o \) would invariably cause the perimeter length to exceed the value of \( P_{bm} \) defined by Eq. 2, simulation stops and the maximum (Max) amount of shortening are calculated as follows

\[ \text{Max shortening} = 2\pi(R_o - r_o) \]  

(4)

The area of the lumen (A_{lumen}) in the maximally constricted airway equals the area \( \pi r_o^2 \) minus the L-S area \( \pi(R_o^2 - R_i^2) \) (Eq. 1). The area of the lumen therefore is

\[ A_{lumen} = \pi[r_o^2 - (R_o^2 - R_i^2)] \]  

(5)

Because of the assumed symmetry, simulation is carried out for the angular domain of \( \pi/n \) only, where n is the number of folds (or tethers).

**RESULTS**

Figure 4 is a computer-generated plot simulating constriction of four bronchi with the same initial \( R_o \) and \( R_i \) but with different values of n. Figure 4, top left,
depicts a fully dilated airway cross section, with a fully extended basement membrane (thick curve). The area bounded by the thick and thin circles is the L-S area, which is assumed to remain constant throughout contraction. The thickness of the L-S layer is assumed to be 20% of \( R_o \) in this particular simulation. Tethers are not shown for sake of clarity, but it is assumed that each fold is associated with a tether, as illustrated in Fig. 3. For the cases of \( n \) equal to 8, 16, and 24 (Fig. 4), the airways are fully constricted in each case. Any further constriction of the outer perimeter (thin circles) will invariably result in stretching the basement membrane (thick curves) or breaking the tethers. The L-S area is conserved in each case. It is observed that, as the number of folds or tethers decreases, the airway is able to shorten further before it reaches the point at which geometric and kinematic limitations in the L-S layer prevent the smooth muscle from further shortening. Because of the assumptions that the basement membrane and the tethers are inextensible and the L-S material is incompressible, the pressure (resulting from smooth muscle contraction and the geometric-kinematic restrictions of the airway wall structure) in the L-S layer would be infinite if shortening continues beyond the point at which the membrane and tethers are fully stretched.

Figure 5 is another computer-generated plot simulating constriction of four bronchi with the same initial \( R_o \) and \( n (n = 16) \) but with different values of \( t \). The initial (precontracted) lumen areas are different, that is, larger with a thinner L-S layer. In the maximally contracted state (as plotted), the largest fractional change in lumen area occurs where the L-S layer is thinnest, illustrating the effect of the thickness of L-S layer on airway narrowing. In terms of absolute lumen area, the effect of L-S layer thickness is not as straightforward. With a fixed \( R_o \), an extremely thick L-S layer could occlude most of the airway even in the relaxed state. The thick-walled airway, however, is not able to narrow much as the simulation suggests. There appears to be an optimal value for \( t \) (in this simulation, a \( t/R_o \) value of \( \sim 0.2 \)) for maintaining the largest absolute lumen area in maximal contraction.

The maximal amount of shortening calculated according to Eq. 4 and the associated minimal lumen area (relative to the initial area) calculated according to Eq. 5 are plotted in Fig. 6 as functions of \( n \). The minimum number of \( n \) in this case (where \( t/R_o = 0.2 \)) is 5. Any further decrease in \( n \) would result in touching of the opposite sides of the basement membrane (the epithelial layer is neglected in the simulation), a situation that requires a more complicated simulation to resolve. Graphic solutions for maximal shortening and minimal relative lumen area for \( n = 8, 16, 24 \) can be obtained directly from Fig. 4.

Figure 7 summarizes the relations among maximal fractional shortening, \( n \), and \( t \). Figure 8 summarizes the relations among minimal relative lumen area, \( n \), and \( t \). Some of the quantitative information contained in these figures can be visualized in Figs. 4 and 5. In general, as \( n \) or \( t \) increases, the maximal fractional shortening decreases. Although it is not intuitively obvious, the model suggests that an increase in \( t \) will, in most cases, reduce airway narrowing in maximally contracted airways. For example, at \( n = 14 \), the minimal relative lumen area (maximally contracted lumen area divided by precontracted lumen area) is 0.9619 for \( t/R_o = 0.6 \); however, for \( t/R_o = 0.05 \), the relative lumen area is 0.0487. Even in absolute terms, the model predicts that the airway with a thicker L-S layer will maintain a
larger lumen area (excluding extreme cases in which \( t/R_0 \) is much greater than 0.6). With the use of the same example of \( n = 14 \), an airway with \( R_0 = 1 \) and \( t = 0.6 \) will have a final lumen area of 0.4835 \((0.4835 = 0.9619\pi (R_0 - t)^2)\). Another airway with \( R_0 = 1 \) and \( t = 0.05 \) will have a final lumen area of 0.1381 \((0.1381 = 0.0487\pi (R_0 - t)^2)\). The airway with the thicker L-S layer therefore has a final absolute lumen area 3.5 times greater than the one with the thinner L-S layer after both have been maximally constricted. The thicker the L-S layer, the less the folds are required to prevent the membranes on opposite sides of the lumen from touching. The relationship between \( t/R_0 \) and the minimal values for \( n \) is shown in Table 1.

**DISCUSSION**

Histological examination of bronchial sections has revealed that in a constricted bronchus the mucosal layer [which includes the epithelial layer, the basement membrane, and lamina propria (1)] develops numerous folds (Fig. 1), and, even in very constricted bronchi, the mucosal membranes on opposite sides of the lumen do not touch (4, 20). These observations have raised important questions. Why does the mucosal layer develop many folds in a constricted bronchus instead of adopting the more energetically favored twofold conformation (7), such as that seen in a collapsed airway under negative transmural pressure? Why does a bronchus not collapse easily? Mathematical models have been developed in an attempt to explain the folding behavior of the noncartilaginous airways (7, 8, 18). Flexural rigidity of the mucosal layer (especially the basement membrane) is crucial for these models because the source of resistive force is assumed to stem from bending of the layer. Unfortunately, there are no data available for flexural or compressive mechanical properties of the airway basement membrane or the mucosal and submucosal material; therefore, any predictions of the resistive force or pressure by these models can only be regarded as theoretical speculations.

The observation that there is an abundance of collagen fibers in the L-S layer (Fig. 1A) and the fact that most of the collagen fibers are oriented perpendicularly to the muscle layer (Fig. 1B) suggest that the collagen fibers may play a role in the folding of the mucosal layer during bronchoconstriction. It appears that the basement membrane is attached to the muscle layer through these collagen fibers. The collagen fibers therefore act as tethers that anchor points on the basement membrane to the muscle wall. The relatively inextensible basement membrane and collagen tethers combined with the fluidlike L-S material therefore form a structure that is capable of resisting constriction of the muscle layer. High tensile strength of the basement membrane and the collagen tether is important for the structure to function effectively. On the basis of these observations, the load-bearing ability of the L-S layer under compression is assumed, in our model, to stem from the pressure resulting from compression of the L-S material bounded by the constricting muscle wall and the inextensible basement membrane. The L-S layer is assumed to be highly deformable but incompressible, a property shared by incompressible fluids.

The assumption that the basement membrane and the collagen tethers are inextensible is purely for the purpose of simplifying the simulation. For a slightly more complicated simulation, a finite elasticity can be assumed for the membrane and the tethers, and a more realistic result could be obtained. An elastic structure
also allows the muscle to regulate the airway caliber within a range. The conclusions reached by the present simulation, however, will not be altered by the introduction of elasticity to the basement membrane or the collagen tethers.

The many folds that develop in the basement membrane in a relatively symmetrical way during bronchoconstriction suggest that the folding is not random, and some structural basis such as tethering may underlie this phenomenon. Mitzner and Wagner (10) observed in their preparations that there is often a blood vessel at the base of the mucosal fold, suggesting that the folding pattern may be structurally predetermined. We propose that tethers between the basement membrane and the inner muscle wall play an important role in the folding in the basement membrane when the airway is constricted (Fig. 3). The folding is perhaps better described as bulging, since the protrusion is assumed to be due to displacement of L-S material forced into the luminal domain by constricting muscle layer. The importance of having the tethers, from a mechanical point of view, is that the high tensile strength of the basement membrane (10 MPa (17)) can be effectively utilized (in the tensile mode) to withstand the pressure in the L-S layer due to muscle contraction. It also provides a possible explanation of why there are usually many folds of the mucosal layer associated with a constricted airway (which no other models seem to be able to explain). Nature seems to have created a rigid structure out of materials that possess almost no compressive shear strength to counteract the force of muscle contraction and prevent noncartilaginous airways from collapsing.

There is structural evidence supporting some of the assumptions that our model is based on. Conservation of basement membrane perimeter and L-S area assumed in the model is consistent with morphometric measurements made by James et al. (3, 5). The tensile strength of the basement membrane of a renal tubule has been found to be ~10 MPa (17). Similar measurement in bronchial basement membrane has not been done. Because the molecular composition of the renal tubular and bronchial basement membranes is similar (16), it is likely that the tensile strength of bronchial basement membrane is also on the order of 10 MPa, which is about one-third the strength of solid aluminum! Therefore, the assumption that the basement membrane is indistensible is reasonable considering the intraluminal pressure generated by the muscle is far less than 10 MPa.

Figure 4 illustrates that it is possible to construct a compression-resistant structure out of liquidlike material and materials that possess only tensile strength. It should be noted that the resistance stems from the pressure in the L-S layer, which in turn is generated by muscle contraction and the geometric and kinematic constraints of the airway wall. A relaxed airway will collapse easily if it is compressed, just like a deflated rubber raft incapable of resisting bending force of the waves. Figure 4 further illustrates that the more folds in the basement membrane the less the airway can constrict. These findings are similar to those found by Lambert (7) and Wiggs et al. (18) in their simulation but for an entirely different reason. In their model, buckling pressure increases with the number of folds. When an airway develops many folds, it is thus more resistant to the collapsing pressure. In our model, the limiting factor to muscle shortening is not the bending resistance in the mucosal membrane but the restrictive movement of the basement membrane due to tethering.

For a $t/R_o$ value of 0.2, a 40% shortening of the muscle layer will almost totally occlude the airway, as illustrated in Fig. 6. As the number of folds (or tethers) increases, the structure becomes more effective in resisting compression, and the maximal amount of shortening the muscle is capable of producing against the load is accordingly reduced. Besides the number of folds, thickness of the L-S layer in our model is another crucial parameter determining the rigidity of the structure under compression. For the same value of $n$, maximal shortening of the muscle is drastically reduced with an increase in the value of $t$, as shown in Fig. 5. Figure 7 shows the results in terms of maximal fractional shortening; Fig. 8 shows the same results in terms of lumen area. The thinner the L-S layer, the more folds in the basement membrane are needed to prevent the airway from collapsing, and vice versa, as indicated by the values in Table 1. An interesting conclusion derived from these results is that a thicker L-S layer is actually beneficial in terms of maintaining a larger lumen area. This conclusion is supported by morphometric measurement of submucosal area vs. lumen area by Lambert et al. (8) and Okazawa et al. (14). The model simulation of Lambert et al. also reached the same conclusion, although via a different route of reasoning. In their model, both the basement membrane and the L-S layer are assumed to possess flexural rigidity; a thicker layer thus confers more stiffness to the airway wall and renders it more resistant to muscle shortening. In our model, with no flexural rigidity attributed to both the basement membrane and the L-S layer, the ability of a thickened L-S layer in reducing muscle shortening is due to the decreased surface (basement membrane)-to-volume (L-S

### Table 1. Relationship between the relative lamina propria-submucosa layer thickness and the minimum number of folds required to prevent touching of mucosal membranes of opposite sides of the lumen

<table>
<thead>
<tr>
<th>$t/R_o$</th>
<th>0.05</th>
<th>0.10</th>
<th>0.15</th>
<th>0.20</th>
<th>0.25</th>
<th>0.30</th>
<th>0.35</th>
<th>0.40</th>
<th>0.45</th>
<th>0.50</th>
<th>0.55</th>
<th>0.60</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>11</td>
<td>8</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
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<td>2</td>
</tr>
</tbody>
</table>

$t/R_o$, Relative lamina propria-submucosa layer thickness; $n$, minimum number of folds. Note that $n$ is an integer in the model of simulation.
material) ratio that reduces the degree of freedom of the tethered basement membrane and thus increases the effectiveness of the geometric and kinematic constraints that limit airway narrowing. Another more intuitive way of explaining the results graphically illustrated in Fig. 5 is that, for each of the four cases, the same amount of muscle shortening (reduction in $r_o$) results in displacement of equal quantity of L-S material into the space previously occupied by the lumen area. The airway with the thicker L-S layer has less basement membrane surface; the spacing between the tethers on the basement membrane is also smaller. These geometric changes accompanying L-S layer thickening greatly reduce the ability of the airway wall structure to accommodate the movement of L-S material into the lumen domain.

Airway remodeling in asthma and chronic obstructive pulmonary diseases (COPD) is characterized by a thickening of the submucosal layer (6). Although it has been suggested that thickening of this layer may amplify the luminal narrowing produced by a given amount of ASM shortening (19), the present modeling suggests that such thickening could also play a protective role by attenuating the amount of smooth muscle shortening. The same conclusion is reached by Lambert et al. (8). Another implication of the modeling is the proposed nomenclature for quantifying subdivisions of the bronchial wall. Lambert et al. (8) introduced a term for the proportion of smooth muscle shortening in excised canine lung lobes. Lambert et al. (8) defined the geometric and kinematic constraints provided by this structure counteract the force generated by the muscle layer and limit the extent of constriction. Computer simulation indicates that the extent of bronchoconstriction is inversely proportional to the number of tethers (or mucosal folds) and the thickness of the L-S layer.

In conclusion, an effective load-bearing structure in an airway is postulated to be composed of basement membrane and collagen tethers that confine the L-S material. The geometric and kinematic constraints provided by this structure counteract the force generated by the muscle layer and limit the extent of the constriction. Computer simulation indicates that the extent of bronchoconstriction is inversely proportional to the number of tethers (or mucosal folds) and the thickness of the L-S layer.

This work was supported by operating grants from the Medical Research Council of Canada (MRC) and British Columbia Lung Association to C. Y. Seow and P. D. Pare. C. Y. Seow is the recipient of a MRC scholarship. L. Wang is the recipient of a MRC/British Columbia Lung Association fellowship.

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Received 23 December 1998; accepted in final form 22 October 1999.