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# Possible role of differential growth in airway wall remodeling in asthma

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**Moulton DE, Goriely A.** Possible role of differential growth in airway wall remodeling in asthma. *J Appl Physiol* 110: 1003–1012, 2011. First published January 20, 2011; doi:10.1152/japplphysiol.00991.2010.— Airway remodeling in patients with chronic asthma is characterized by a thickening of the airway walls. It has been demonstrated in previous theoretical models that this change in thickness can have an important mechanical effect on the properties of the wall, in particular on the phenomenon of mucosal folding induced by smooth muscle contraction. In this paper, we present a model for mucosal folding of the airway in the context of growth. The airway is modeled as a bilayered cylindrical tube, with both geometric and material nonlinearities accounted for via the theory of finite elasticity. Growth is incorporated into the model through the theory of morphoelasticity. We explore a range of growth possibilities, allowing for anisotropic growth as well as different growth rates in each layer. Such nonuniform growth, referred to as differential growth, can change the properties of the material beyond geometrical changes through the generation of residual stresses. We demonstrate that differential growth can have a dramatic impact on mucosal folding, in particular on the critical pressure needed to induce folding, the buckling pattern, as well as airway narrowing. We conclude that growth may be an important component in airway remodeling.

mucosal folding; chronic asthma; growth; elasticity; instability

ASTHMA IS A DISEASE CHARACTERIZED by a narrowing of the airway and reduced lung function. Chronic asthma is often accompanied by irreversible structural changes to the airway wall, collectively referred to as airway remodeling (43). Airway remodeling is a complex process occurring at multiple time and length scales and involving many different chemical, biochemical, and physical stimuli. Despite a wealth of research it is still not clear how each of the different structural changes individually affects airway function (51), nor is it known whether these different changes are beneficial or detrimental to asthmatic patients (32). A well documented key feature of airway remodeling is an increase in airway wall thickness, detected at all levels of the bronchial tree and all layers of the airway wall (19, 22, 24, 36).

In this theoretical paper, we focus on the mechanics of airway wall thickening and the mechanism of mucosal folding at a macroscopic level by building a model based on the most sophisticated constitutive theory for elastic tissue available in the bioengineering literature. In response to certain stimuli, the smooth muscle surrounding the airway wall contracts and the luminal boundary folds or buckles—this is the phenomenon of mucosal folding. In "normal patients," such an event is marked by only modest narrowing of the airway (34). In asthmatic patients, however, this airway narrowing tends to occur for lower stimuli and also leads to exaggerated narrowing (23).

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Mucosal folding is also observed in the esophagus (28, 57), blood vessels (27), and gastrointestinal tract (30). On a mechanical level, this folding indicates an instability of the inner mucosal edge in response to an external pressure provided by the contraction of smooth muscle. A number of models have looked at mechanical and geometrical aspects of mucosal folding. Some of the key issues from a modeling perspective are: determining the critical buckling pressure, critical buckling mode (i.e., the number of folds in the buckled state), and the degree of airway narrowing; finding relationships between these quantities; and determining the impact of airway wall thickness. Lambert (25) modeled the basement membrane as a single layer elastic tube and showed that the buckling mode can have a dramatic impact on airway narrowing; in particular that an airway with fewer folds will have a greater degree of occlusion if the folds extend until epithelial cells come into contact. This basic model was expanded on in Ref. 26, in which a geometric constraint was included as a mechanism for selecting the number of folds and was further expanded to include a thin layer of fluid on the inner edge of the airway allowing for possible surface tension effects (15). Other geometry based models have been proposed (including Ref. 47) in which inextensibility of the basement membrane was taken as a geometrical constraint, and the number of folds was directly connected to tethers between the airway and smooth muscle; and Donovan and Tawhai (6), who studied effective airway radius given fixed folding geometry. Wiggs et al. (54) put the problem on a more mechanical level, in which the airway was modeled as a bilayered elastic tube. Solving the buckling problem in a finite element analysis, they found wall thickness to have a significant effect on the buckling mode and degree of narrowing. Similar models, also solved with finite elements, were presented a few years later, also incorporating inertial effects of the basement membrane (3) and a comparison with buckling experiments with rubber tubes (18).

There are two potential drawbacks to previous models that should be elucidated. First, it is important to note that none of these models allowed for nonlinear material responses to large deformations, which are common in airway narrowing (37). Over the past decade, it has become increasingly clear in studying the mechanical properties of biological tissues that nonlinear tissue response, inhomogeneity, and remodeling are important, if not crucial, features (8). The importance of nonlinear elasticity in biological systems is well documented and appreciated in the case of arteries (9, 13, 17, 40, 48), heart (29), muscles (49), brain tissue (55), and many other plants (12, 50) and biological systems (48). It is clear that to understand both the mechanical response and remodeling processes in airways, a constitutive theory based on nonlinear elasticity is required.

Second, a potentially important assumption in previous mechanical models is that the mechanical properties of the airway wall do not vary during remodeling, despite evidence that these

properties might be altered (21). That is, airway wall thickness is explored by varying reference dimensions, without any account for how the dimensions might have changed and whether mechanical properties might have varied in the process. This is a key distinction, and underlies the primary question we seek to answer in this paper: could growth significantly impact the mechanical response of the airway to smooth muscle contraction beyond the change in geometry and thus be an important factor in airway remodeling?

The structural changes involved in airway remodeling fall into the large category of processes known in the bioengineering literature as growth and remodeling of elastic tissues. Growth in biological systems can be the result of many different processes. Continuum mechanics and the theory of elasticity have long been used to study growth processes and the mechanical properties of growing tissues. It is now understood that biological materials commonly exhibit differential growth; that is the tissue does not grow equally in all directions and/or different parts of the tissue grow at different rates. Differential growth can profoundly alter the geometry and mechanical properties of a material. Local changes of mass induce not only a change in the geometry but also elastic stresses that cannot be eliminated geometrically and thus generate so-called residual stresses, which persist in the absence of external loads on the material. Residual stress is a hallmark of biological tissues and plays a key role in the regulation of many biological systems, including arteries (13, 16, 20), blood vessels (7), the human aorta (17), and plant stems (50).

In this paper, we model the airway as a two-layer cylindrical structure and take into account both geometrical and material nonlinearities by using the theory of finite elasticity (39). The growth of the airway is described via the theory of morphoelasticity and the buckling of the airway is computed using an incremental deformation stability analysis (2). As mentioned, the model presented here combines both the nonlinear response of the tissues in large deformation and the effect of growth, features that are absent from previous modeling attempts. [Note Yang et al. (57) recently presented an interesting analysis using the same machinery of finite elasticity for a model of the esophagus, but did not consider growth.] Using this model, we demonstrate that differential growth, in particular anisotropic growth, can have a dramatic impact on the critical pressure exerted by smooth muscles needed to trigger buckling, the number of folds, the buckling pattern, and the degree of airway narrowing. Growth can also alter stability properties and lead to seemingly counterintuitive results, for example an airway wall may become thicker while losing stability. Our results highlight the importance of mechanical effects due to growth and suggest a need for further experimental research along these lines. Indeed, our hypotheses may be tested by direct measurement of residual stress (31).

## MODEL AND METHODS

We model an airway segment as a bilayer cylindrical structure, considering only tissue interior to the smooth muscle. Following the model given by Wiggs et al. (54), a stiff and thin inner layer corresponds to the mucosal region, consisting of the basement membrane, the lamina propria, and the epithelium (1). Surrounding this is a portion of the submucosa region, consisting of loose connective tissue. The inner layer is much thinner and stiffer than the outer layer.

The airway smooth muscle (ASM) surrounds the outer layer, with ASM contraction providing a force that deforms and eventually buckles the tube. ASM contraction is a fairly complex process, and several models have been formulated to couple the underlying chemical processes to mechanics (5, 42, 53). The net mechanical effect of ASM contraction is a normal force applied at the airway wall-smooth muscle interface (42). Since our purpose here is to focus on growth and buckling, ASM contraction is taken into account as an applied normal pressure boundary condition at the outer edge. Also, since mucosal folding occurs at the mucosal region while the smooth muscle remains roughly circular (26), we impose the boundary condition that the outer edge remain circular in the deformed, buckled state.

The setup is depicted in Fig. 1. Material dimensions for the undeformed, reference airway are the inner radius $A$, the thickness of the inner layer, $B - A$, and the thickness of the outer layer $C - B$. We assume an isotropic, incompressible hyperelastic material (4). To characterize the difference in stiffness between the two layers, the value of the shear modulus is assumed different in each layer; thus we have the parameters $\mu_1$ and $\mu_2$.

The model is three dimensional but assumes only plane strain deformation, so that the deformation is uniform along the tube axis. The basic idea behind the analysis is that as the smooth muscle contracts, it creates a pressure normal to the circular cross section and the tube deforms in a symmetric fashion, maintaining its circular shape, until a bifurcation point is reached at a critical pressure, at which point the cylinder "buckles" to an asymmetric state. The typical output of our mathematical model will be the value of the critical pressure. Physiologically, this can be linked to the magnitude of contractile force of the ASM necessary to induce buckling of the airway. While the precise relationship between normal pressure and contractile force is nontrivial and would require knowing material properties of the smooth muscle, it is a monotonic relationship. Thus an increase in critical pressure corresponds to a greater contractile force for buckling. In terms of airway hyperreponsiveness, buckling pressure (or contractile force of ASM for buckling) provides a good measure of the "strength" of an airway. This issue is discussed more fully in the DISCUSSION.

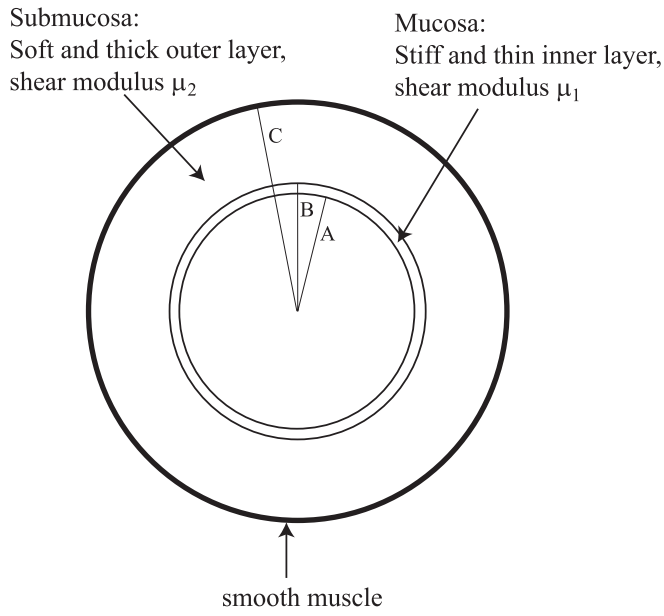


Fig. 1. Bilayer model of airway wall, consisting of a stiff and thin inner layer, the mucosa, and a soft and thick outer layer, the submucosa. Surrounding the submucosa is smooth muscle, which applies a normal pressure when it contracts.

The buckling analysis follows the incremental theory (52). Mathematically, it consists of a linear stability analysis for a solution of mechanical equilibrium in finite elasticity. A nonsymmetric perturbation is added to a symmetric finite deformation, and the equations of mechanical equilibrium are expanded in terms of the perturbation parameter, resulting in a fourth-order differential equation for the radial displacement of the nonsymmetric deformation. A solution to the bifurcation equation indicates buckling of the tube. In this formulation, the pressure due to ASM contraction appears as a boundary condition for the initial symmetric deformation while the requirement that the outer edge always remains circular appears as a boundary condition when solving for the nonsymmetric deformation. Also, note the distinction that large deformations and nonlinear tissue response are built into the model by the use of the theory of finite elasticity, but the buckling parameters are determined via a linear stability analysis. This approach has the advantage that buckling properties can be analyzed efficiently without the need for complex and expensive numerical techniques. The drawback, which we return to in the DISCUSSION, is that the deformation cannot be tracked beyond the instability. A full derivation of the growth and bifurcation equations, as well as our approach to solving the bifurcation equation, can be found in Ref. 35.

The buckling mode number, which is the number of folds in the buckled state, enters as a parameter in the bifurcation equation. For each mode number, a critical pressure is found. This critical pressure represents the pressure necessary to induce buckling at that particular mode. The actual buckling pressure observed in an ideal experiment is the smallest critical pressure over all modes, and the corresponding mode defines the expected buckling pattern.

Growth is included in the analysis via the theory of morphoelasticity and multiplicative decomposition of the deformation tensor (11, 46). The basic concept is that the deformation of the body is due to a local change of mass and to an elastic deformation. Since the change of mass is expressed locally, neighboring "cells" can grow differentially. In the absence of elastic deformation, this can induce incompatibilities such as overlapping cells or separation of tissue. The elastic deformation then brings the material back to a compatible configuration; this step can be seen as an elastic response to growth and can induce residual stress in the material.

The effect of symmetric growth in each layer is captured by two parameters per layer, instructing the gain or loss of mass in the radial and circumferential directions. We denote these growth parameters $\gamma_r^{(i)}$, $\gamma_\theta^{(i)}$, $\gamma_r^{(o)}$, $\gamma_\theta^{(o)}$. Here $\gamma_r$ corresponds to radial growth, with a gain or loss of mass in the radial direction if $\gamma_r$ is greater than or less than 1. The addition or loss of mass in the circumferential direction is captured by $\gamma_\theta$, where $\gamma_\theta > 1$ corresponds to circumferential growth and $\gamma_\theta < 1$ to circumferential resorption. Figure 2 gives a schematic of radial vs. circumferential growth. The superscript differentiates the inner and outer layers. In general, these parameters can be functions of radius, which would signal the case of different "rings" of the airway growing at different rates. Here we consider anisotropic but homogeneous growth in each layer, thus the $\gamma$s are constant but not equal.

As our results are largely focused on varying these parameters, it is instructive to further clarify their meaning via a simple example. Consider a single layer tube with radii $A = 1$, $B = 2$, with no applied pressure and three different forms of growth:

*1*. $\gamma_r = 2$, $\gamma_\theta = 2$. The parameter values imply that there is a doubling of mass in both the radial and circumferential directions. Since growth is isotropic and no other forces are applied to the system, the deformed grown tube has radii $a = 2$, $b = 4$, highlighting a doubling of all radial and circumferential lines. In this case, no residual stress is generated.

*2*. $\gamma_r = 1$, $\gamma_\theta = 2$. In this case, there is growth only in the circumferential direction. To account for the anisotropic growth, the tube expands to a larger total radius, while keeping nearly the same length of radial lines. A numerical computation gives that the tube after growth has radii $a = 2.48$, $b = 3.49$. The growth induces a slight tensile radial stress. There will also be circumferential stress, namely the inner edge will be in tension and the outer edge in compression.

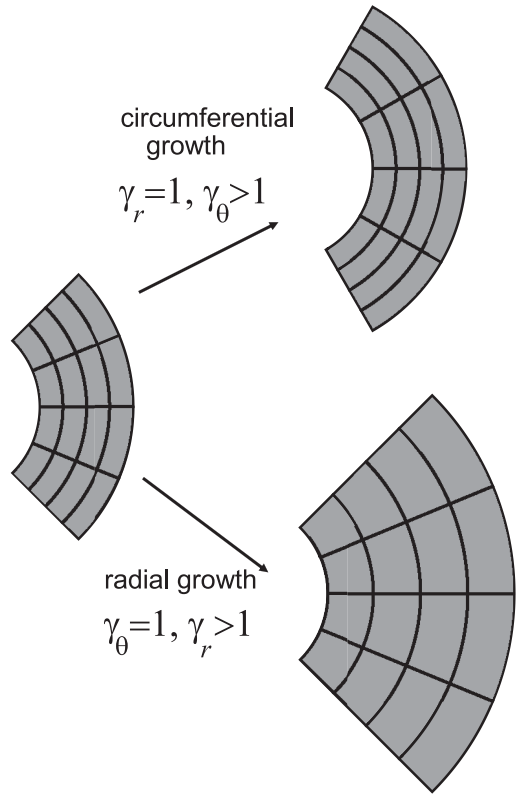


Fig. 2. Transformation of an area element under circumferential vs. radial growth.

*3*. $\gamma_r = 2$, $\gamma_\theta = 1$. Here, growth occurs only in the radial direction. A numerical computation gives the radii after growth as $a = 0.69$, $b = 2.54$; in this case radial lines want to double in length but are constrained, thus the anisotropic growth induces a compressive radial stress.

To further understand the effect of growth, if we were to plot pressure-area curves (prebuckling), the area would decrease more rapidly with increased external pressure in *case 2* than in *case 3*. This can be understood in terms of the stress induced by the growth. In *case 2*, the inner edge is in tension, i.e., there is a positive circumferential stress, whereas the inner edge is in compression in *case 3*, corresponding to the compressive radial stress. Thus, in *case 2* the inner edge tends to shrink to relieve the tension, and the area will decrease more rapidly with applied pressure.

### *On Material Properties*

In this paper we will present results for a neo-Hookean strain energy function $W$, given by $W = (\mu/2)(\alpha^{-2} + \alpha^2 - 2)$, where $\mu > 0$ is the shear modulus, and $\alpha$ is the circumferential elastic stretch. Lacking data to classify the exact material properties of the airway wall, it is worthwhile to check the implications of using a neo-Hookean strain energy. Note that a neo-Hookean material exhibits strain-softening properties. A common strain-energy function for biological tissues that exhibits strain-stiffening is the Fung model, given by $W = (\mu/2\beta)\{\exp[\beta(\alpha^{-2} + \alpha^2 - 2)] - 1\}$. The parameter $\beta$ typically takes a value between 3 and 20 for soft tissues (10), and the Fung model approaches the neo-Hookean model in the limit of $\beta \rightarrow 0$. In Fig. 3, we plot pressure vs. area for the symmetric deformation of a bilayered tube for the neo-Hookean model, Fung model with both $\beta = 3$ and $\beta = 20$, and also for a linear elasticity model. Each model

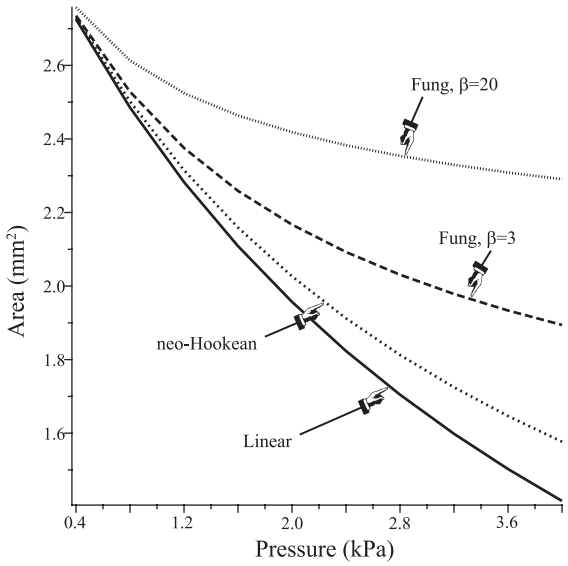


Fig. 3. A comparison of pressure vs. area for the symmetric deformation of a bilayered tube for 4 different forms of model. Parameters are A = 0.98, B = 1, C = 1.5, $\mu_1 = 40$, and $\mu_2 = 4$.

gives qualitatively similar pressure area relationships as expected, but a significant quantitative difference exists between each curve. Thus the importance of including nonlinearity should be clear; in particular there is a significant difference between the linear model and the Fung model at large pressure. As there is also a significant quantitative difference between the neo-Hookean and Fung curves, the question remains how dependent our results are on the choice of strain-energy. Although the results presented below are only for the neo-Hookean model, we also explored the same relationships for a Fung model and have found the same qualitative results, with the quantitative difference that effects are amplified, i.e., a more drastic change in buckling pressure and mode occurs. Since our intent is to provide a general framework for understanding the impact of growth on mucosal folding and asthma, and for a more streamlined presentation, we omit results with the Fung model.

## RESULTS

The bilayer model described above, with two growth parameters for each layer, admits a large parameter space. As our goal is to investigate the effect of growth on the buckling of a normal vs. a remodeled airway, we will primarily keep reference dimensions of the airway fixed and change the thickness of the airway by varying the growth parameters. In this way the growth defines a deformation from the normal airway to the remodeled airway. In prior studies, thicker airways have been studied by changing the reference dimensions themselves, without any particular mechanism to account for the change. By keeping the reference dimensions fixed and altering the growth parameters, we can explore the effect of thickness on the buckling, but we are able to account for the change of thickness as well as the changes in material properties resulting from additional residual stresses. We use as reference "normal airway" dimensions the base values A = 0.98, B = 1, C = 1.5, $\mu_1 = 40$, and $\mu_2 = 4$, giving a stiffness ratio $\mu_1/\mu_2 = 10$. Here the radius values are in units of millimeters and the shear moduli in units of kilopascals. The critical pressures appearing in this paper are also measured in kilopascals. These values are motivated by physiological measurements (22, 38) and would correspond roughly to a medium sized cartilaginous airway with inner perimeter ~6.16 mm and Youngs modulus of the inner layer of 120 kPa; this choice of base values has also been used in previous airway models (18, 54). It should be noted that obtaining precise values for thickness and stiffness ratios is a challenging task and varies over generations of the bronchial tree. Thus we also explore the effect of changing reference dimensions in *Airway size*.

*Isotropic growth.* The first effect we consider is isotropic growth, but with different growth rates in each layer. That is, we assume $\gamma_r = \gamma_\theta$ in each region but that $\gamma^{(i)} \neq \gamma^{(o)}$. As an example, we let $\gamma^{(o)} = 1.2$ and vary $\gamma^{(i)} > 1$. We plot in Fig. 4 the critical pressure (Fig. 4*A*) and critical buckling mode (Fig. 4*B*) as a function of $\gamma^{(i)}$ ranging from 0.9 to 1.4. In Fig. 5 the same plots are shown with $\gamma^{(i)} = 1.2$ fixed and $\gamma^{(o)}$ ranging from 0.95 to 1.5. It should be noted that the critical buckling pressure only depends on the ratio $\gamma^{(i)}/\gamma^{(o)}$. Different values with the same ratio are equivalent up to an isotropic and equal growth multiple in each layer, so that the critical pressure does not differ (note that the airway dimensions will vary by the same scalar multiple). Thus the critical pressure for $\gamma^{(i)} = 1.2$ in Fig. 4, and for $\gamma^{(o)} = 1.2$ in Fig. 5, corresponds exactly to the critical pressure in the absence of growth (as shown by the

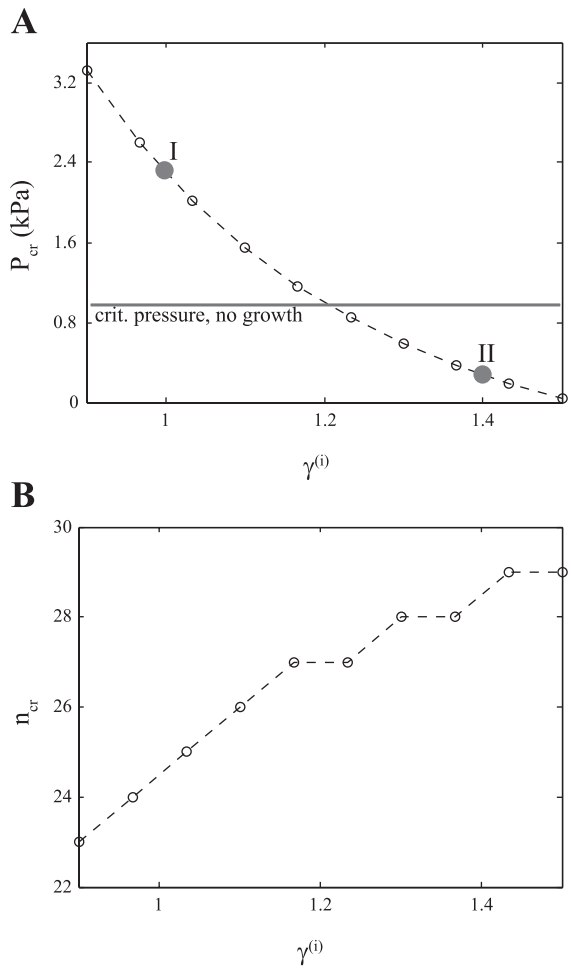


Fig. 4. Critical buckling pressure (*A*) and buckling mode (*B*) as a function of isotropic growth of the inner layer, for fixed isotropic growth in the outer layer, $\gamma^{(o)} = 1.2$.

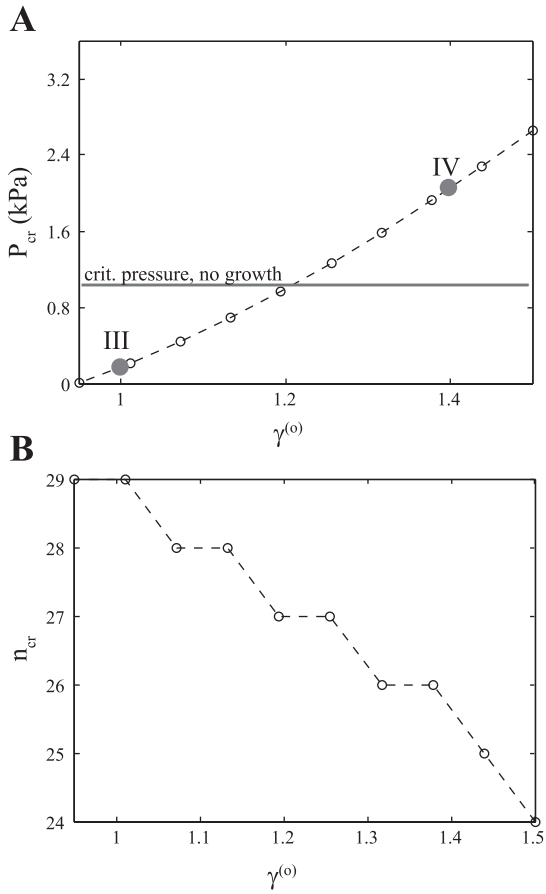


Fig. 5. Critical buckling pressure (*A*) and buckling mode (*B*) as a function of isotropic growth of the outer layer, for fixed isotropic growth in the inner layer, $\gamma^{(i)} = 1.2$.

horizontal line on the figures). Comparing the critical pressure to this reference case, it is interesting to note that when the ratio $\gamma^{(i)}/\gamma^{(o)} > 1$, the airway is less stable, i.e., it buckles at a lower pressure. On the other hand, a greater pressure is required when this ratio is less than one. In other words, the airway is weaker with respect to buckling when the inner layer grows at a greater rate than the outer layer, and likewise stronger when the outer layer grows faster. Observe that this effect is significant as the change in critical pressure increases by a factor of ~8 as $\gamma^{(o)}$ changes from 1 to 1.5.

As stated, the linear stability analysis enables us to find critical buckling parameters, but once buckling occurs we have no direct information on the magnitude of the deformation. Thus we cannot comment directly on the exact amount of narrowing of the airway after buckling occurs. Nevertheless, we can make relative comparisons of the size of the nonsymmetric deformation for different parameters. In this way, we can determine if buckling at one set of parameters should result in more or less narrowing (initially) than buckling at another set of parameter values. Buckling patterns for the points marked *I–IV* in Figs. 4*A* and 5*A* are shown in Fig. 6. Comparing *I* and *II*, in the case of $\gamma^{(o)} = 1.2$ fixed, each type of growth can be argued to have advantageous and disadvantageous features. At the lower value of $\gamma^{(i)}$, the buckling pressure is much higher but the airway narrows significantly more. If an airway were to grow with the growth rates at *point I*, it would have a greater resistance to ASM contraction but would have exaggerated narrowing when buckling occurs. At the higher value, it is the opposite: the airway narrowing is reduced but the buckling pressure is much lower. There is essentially a tradeoff between the two growth rates. This trade off does not occur in the case of fixed $\gamma^{(i)}$ (Fig. 5). The larger value of $\gamma^{(o)}$ (*point IV*) has a higher resistance to buckling and comparable narrowing to the smaller value of $\gamma^{(o)}$ (*point III*). Note that the growth ratio is nearly equal at *points I* and *IV*, but both values of $\gamma$ are higher at *IV*, and the increased growth leads to a larger airway area. Between the destabilizing growths, *III* is more detrimental to airway function as it has greater airway narrowing.

Referring to Figs. 4–5, it seems counterintuitive that more growth in the outer layer is required to strengthen the airway wall, since the inner layer is stiffer. In fact, a primary result of Wiggs et al. (54) was that increasing the thickness in the inner layer has a greater impact on buckling than increasing the thickness of the outer layer. The reasoning behind this is that differential growth creates residual stress, which induces a competition between mechanics and geometry. In particular, when the inner layer grows, it pushes against the outer layer, creating a compressive residual stress in each layer. This mechanical effect is destabilizing against external pressure, so that although geometrically the tube may seem stronger, this is outweighed by the mechanical destabilization. (Conversely, when the outer layer grows faster, it pulls the inner layer, creating a stabilizing tensile stress.) This seemingly counterintuitive result almost directly contradicts the findings of Wiggs et al. and hence highlights the important mechanical role of differential growth.

*Anisotropic growth.* In this section we consider anisotropic growth. For simplicity, we assume that the outer layer does not grow and explore buckling as a function of anisotropic growth in the inner layer by varying the ratio $\gamma_r^{(i)}/\gamma_\theta^{(i)}$. Thickening of the inner layer only occurs with radial growth. In Fig. 7, the critical pressure is plotted for $\gamma_\theta^{(i)} = 1$ fixed and $\gamma_r^{(i)}$ varying from 1 to 2. As $\gamma_r^{(i)}$ increases, the inner layer becomes thicker—it doubles in size from $\gamma^{(i)} = 1$ to 2. Correspondingly, the buckling pressure increases in a linear fashion. Again, there is a competition between mechanics and geometry: radial growth causes the inner layer to be relatively thicker—this is a stabilizing geometric effect—but at the same time creates a radial compressive stress, which is destabilizing mechanically. In this case, since the inner layer was very thin to begin with, the geometric effect is stronger and the resultant airway is more stable than before growth.

In terms of the degree of narrowing, with increasing growth the buckling mode decreases monotonically and significantly, from $n = 27$ at $\gamma_r^{(i)} = 1$ to n = 14 at $\gamma_r^{(i)} = 2$. Included in Fig. 7 are the form of the deformation at the values $\gamma_r^{(i)}$ equals 1.2 and 2. Here the effect of buckling mode is apparent. In both cases, the inner radius at the point of bifurcation is ~0.87, and both plots are produced using the same sized perturbation in the incremental deformation, but the airway narrowing is exaggerated at the point with the lower mode, $\gamma_r^{(i)} = 2$. Defining the effective lumen as the area inside the innermost point of the folds (the shaded circles), we compute that this area is 18% greater in the case $\gamma_r^{(i)} = 1.2$. Interestingly, if the anisotropic growth of the inner layer is accompanied by an isotropic swelling of the outer layer, the critical pressure is

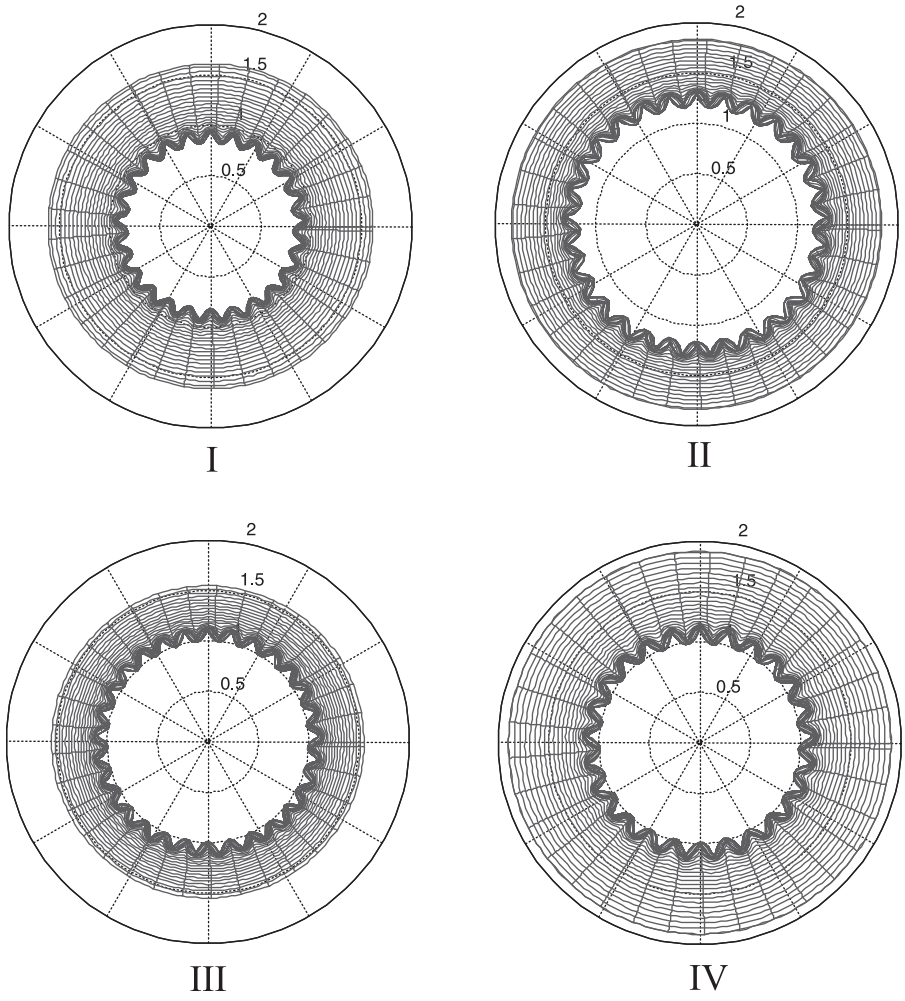


Fig. 6. Buckling patterns, or tube deformation, after bifurcation for the points marked *I-IV* in Figs. 4*A* and 5*A*.

almost doubled, while the lumen area stays roughly the same (plot not shown).

*Fixed outer radius.* The model as it has been presented does not restrict outward growth. For instance, in *case IV* of Fig. 6, notice that the outer edge is well beyond the location of the smooth muscle cells boundary before deformation (the outer radius of the reference state, equal to 1.5). This may not be realistic. It is likely that ASM, even before contracting, places a geometric constriction on the growth of the outer layer, so that the airway is restricted to grow radially outward, and must otherwise grow radially inward. The exact form of this constraint is complicated by the fact that the smooth muscle also grows during remodeling (23) and a detailed understanding of the growth relationships between the various layers of the airway is required. Nevertheless, some insight on the effect of a geometric constraint can be obtained if we fix the size of the outer radius during deformation. Mathematically, this changes the structure of the problem through the boundary condition since growth and pressure become interdependent. Fixing growth parameters automatically sets the pressure—a given growth creates pressure at the outer wall since the outer edge pushes against the smooth muscle. In this case, pressure is not a control parameter but is slaved to the growth parameters.

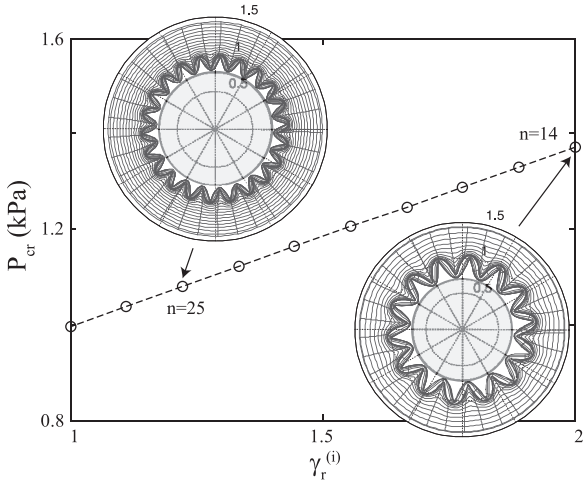


Fig. 7. Critical pressure as a function of anisotropic growth of the inner layer. All other growth parameters are set to unity.

In Fig. 8*A*, we plot the bifurcation relationship between $\gamma^{(o)}$ and $\gamma^{(i)}$ for fixed outer radius. A given value of $\gamma^{(i)}$ and the corresponding $\gamma^{(o)}$ represent a form of growth that induces buckling. For each growth pair, the corresponding pressure is plotted in Fig. 8*B*.

There are different ways to view these plots and this version of the model. If we assume that the ASM interface is rigid and does not allow any outward growth, then Fig. 8*A* shows the

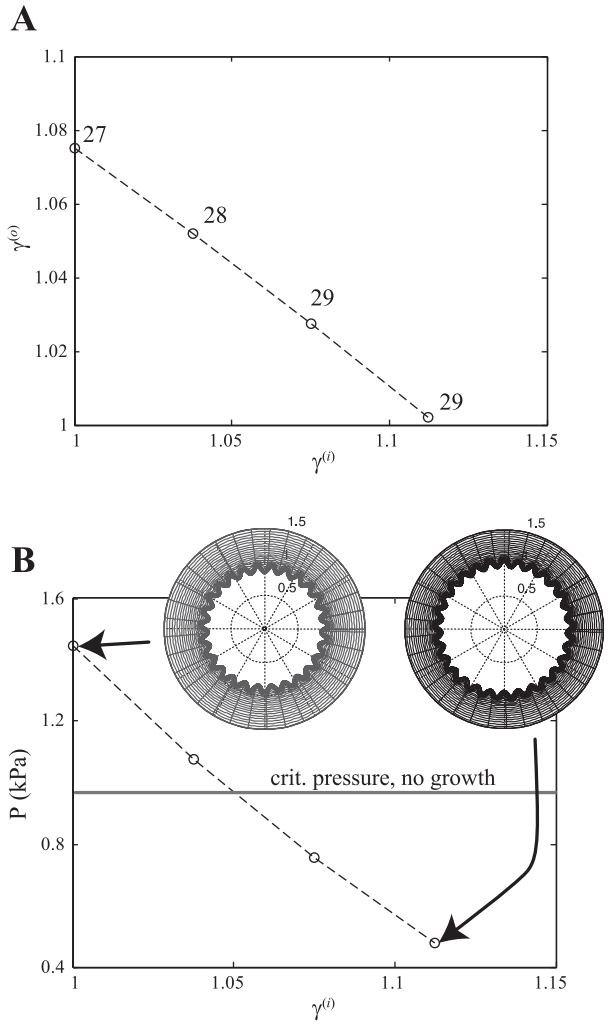


Fig. 8. Critical outer growth $\gamma^{(o)}$ (*A*) or alternatively critical pressure (*B*) as a function of inner growth $\gamma^{(i)}$, for the model with fixed outer radius. The buckling mode at each point is marked in *A*. Buckling patterns at the end points are provided in *B*.

critical growth that induces buckling and Fig. 8*B* is the pressure induced at the ASM interface due to the growth. In this sense, growth itself is inducing buckling without any required contraction of the ASM. Alternatively, if the ASM layer is compliant, then some outward growth can occur, and when the ASM contracts, the fixed outer radius requirement pushes the outer edge back to its original position. The biggest effect of the fixed outer radius condition is that the amount of growth is greatly restricted. Only the lower-left triangular region in Fig. 8*A* constitutes valid growth. Viewing Fig. 8*B*, growth can be stabilizing or destabilizing. Buckling patterns are included at the select points, indicating again a trade off whereby the stronger airway is also narrower.

*Inverse problem.* It is clearly very difficult to determine experimentally the growth rates in the different layers. However, some geometric parameters, such as the thicknesses of normal airway and asthmatic airways are accessible. This raises the question: if we knew exactly how much thicker each layer of the airway wall became during remodeling and the pressure applied by the smooth muscle, could we determine the growth parameters and the amount of differential growth that occurred? We refer to this as the inverse problem: given the details of the deformation and the buckling, can we determine the type of growth that induced the deformation? Surprisingly, this can be done. A detailed analysis of this idea is given in a companion paper (35). Mathematically, the argument can roughly be made by counting equations—there are four equations involved in determining the bifurcation of a bilayered cylinder. Since there are also four growth parameters, the inverse problem is well formulated and a solution can in principle be found. A mathematical proof of this is lacking, but in all of the simulations we have attempted, a solution has been found.

We demonstrate here with a suggestive example. We start with a reference system in the absence of growth where the critical pressure is $P^* = 0.2492$, the buckling mode is $n = 27$, and the radii at the point of buckling are $a = 0.8750$, $b = 0.8974$, and $c = 1.4336$. We now ask whether growth could occur such that each layer is twice the thickness at the point of buckling and the buckling pressure is halved. We keep the same value of $b$ and double the relative thickness of each layer by taking $a = 0.8526$ and $c = 1.9698$. Then setting $P = P^*/2 = 0.1246$, we find that the inverse problem has the solution $\gamma_r^{(i)} = 1.92$, $\gamma_\theta^{(i)} = 1.03$, $\gamma_r^{(o)} = 2.35$, and $\gamma_\theta^{(o)} = 1.05$. Notice that the ratio $\gamma_r/\gamma_\theta$ is greater than one in each layer. The interpretation is that if growth is faster in the radial direction in each layer at these particular values, the walls would grow such that the thickness at the point of buckling is doubled while at the same time buckling occurs at half the critical pressure compared with the case with no growth. (Conversely, a solution could also be found with half the thickness and double the pressure.)

Again, the rationale for the existence of these solutions relates to the competing effects of residual stress and geometric effects. Given the large range of possibilities with anisotropic growth in two layers, there is sufficient flexibility in the growth variables that residual stress effects can be made dominant. For the example given, the growth causes a large compressive radial stress that dominates the geometric effect of the thicker inner layer. To further illustrate this effect, in Fig. 9 we plot the radial stress profile in the tube. The dashed line is the stress due to growth alone, i.e., with no pressure applied, and the solid line is the stress at the point of bifurcation. We see that growth creates a strong compressive stress, so that only a small amount of additional pressure is required to induce buckling.

The point of this example is not to suggest that this exact value of growth may be occurring in airways, but rather to demonstrate the very significant impact that differential growth can have. If residual stress is generated, simply measuring airway dimensions and changes in dimensions could potentially be misleading as far as understanding mechanical stability.

*Airway size.* To focus on the effect of growth, we have thus far kept fixed the reference dimensions and stiffness ratio. Our choice of reference parameters was motivated by the general observation that the mucosa is significantly stiffer and thinner than the submucosa. However, one set of parameters certainly does not characterize all generations of the bronchial tree (22) and the values are also dependent on where you define the submucosa layer as ending. In this section, we briefly explore the impact of varying the reference parameters.

To do this, we fix the growth parameters at $\gamma^{(i)} = 1.4$, $\gamma^{(o)} = 1.2$, and vary the inner layer thickness, outer layer thickness, and stiffness ratio. The result is plotted in Fig. 10. As the inner layer thickness is increased (Fig. 10*A*), the critical pressure

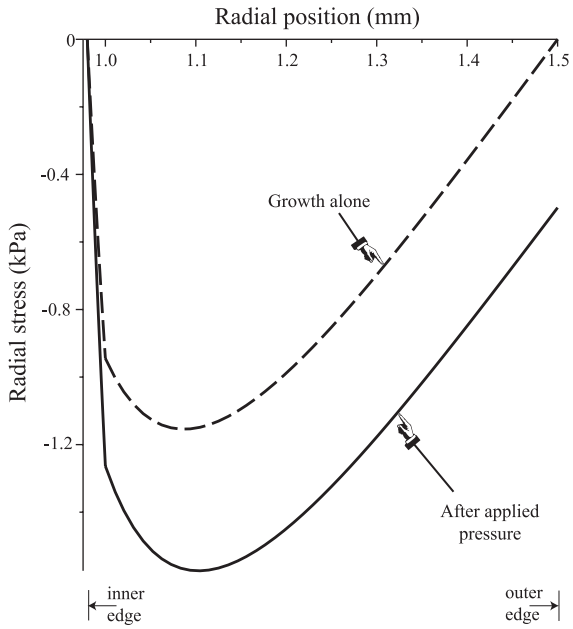


Fig. 9. Radial stress as a function of position after unconstricted growth, i.e., with no applied pressure (dashed line), and at the point of buckling. The compressive stress generated by the growth accounts for the decrease in stability although the walls are thicker.

increases and the buckling mode decreases. Observe that both critical pressure and buckling mode vary quite significantly; for instance starting from the base value A = 0.98, if the thickness of the inner layer is doubled to A = 0.96, the critical pressure increases by more than a factor of 2, while the critical mode decreases from 29 to 14. There is a key distinction between this result and those shown in *Isotropic growth*: here we increased the inner layer thickness in the reference dimensions, which is mechanically stabilizing, whereas in *Isotropic growth* it was shown that increasing the inner layer thickness through differential growth can have the opposite effect and be destabilizing. Interestingly, an increase in thickness of the outer layer (Fig. 10*B*) leads to a decrease in the critical pressure. The explanation for this is that, as explained in *Isotropic growth*, the given growth parameters are destabilizing because the inner layer pushes against the outer layer and creates a destabilizing compressive stress. Increasing the outer layer thickness results in a harder body for the inner layer to push against, and thus leads to further destabilization. Nevertheless, we observe that the change in magnitude in critical pressure is quite small, and the buckling mode is essentially unaffected. This suggests that buckling behavior is not strongly dependent on small changes of submucosa thickness. Finally, as seen in Fig. 10*C*, varying the relative stiffness of the layers does not have a dramatic impact either, except in the limit when the stiffness ratio approaches unity.

## DISCUSSION

Similar to previous modeling attempts, in this paper we studied the mechanical effect of airway wall thickness on mucosal folding and airway narrowing. The major addition in the present work that has not been included in any prior studies is that airway thickening occurs as a consequence of differential growth. Doing so, we were able to study changes in

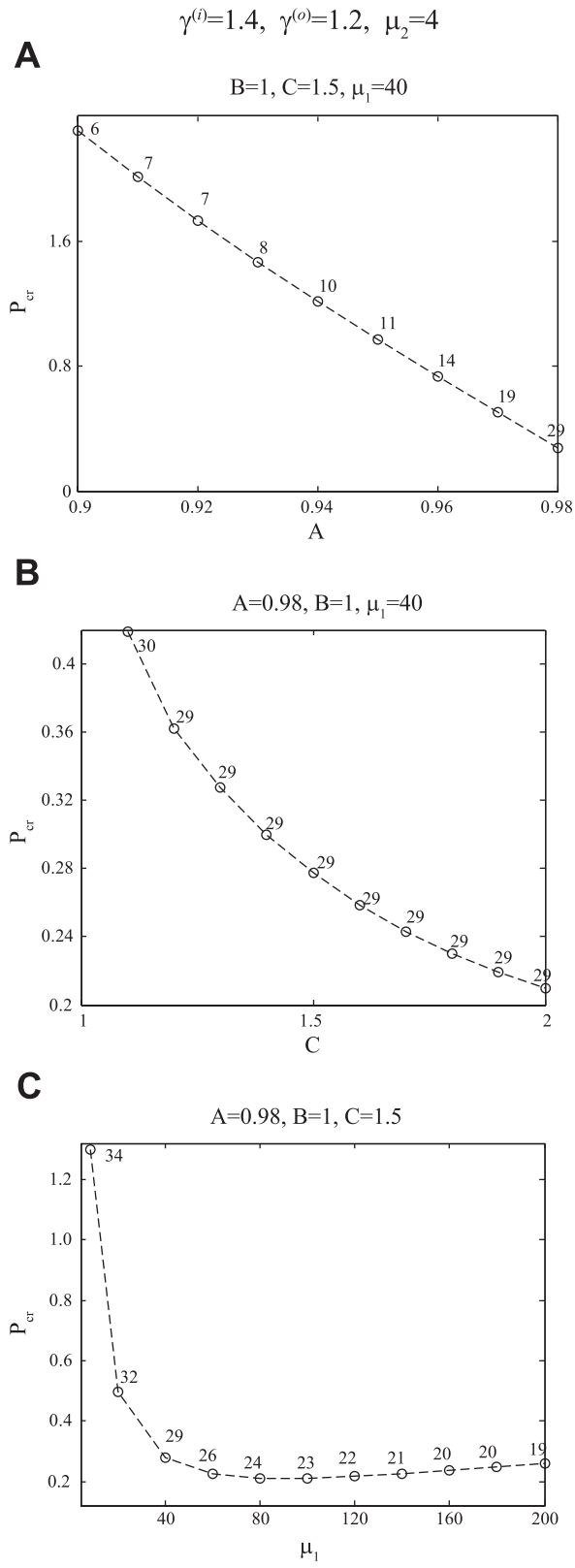


Fig. 10. Buckling pressure for fixed growth parameters $\gamma^{(i)} = 1.4$, $\gamma^{(o)} = 1.2$, as the inner layer thickness (*A*), outer layer thickness (*B*), and stiffness (*C*) are varied. Buckling mode is labeled at each point. Length variables are measured in mm.

material properties, in particular stability properties, due to the generation of residual stress.

Generally speaking, we showed that differential growth can have a significant effect on airway buckling and therefore may be an important contributing factor in understanding the mechanical behavior of airways that have undergone airway remodeling. Note that only differential growth was considered, because it is the competition between geometry and mechanics that occurs as a result of the locally incompatible nature of differential growth that leads to interesting and counterintuitive behavior. Still, there are many ways in which differential growth could occur, and we have explored only a few possibilities here. Isotropic growth with differing rates in each layer led to the somewhat surprising conclusion that if the stiff mucosa grows at a faster rate than the soft submucosa, the airway actually becomes less stable. Anisotropic growth of the inner layer led to a strengthened airway but significantly decreased the buckling mode. Fixing the outer radius so as to account for the growth constriction of the smooth muscle greatly limited the amount of growth.

Our analysis provides a general framework to understand the mechanical effect of growth and remodeling, and our approach gives the ability to test hypotheses regarding growth and changes in airway stability. However, many open questions remain before anything definitive may be said. Differential growth provides a mechanism to explain otherwise contradictory structural changes, for instance an airway wall becoming thicker and at the same time less stable. But airway remodeling involves more complex changes than just an increase of the mucosal and submucosal layers. The ASM layer also gains mass and there is uncertainty as to whether the contractile potential changes (41). Thus whether the airways are actually less stable after remodeling is not yet established.

An obvious question is whether any direct evidence exists of differential growth in airway remodeling. We contend that more information is needed to conclude whether individual airway layers grow anisotropically, although anisotropic growth is known to occur in arteries (20, 33). On the other hand, it seems quite likely that different layers of the airway grow at different rates, since the material composition varies drastically, and there is good evidence to suggest that this form of differential growth is present in airway remodeling (44). It should be noted, however, that in actuality growth is complex and cannot be fully captured by constant parameters $\gamma_i$ as used here, since the mass that is added may be of a different density or type than the normally present material (45).

If airway walls grow differentially and induce residual stress, as we have postulated here, this can be detected by opening-angle experiments, in which a ring of airway wall is cut radially. Any residual stress is relieved by the cut and the ring opens up. Such experiments are difficult and have been carried out in only one study (31), where they reached the conclusion that human airways are essentially free of residual stress. However, it is important to note that none of the human lungs in that experimental study came from humans with asthma. This is a critical distinction, because our hypothesis is that normal airways are in a zero stress state and that stress might be introduced through airway remodeling, in which case only asthmatic lungs would show an opening angle. Hence, opening angle experiments would need to be carried out on normal and asthmatic airways to confirm or deny the possibility of differential growth.

We now turn to the shortcomings of an idealized model. The airway is a complex structure, composed of multiple layers, which we modeled as a bilayer cylindrical tube. This is certainly a simplification, although the purpose is to provide insight into the effect of growth in mucosal folding and an idealized model is sufficient to investigate these generic effects. The two-dimensional nature of the model and the plane strain assumption are supported by the fact that folds in airways are observed as longitudinal ridges (56). The linear stability analysis has the drawback that it only provides information on the deformation up to the point of the buckling. Nevertheless, knowledge of the buckling pressure is a good measure of the "strength" of an airway, and previous studies have shown that a tube becomes much more compliant after buckling (54), suggesting that narrowing occurs more rapidly after buckling. This is also apparent by an increased negative slope in pressure-area curves after buckling (54). Thus, given two airways with different buckling pressures and all other characteristics equal, the airway with lower buckling pressure would be prone to greater hyper-responsiveness. Buckling pressure would hence seem to be a valid measure for investigating the mechanical impact of growth on airway narrowing. Moreover, the conclusion from prior models that buckling mode may be a significant indicator of airway narrowing seems to be supported by our analysis as well. Still, a proper analysis of occlusion and the change in cross sectional area would necessitate continuing the deformation beyond the point of buckling, which would require a much more computationally heavy numerical approach such as finite elements. Such an analysis coupled with growth would be an interesting direction for future modeling attempts. One should also keep in mind that while our focus has been on stability in terms of buckling pressure, physiologically this pressure is generated by smooth muscle contraction; thus any conclusions regarding growth and changes in airway response must take into account the exact relationship between ASM contraction and induced pressure at the airway wall as well as any possible changes in contractile potential of the ASM.

The study we have presented is a preliminary examination of growth and mechanics in airways and is largely qualitative. While we have attempted to use physiologically reasonable parameter values, exact values, in particular of the growth parameters, are unknown to us. Regarding the buckling pressure, which relates the normal force induced at the interface due to smooth muscle contraction, experiments have found that canine airways can generate pressures ~3 kPA (14). This seems to be in line with our findings, as the critical pressure in our simulations ranged from ~0.7 to 3.2 kPa. Note that these values corresponded to a neo-Hookean material; the strain-stiffening Fung model leads to an increase in the critical stress.

Finally, the results presented here might also suggest a future direction of research. The structural changes associated with airway remodeling are generally considered uncontrollable and detrimental. However, if airways can be stimulated to grow in a particular way, growth can potentially both strengthen the airways against narrowing and reduce the degree of narrowing. In this sense, an analysis such as the one presented here could serve as a guideline for the type of growth necessary to achieve this.

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