Lung parenchymal shear modulus, airway wall remodeling, and bronchial hyperresponsiveness

RODNEY K. LAMBERT AND PETER D. PARÉ
Department of Physics, Massey University, Palmerston North, New Zealand 3520; and Respiratory Health Network of Centres of Excellence, University of British Columbia Pulmonary Research Laboratory, St. Paul’s Hospital, Vancouver, British Columbia, Canada V6Z 1Y6

Lambert, Rodney K., and Peter D. Paré. Lung parenchymal shear modulus, airway wall remodeling, and bronchial hyperresponsiveness. J. Appl. Physiol. 83(1):140–147, 1997.—When airways narrow, either through the action of smooth muscle shortening or during forced expiration, the lung parenchyma is locally distorted and provides an increased peribronchial stress that resists the narrowing. Although this interdependence has been well studied, the quantitative significance of airway remodeling to interdependence has not been elucidated. We have used an improved computational model of the bronchial response to smooth muscle agonists to investigate the relationships between airway narrowing (as indicated by airway resistance), parenchymal shear modulus, adventitial thickening, and inner wall thickening at lung recoil pressures of 4, 5, and 8 cmH2O. We have found that, at low recoil pressures, decreases in parenchymal shear modulus have a significant effect that is comparable to that of moderate thickening of the airway wall. At higher lung recoil pressures, the effect is negligible.

dose-response; airway mechanics

The primary function of the lung parenchyma is gas exchange. However, its elastic properties play an important role in maintaining the patency of the conducting airways. Parenchymal tissue transmits pleural pressure to the peribronchial region, thus preventing the collapse of the bronchi under the action of their own wall tension. The Laplace relationship can be used to estimate this wall tension from the transmural pressure and the radius of the airway. The radius can be estimated from the airway area-pressure relationship. When airway smooth muscle contracts and the airway narrows, the parenchyma is locally distorted and provides an additional stress that opposes the muscle contraction. The magnitude of this stress can be calculated from the following relationship (19)

$$\tau_r = 2\mu \frac{\Delta r_o}{r_o}$$

where $$\tau_r$$ is the increase in radial peribronchial stress (that is, transbronchial pressure difference ($$P_{tb}$$)) maintaining airway patency, $$\mu$$ is the elastic shear modulus of the parenchyma, and $$\Delta r_o$$ is the decrease in the airway outer radius ($$r_o$$). The shear modulus has been shown to be proportional to the recoil pressure of the lung ($$P_L$$). For dog lungs it is equal to 0.7$$P_L$$ (14), and for rabbit lungs it is 0.5$$P_L$$ (34).

During chronic inflammatory disease processes such as asthma, the airway wall thickens (10). Morphometric examination of airway cross sections has allowed quantification of the thickening of the airway wall subdivisions (2, 13). The manner in which the thickening of the inner wall, which decreases airway luminal cross-sectional area, increases the resistance to flow and amplifies the effect of airway smooth muscle shortening has been well described (9, 22). It has also been shown that this thickening can contribute to bronchial hyperresponsiveness (9, 18, 22, 36–38). However, the potential effect of thickening of the adventitia has only recently been studied quantitatively (18, 21, 25). There are two mechanical consequences of adventitial thickening. First, the airway smooth muscle is less tightly coupled to the parenchyma. This is a geometrical effect and results in the muscle having to generate less tension for a given amount of thickening. That is, the muscle experiences a decreased afterload. Second, the increased thickness of the adventitia causes a local reduction in peribronchial stress through the airway encroaching into the parenchyma. Thus there is less preload on the airway muscle. As a result of the altered peribronchial pressure, the effective $$P_{tb}$$ is reduced and the airways narrow. At low values of $$P_L$$, the peribronchial pressure can even become positive with respect to luminal pressure, as noted by Macklem (21). Thus thickening of the adventitia should result in an increase in both baseline resistance ($$Raw_{base}$$) and in responsiveness to muscle stimulants.

The effects of some structural alterations in the airways on airway responsiveness have been modeled (18). The model produces simulated dose-response curves, in which the bronchial tree responds to a smooth muscle agonist and narrowing is indicated by increased airway resistance ($$Raw$$). The model incorporates the geometrical effects of airway wall thickening described by Moreno et al. (22) and the simulated computational dose-response curve introduced by Wiggs et al. (36–38). In a previous paper, morphometric data concerning the amount of airway wall smooth muscle were used to determine the limiting stress in each generation of airways (18). In this report we have quantified the effect of different transpulmonary pressures, adventitial thickness, and parenchymal shear modulus on the mechanics of airway narrowing. The results show that adventitial thickening and changes in parenchymal shear modulus have little effect at higher transpulmonary pressures but a substantial effect at lower pressures. Macklem (21) has reached similar conclusions. The results also show that the same fractional increase in adventitial thickness and inner wall thickness do not have equal effects on $$Raw$$. Increases in inner wall thickness have a larger effect on both $$Raw_{base}$$ and maximal $$Raw$$ ($$Raw_{max}$$).
MODEL

The model (18) airways are based on the symmetrically bifurcating bronchial tree described by Weibel (35). The passive compliance of the airways is described by the equations developed by Lambert et al. (20). The cross-sectional areas of airway wall subdivisions are specified generation by generation by using morphometrically derived relationships that give area as a function of airway internal perimeter (13). It is assumed that these areas stay constant during muscle contraction. Shortening of airway smooth muscle is calculated from a simulated dose-response curve as a result of a step in dose of simulated muscle agonist. Generation-by-generation airway luminal area ($A_i$) and $\rho$ are then calculated. Shortening is halted in any generation when the muscle in that generation reaches its stress limit. This stress limit is defined by the maximally activated length-stress relationship of porcine airway smooth muscle acting against elastic loads (7). The plateau of the dose-response curve is reached when all airway smooth muscle has reached its limiting stress.

Previously, the model took no account of encroachment of increased (above control) adventitial tissue thickness into the surrounding parenchyma. We have now corrected this by calculating the altered peribronchial pressure caused by the parenchymal encroachment by using the continuum mechanics approach used previously (18, 19)

$$\Delta P = 2\mu \frac{\Delta r_o}{r_o}$$

In Eq. 1, $\Delta P$ is the change in $P_{tb}$ resulting from a change in the radius of the outer boundary of the adventitia ($r_o$), and $\mu$ represents the shear modulus of the parenchyma. In the unchallenged airway, $A_i$ is determined by $P_{tb}$ and the pressure-area relationship of that airway. Thus when $P_{tb}$ is reduced by a thickening of the adventitia, $A_i$ must also be reduced. We calculated this new area by deflating the airway until $P_{tb}$ was just balanced by passive wall tension. Both passive tension and $P_{tb}$ change during this deflation.

The model was further corrected by allowing thickening of thickened inner wall into the lumen. We did this by assuming that the radius of the outer boundary of the smooth muscle ($r_{mo}$) is unchanged by the changes in the inner wall. $A_i$ is calculated by subtracting inner wall area ($WA_i$) from the area inside the outer boundary of smooth muscle in the control case

$$A_i = \pi r_{no}^2 - WA_i$$

The increase in inner wall thickness observed in chronic asthma is a result of edema, cellular infiltration, tissue cell hypertrophy and hyperplasia, and connective tissue deposition (9, 10). It has been suggested that the increase in the thickness of the lamina propria that accompanies thickening of the inner wall causes an increase in airway stiffness by increasing the airway’s resistance to folding (17, 26). This theoretical contention is supported by histological observations that airways with thicker submucosas are less narrowed in both passively deflated lungs (17) and in lungs that have been challenged with a muscle agonist (27). However, the data that would allow a proper incorporation of the effects of a stiffened folded membrane have not yet been obtained. We, therefore, chose to disregard this potential stiffening.

In previous work with this model, $\rho$ was calculated by using a formula developed by Pedley et al. (28). This formula provides a reasonable estimate of pressure losses in the large airways but a poor estimate in the peripheral airways. In fact, it yields pressure losses smaller than those predicted for fully developed laminar flow, the smallest possible pressure loss. Because a major part of $\rho$ in narrowed airways occurs in the peripheral airways, this is an unsatisfactory state of affairs. Therefore, we have substituted the relationship developed by Reynolds (30), which gives a much better estimate of peripheral pressure losses and has been used before in modeling respiratory airflow (16).

As before, the control values for airway cross-sectional areas were taken from the work of Kuwano et al. (13). The model was programmed in a spreadsheet on a personal computer under the control of a macro. In use, the sheet is initialized to set up the correct starting values at zero dose of muscle stimulant. The model is then run by incrementing the dose of simulated stimulant. This controls percent muscle shortening through a dose-response relationship. The muscle stress is deduced by calculating the muscle tension for a given level of shortening from the force balance for the airway wall. $A_i$ and thus flow resistance in each generation of airways are calculated from each new value of percent muscle shortening. An airway stops constricting when its muscle reaches the stress limit for elastically loaded airway smooth muscle. The plateau of the dose-response curve occurs when the muscle in every airway has reached its stress limit. The dose step was controlled such that the increment in $\rho$, for a step change in dose, never exceeded 5 cmH$_2$O·l$^{-1}$.s. This was done to better define the sharp increase in resistance that preceded the development of the plateau.

 Provision was made in programming the spreadsheet for easy alteration of $P_L$, $\mu$, and a generation-by-generation change of outer wall area ($WA_o$) and $WA_i$. Any desired combination of these parameters can be selected. For the results reported here, any fractional change in airway dimensions was applied uniformly throughout the bronchial tree.

SIMULATIONS

The predicted dependence of $\rho$ on $P_L$ for the control case is not qualitatively different from that reported previously (18) (Fig. 1). At $P_L = 2$ cmH$_2$O, the plateau resistance exceeds 300 cmH$_2$O·l$^{-1}$·s, whereas $\rho_{base}$ is < 2 cmH$_2$O·l$^{-1}$·s. At $P_L = 8$ cmH$_2$O, the plateau resistance is only twice the baseline value.
The parenchymal shear modulus is programmed into the spreadsheet as

\[ \mu = kP_L \]

where \( k \) is an adjustable parameter. The model was run at \( P_L \) values of 4, 5, and 8 cmH\(_2\)O, with \( k \) varying from 0 to 1.5, a range that encompasses the values for dog and rabbit lungs (0.5–0.7\( P_L \)) (14, 34). The results for plateau resistance (i.e., \( R_{\text{wa,max}} \)) are shown in Fig. 2. They show that at \( P_L = 4 \) cmH\(_2\)O, even small reductions in \( k \) result in large changes in \( R_{\text{wa,max}} \). For example, changing \( k \) from 0.7\( P_L \) (the value for dog lungs) to 0.5\( P_L \) (the value for rabbit lungs) at \( P_L = 4 \) cmH\(_2\)O increases \( R_{\text{wa,max}} \) from 16 to 36 cmH\(_2\)O·l\(^{-1}\)·s. On the other hand, changes in \( k \) at \( P_L = 8 \) cmH\(_2\)O cause only minor changes in \( R_{\text{wa,max}} \).

Alterations to \( R_{\text{wa,base}} \) over a range of values of \( P_L \) for several values of \( W_A^o \) and \( W_A^i \) are shown in Fig. 3. It is apparent that doubling of \( W_A^i \) increases \( R_{\text{wa,base}} \) more than does doubling of \( W_A^o \). However, in neither case is the resulting resistance abnormal.

To investigate the significance of thickening of the adventitia, the model was run with values of \( W_A^o \) up to four times the control value, with \( P_L \) set to 5 cmH\(_2\)O (Fig. 4). Quadrupling \( W_A^o \) resulted in an increase in \( R_{\text{wa,max}} \) to 130 cmH\(_2\)O·l\(^{-1}\)·s. However, there was no

---

**Fig. 1.** Baseline (\( R_{\text{wa,base}} \)) and maximal (\( R_{\text{wa,max}} \)) airway resistance plotted as functions of lung recoil pressure (\( P_L \)). All parameters other than \( P_L \) were held at control values.

**Fig. 2.** Variation of \( R_{\text{wa,max}} \) with parenchymal shear modulus (\( \mu = kP_L \)) at 3 values of \( P_L \): 4, 5, and 8 cmH\(_2\)O.

**Fig. 3.** \( R_{\text{wa,base}} \) as a function of \( P_L \). A: outer wall area (\( W_A^o \)) isopleths. B: inner wall area (\( W_A^i \)) isopleths. *, Multiplication.

**Fig. 4.** Dose-response curves showing response of model airways to thickening of adventitial area (\( W_A^o \)). All parameters other than \( W_A^o \) were held at control values. \( P_L = 5 \) cmH\(_2\)O. *, Multiplication.
leftward shift in the onset of the plateau with increasing $WA_o$.

To provide a comparison with the effects of adventitial thickening, the model was also run with control values of all parameters except $WA_i$, which was increased up to double the control value (Fig. 5). A doubling of $WA_i$ resulted in $Raw_{max}$ exceeding 300 cmH$_2$O·l$^{-1}$·s$^{-1}$. This was accompanied by a small leftward shift in the onset of the plateau. It is apparent that the model airway is more sensitive to changes in $WA_o$ than to changes in $WA_i$.

The interaction among changes in $WA_o$, $WA_i$, and $PL$ was investigated by running the model at values of $WA_i$ up to twice the control value and, at each value, varying $WA_o$ by up to four times the control value at three values of $PL$. Isopleths of constant $Raw_{max}$ (at values of 25, 50, and 100 cmH$_2$O·l$^{-1}$·s$^{-1}$) were deduced from these results and are shown in Fig. 6.

**DISCUSSION**

Modification to the model. Airway wall remodeling often occurs in respiratory diseases, and the resulting changes in the geometry of the wall impact on the mechanics of the airway and its ability to conduct airflow. Biological materials exhibit viscoelastic behavior, sometimes with large time constants. Where muscle shortening is involved, there is also the time involved in that process. In trying to model the mechanics of airway deformation, we have chosen to ignore the time-dependent behavior of the tissues involved. Our analysis is based on estimating the sum of the elastic forces from the nonmuscular tissues of the lung, assuming mechanical equilibrium, and thus deducing the force generated by the shortening muscle. We make no assumptions as to how the muscle generates this force, whether with slowly cycling latch bridges or with rapidly cycling cross bridges.

The model used here and its major assumptions have been discussed previously (18). The model is based in part on data, but it also contains much guesswork (albeit informed guesswork). We have neither good nor sufficient data on the mechanical properties of human airways. Nonetheless, the modifications to the model that are described above improve the description of airway mechanics in situ over the earlier model, which, itself, provided results in reasonable qualitative accord with experimental data (18). All changes to airway parameters were applied to all generations of the bronchial tree. The dose of muscle agonist was also assumed to be uniformly distributed and to be uniformly active throughout the bronchial tree. The length-stress relationship of airway smooth muscle was assumed to be uniform throughout the tracheobronchial tree. We shall now discuss only the new assumptions introduced in this study.

We have developed the model to better account for the mechanical effects of changes in airway wall subdivisions that occur during remodeling. We have incorporated thickening of the adventitia in such a way that, when it encroaches into the surrounding parenchyma and thereby lowers $P_{tb}$, the airway shifts to a more compliant part of its cross-sectional area vs. transmural pressure curve. This fixes a weakness of the earlier model that has been pointed out by Macklem (21). The result is a small narrowing of the unchallenged airway to achieve static force balance across the airway wall. There is thus an increase in $Raw$ at all states of muscle shortening. The mechanical description of this process is basic physics. The only assumption is that the process can be described with standard linear elasticity theory, that is, with a small-strain analysis. The relationship for calculating $\mu$ was derived from a relatively large-strain experiment by using standard elasticity theory (14). Use of nonlinear elasticity theory seemed to us not to be justified.

It has been argued that with the reduction of $P_{tb}$ there is a concomitant reduction in the local value of $\mu$, and thus smaller values of $\mu$ should be used as the adventitia thickens (11). This argument can be coun-

![Fig. 5. Dose-response curves showing response of model airways to thickening of $WA_i$. All parameters other than $WA_i$ were held at control values. $PL=5$ cmH$_2$O. * Multiplication.](image)

![Fig. 6. Isopleths of constant $Raw_{max}$ (25 ($\triangle$), 50 (■), and 100 cmH$_2$O·l$^{-1}$·s$^{-1}$ (○)) at 3 values of $PL$ (4 (dashed lines), 5 (solid lines), and 8 cmH$_2$O (dotted lines)). Isopleths show combination of $WA_i$ and $WA_o$ that will give 1 of 3 plateau resistances at chosen value of $PL$.](image)
tered with the observation that the relationship between \( \mu \) and \( P_{\text{L}} \) is deduced from an experiment that used relatively large strains, in which the local deformation was substantial (14). This was equivalent to a local reduction in \( P_{\text{b}} \). If we were to make \( \mu \) a function of \( P_{\text{b}} \) rather than \( P_{\text{L}} \), we would have to reinterpret the experiments from which the relationship for \( \mu \) was obtained. We believe that the calculation of \( \mu \) that we have used gives an average value applicable over the range of deformations that we studied. The model also includes the case of an airway with swollen adventitia at very low \( P_{\text{L}} \), for which the peribronchial stress can be increased load on the airway muscle and the muscle’s consequent inability to shorten as much as in more compliant airways. It has been shown in one model that the decrease in \( R_{\text{aw, max}} \) caused by the reduction in muscle shortening is outweighed by the increase in \( R_{\text{aw, max}} \) caused by the encroachment of the thickened wall into the lumen (25). We have no evidence as to whether this is a reasonable result. Thus we chose to ignore the potential stiffening effect of a thickened inner wall.

In the earlier version of the model, the (non-dimensional) step in dose was fixed, arbitrarily, at two. This is of little consequence for airway geometries not too different from control. However, when the region interior or exterior to the muscle is thickened and the resistance plateau becomes high, the calculated value of the plateau resistance becomes dependent on the size of the dose step. To better control this, we now require the increment in resistance to be \(<5 \text{ cmH}_2\text{O·l}^{-1}\cdot\text{s} \) by reducing the step in dose until this is true. When the increment in resistance is small, the step size is increased.

Use of the Reynolds expression for \( R_{\text{aw}} \) results in an increase in \( R_{\text{aw, base}} \) of \( 7\% \) and in plateau resistance of \( \sim40\% \) in the control case over that calculated with the Pedley expression. The zero-dose resistance in the control case is \( 1.07 \text{ cmH}_2\text{O·l}^{-1}\cdot\text{s} \) as opposed to \( 1.0 \text{ cmH}_2\text{O·l}^{-1}\cdot\text{s} \) in the previous study, and the plateau resistance is \( 5.3 \text{ cmH}_2\text{O·l}^{-1}\cdot\text{s} \) as opposed to \( 3.8 \text{ cmH}_2\text{O·l}^{-1}\cdot\text{s} \) previously. We decided that this was of no great significance because these results also fall within the bounds of “normal” response.

The “control” airway morphometry is that of Kuwano et al. (13). In the central airways, airway dimensions were obtained by extrapolation from the data for the peripheral airways.

The simulations. All conclusions drawn from a model study such as this must be tempered by the knowledge that it is a model study and not reality. Nonetheless, the previous version of this model has been shown to give results that are in qualitative accord with experimental data. The modifications discussed above are designed to incorporate some features of real airways in a more realistic manner. We will now discuss how the model predictions compare with experimental data.

Figures 1 and 2 appear to have some interesting implications for respiratory disease. It is apparent from Fig. 1 that a decrease in \( P_{\text{L}} \) at which \( R_{\text{aw, max}} \) is calculated results, in itself, in a heightened susceptibility to muscle stimulants, as has been observed experimentally in human subjects (3) and in animals (1). Reduction in \( P_{\text{L}} \) results in a narrowing of the airways and thus in an increase in \( R_{\text{aw}} \), regardless of whether there is bronchoconstriction. However, because \( \mu \) is proportional to \( P_{\text{L}} \), the support of the parenchyma for the airway during muscle shortening is also lowered and this, too, causes an elevation of \( R_{\text{aw}} \) but only during bronchoconstriction. Additionally, the compliance of the airway (in this model) increases with decreasing \( P_{\text{L}} \) until \( P_{\text{L}} \) reaches zero. This is significant because part of the load on the shortening smooth muscle is calculated from the airway compliance curve.
Values for $R_{aw_{max}}$ are given in Fig. 1 to indicate that, in the model, there is a plateau. In a real experiment, plateaus for values of $P_l < 3.5 \text{ cmH}_2\text{O}$ would not be observed because the experiment would be stopped before the required dose was reached. Thus, in terms of experiments with live subjects, the model predicts an abolition of the dose-response plateau at $P_l$ values of $<3.5 \text{ cmH}_2\text{O}$ in accord with the experiments of Ding et al. (3). That is, the model predicts that normal subjects breathing at low lung volumes respond to muscle stimuli in a similar manner to asthmatic subjects breathing at normal functional residual capacity (FRC), whereas, at lung volumes greater than FRC, normal subjects show only a small elevation of the plateau above baseline.

The results shown in Fig. 2 are an attempt to evaluate the importance of $\mu$, on its own, in supporting the airway against muscle shortening. The elasticity of the parenchymal tissue keeps the airways open. This tissue also stretches locally near an airway in which the muscle is shortening. The curves in Fig. 2 are concerned with only the latter effect. It is assumed for this analysis that the airway $A_i$ in the control state at the particular value of $P_l$ is not influenced by the change in $\mu$. Thus the intersections of the curves with the $R_{aw_{max}}$ axis indicate the effect of the total absence of parenchymal resistance to local deformation caused by airway narrowing; that is, this is analogous to the response of an excised airway. At high values of $P_l$, removal of parenchymal support is of little consequence because it results in only an approximate doubling of $R_{aw_{max}}$ at a $P_l$ of $8 \text{ cmH}_2\text{O}$ compared with the control value. However, at FRC (assumed to be the volume corresponding to $P_l = 5 \text{ cmH}_2\text{O}$) and lower volumes, the lack of parenchymal support has serious consequences, with $R_{aw_{max}}$ at FRC going from $5.3 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$ in the control condition to $\approx 90 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$ when $\mu$ is zero. Thus we conclude that the parenchymal shear modulus plays a significant part in opposing the narrowing of airways. A reduced shear modulus results in an increased response to muscle agonists.

In trying to confirm these model results by comparison with experimental data in the literature, we must first decide what is being modeled when we alter $k$. An increase in $k$ implies a stiffened parenchyma, that is, one in which the parenchymal elastance (EL) has been increased. There is evidence that the administration of aerosolized methacholine (MCh) in rabbits increases EL (23). Concomitant increases in whole lung resistance ($R_L$) and tissue vascularity were also observed. However, the increases in $R_L$ failed to reach statistical significance. The model predicts that when $k$ is increased, as it appears to have been in the above experiments and possibly is in experiments with live human subjects when MCh is used, the measured value of $R_L$ should be smaller than would be produced by an agonist that had no effect on other lung tissues. This is qualitatively consistent with the experimental results.

In another set of experiments by the same group, but one using dogs instead of rabbits, EL was again observed to increase with increasing doses of MCh (32). Raw of the maximally constricted airways fell dramatically when the level of positive end-expiratory pressure (PEEP) was raised from 5 to $7.5 \text{ cmH}_2\text{O}$ and more than doubled when PEEP was reduced from 5 to $2.5 \text{ cmH}_2\text{O}$. These results are consistent with the model predictions, but it is not possible to deduce from the experimental results what contribution the stiffened parenchyma played in moderating the changes in Raw. The observed increase in $R_{aw_{max}}$ with the decrease in PEEP is considerably less than the model predicts or than is seen in humans (3).

Reductions in the value of $k$ below the nominal normal value of 0.7 might be expected to mimic the effects of emphysema. Both elastase and papain have been used in animals to destroy some parenchymal tissue to model human emphysema (1, 12, 24, 29). In the earlier experiments (12, 24, 29), muscle agonists were not administered. The unchallenged airways showed a reduced maximal forced expiratory flow at any given lung volume (12, 24) and an increased peripheral resistance (29) after the induction of emphysema. The model under discussion here does not predict maximal flows, but it does predict an increase in peripheral resistance with decreasing values of $k$ in accord with experimental data. However, it does not predict the observed decrease in central resistance observed experimentally (29). We do not understand this experimental finding. Bellofio et al. (1) used elastase to induce emphysema in rats and then measured airway responsiveness to MCh. Induction of emphysema increased the responsiveness of the lung to MCh as measured by $R_L$. Because MCh appears to stiffen the parenchymal tissue, the effect of the emphysema in reducing Raw would appear to be being offset by the increase in $k$ from the MCh. However, in these experiments only $R_L$ was measured, not Raw. Thus it is not clear how much of the response is attributable to airway narrowing. Nonetheless, the increase in resistance is in the same direction as that predicted by the model when there is a reduction in $k$.

We performed the rest of the simulations shown in Figs. 3–6 in an attempt to assess the significance of changes in shear modulus in relation to the effects of thickening of the inner and outer airway wall. We excluded changes in muscle thickness from these considerations because the importance of the muscle in this model has already been pointed out (18, 25). Also, the maximal length-stress characteristic of the muscle is that of porcine airway smooth muscle. There is some evidence that human airway smooth muscle is unable to shorten as much as porcine muscle (8). Thus any further investigation of the sensitivity of the model to muscle mass could be misleading.

Encroachment of the wall into the lumen (as a result of inner wall thickening) and encroachment of the wall into the parenchyma (as a result of outer wall thickening) both result in small increases in $R_{aw_{base}}$ as a result of luminal narrowing (Fig. 3). This is in contrast to the earlier study in which changes in wall areas were constrained from producing changes in $R_{aw_{base}}$ (18). It is apparent from Fig. 3 that increases in WA have a
greater effect on $R_{\text{wa}}$ than increases in $WA_o$, although neither increase is significant in absolute terms. At $PL = 5 \text{ cmH}_2\text{O}$, doubling of $WA$ results in a 14% increase in $R_{\text{wa}}$ whereas doubling of $WA_o$ results in only a 4% increase. At lower values of $PL$, the fractional increase in $R_{\text{wa}}$ is greater. Whereas these changes in $R_{\text{wa}}$ are not functionally significant, the changes in the airway wall that cause them are significant in determining airway response to muscle agonists, as shown in Figs. 4 and 5.

It can be seen from Fig. 3A that the increase in $R_{\text{wa}}$ induced by adventitial thickening is greater at low values of $PL$. This is a result of resistance increasing strongly with reductions of $A_i$ and because the airway becomes more compliant at lower values of $PL$, and thus the effect of adventitial thickening on $A_i$ is increased.

Figures 4 and 5 show that increases in either $WA_o$ or $WA_i$ result in increased $R_{\text{wa}}$. The model is much more sensitive to changes in $WA_i$ than to changes in $WA_o$. For instance, a quadrupling of $WA_i$ results in $R_{\text{wa}}$ increasing to ~130 cm$^2$H$^{-2}$O·l$^{-1}$·s (experimentally, this is an abolition of the plateau), whereas the same increase in $R_{\text{wa}}$ is achieved with a little more than a 60% increase in $WA_o$. The other difference between the two sets of results is the slight leftward shift of the dose-response curve with increasing $WA_i$, but not with increasing $WA_o$.

The increase in $R_{\text{wa}}$ caused by a quadrupling of $WA_i$ is almost exactly the same as the increase caused by the reduction of $PL$ to 2.5 cm$^2$H$^{-2}$O. This is very similar to the result predicted by Macklem (21).

To show the interaction among $WA_o$, $WA_i$, and $PL$, we calculated three isopleths of $R_{\text{wa}}$ (at values of 25, 50, and 100 cm$^2$H$^{-2}$O·l$^{-1}$·s) while varying $WA_o$ and $WA_i$ at three values of $PL$ (4, 5, and 8 cm$^2$H$^{-2}$O). These values are ~5, 10, and 20 times $R_{\text{wa}}$ in the control case. The results are shown in Fig. 6. There is a remarkably linear relationship between the values of $WA_o$ and $WA_i$ necessary to achieve a given $R_{\text{wa}}$ at all values of $PL$. The coordinates of any point on any of the lines give the values of $WA_o$ and $WA_i$, which, together, cause the model to yield the plateau resistance pertaining to that line. Thus, at a $PL$ of 4 cm$^2$H$^{-2}$O, a plateau resistance of 100 cm$^2$H$^{-2}$O·l$^{-1}$·s can be obtained by a 20% increase in $WA_i$ combined with a 60% increase in $WA_o$. The same resistance can be obtained at 8 cm$^2$H$^{-2}$O by an 80% increase in $WA_o$ and a quadrupling of $WA_i$. By way of comparison, at a $PL$ of 4 cm$^2$H$^{-2}$O, the same elevation of plateau resistance is obtained with a reduction of shear modulus to 0.3$PL$ (compared with the control value of 0.7$PL$), whereas at a $PL$ of 8 cm$^2$H$^{-2}$O, total removal of parenchymal support from the airway during airway narrowing (that is, assuming that the airway has a constant distending transmural pressure difference of 8 cm$^2$H$^{-2}$O) has almost no effect.

These results appear to correlate with clinical observations. Patients with chronic obstructive pulmonary disease do not have very marked airway wall thickening, but they do breathe at lower $PL$ despite an increased end-expiratory lung volume (31). The decreased $PL$, which is caused by proteolytic lung destruction, will be accompanied by a decrease in parenchymal shear modulus. The results in Fig. 2 show that a combination of a 1-cm$^2$H$^{-2}$O reduction in $PL$ to 4 cm$^2$H$^{-2}$O and a reduction in $\mu$ to 0.4$PL$ results in a >10-fold increase in $R_{\text{wa}}$ over the control case ($PL = 5 \text{ cmH}_2\text{O}, \mu = 0.7PL$). Quantitative comparison with experimental data is difficult, as discussed above, because it is not clear how to associate $k$ with severity of emphysema. However, elastase-induced emphysema in rats produced qualitatively similar behavior to that of the model (1). Interestingly, after induction of emphysema in the rats, the volume dependence of the dose-response curve for $R_{\text{wa}}$ disappeared. This could be a reflection of the altered compliance of the lung, in that a significant increase in volume was caused by a very small change in $PL$.

It is not certain whether some of the increase in $R_{\text{wa}}$ in asthmatic subjects is caused by changes in lung parenchyma. Although these subjects may breathe at increased lung volumes, $PL$ values (and, presumably, shear modulus) are often normal, although they can be reduced in cases of severe childhood asthma. However, the inner and outer walls of asthmatic airways are markedly thickened. These changes can have profound effects on $R_{\text{wa}}$, especially at low $PL$ values (Fig. 6).

There is evidence that the heightened response at low $PL$ values seen in asthmatic subjects is seldom reversible by a deep inspiration in the way that this model appears to predict (4, 33). It has also been reported that normal subjects who are prohibited from taking a deep inspiration for a prolonged period of time after inhaling MCh (33) also show a lack of reversibility, at least on the first two or three deep inspirations. The model cannot be used to study these effects because they appear to be time dependent. Also, the model cannot distinguish between competing explanations of this effect, such as the surface-driven instability described by Hill et al. (6) and the latch-bridge phenomenon described by Fredberg et al. (5).

We have not addressed the problem of gas trapping and the effect that it has on increased $R_{\text{wa}}$. This model is homogeneous in that every airway of each generation has the same airflow, the same transmural pressure difference, and the same mechanics. Airways in the model do not close (although they can be driven arbitrarily close to closure). Gas trapping is inherently a nonhomogeneous effect and is best addressed with a model that has a built-in allowance for nonhomogeneity.

The results of this study show the potential importance of modest changes in airway wall dimensions and illustrate again the critical role of small changes in $PL$ that can accompany changes in end-expiratory lung volume. Although hyperinflation puts the inspiratory muscles at a mechanical disadvantage and increases the elastic work of breathing, the gains in protecting against excessive airway narrowing may more than offset this disadvantage.

At low $PL$ values, reductions in the parenchymal shear modulus cause significant increases in bronchial
responsive, comparable in magnitude with those caused by moderate thickening of the airway wall. At high Pj values, the shear modulus does not play a significant role in resisting airway narrowing.

This work was supported in part by grants from the Medical Research Council of Canada and the New Zealand Lottery Grants Board.

Address for reprint requests: R. K. Lambert, Dept. of Physics, Massey Univ., Private Bag 11222, Palmerston North, New Zealand 5320 (E-mail: R.Lambert@massey.ac.nz).

Received 18 July 1996; accepted in final form 6 March 1997.

REFERENCES