The appearance of regional mechanical heterogeneity throughout the lung after bronchoconstriction has been well established in studies using the alveolar capsule 
(8, 23) and the alveolar capsule oscillator (1, 5, 28)
techniques. Widespread heterogeneity in the responses of 
individual airways has also been demonstrated by in 
vitro studies on lung explants (4). In principle, such 
inhomogeneities could have an influence on the overall 
mechanical properties of the lung in the manner first 
elucidated by Otis et al. (31). In a recent study, the 
changes in canine lung mechanics occurring during the 
80 s after a bolus injection of histamine at constant 
lung volume were investigated (3). The static elastance 
rose to a plateau within 20 s, but at high histamine dose 
the dynamic elastance continued to increase through-
out the 80-s experimental period. Lung resistance also 
steadily increased throughout the 80-s period, but the 
hysteresivity followed a similar time course to that 
of static elastance. We postulated that these results 
could be explained by the progressive development of 
mechanical heterogeneity in the airways that increased 
the dynamic impedance but not the static recoil of the 
lung. However, the precise nature of this heterogeneity 
is difficult to ascertain in an intact lung. We therefore 
decided to simulate the processes of bronchoconstric-
tion in a computer model that was as anatomically 
accurate as present knowledge permits but, in addition, 
allowed us to introduce controlled levels of heteroge-
nity. The model was based on the Horsfield characteriza-
tion of the canine airway system (15), adapted to allow 
random variations in regional properties. In this study 
we used our model to investigate what kinds of heteroge-
nity in the lung can reproduce the observations of our 
previous experimental study (3).

METHODS

We represented the lung as a branching structure of 
compliant airways on the basis of Horsfield's morphometry, 
terminating each branch with a constant-phase tissue unit. 
Because we wanted to examine the effect of distributed 
inhomogeneities, every individual airway and tissue unit in 
the tree were explicitly represented in the computational 
model. This is in contrast to some other implementors, who 
have taken advantage of the self-similarity of the tree by 
storing only the main branch together with the appropriate 
connecting information (7, 12, 18, 38). We could not do this, 
however, because the self-similarity was destroyed by the 
heterogeneities that we applied. We used a singly linked tree 
structure in which each node, representing a single airway, 
was linked to the two immediately peripheral airways. Each 
branch terminated in a tissue unit, which itself contained no 
links. To reduce the memory requirements, the nominal 
parameters for each airway order were stored in a 
separate parameter array so that the nodes in the tree 
structure only needed to contain values representing 
the deviation of that airway from its nominal characteristics.

Airway tree. In Horsfield's model of the canine lung (15), 
the airways are grouped into 47 orders, with all airways 
in each order having the same dimensions. The trachea is 
of order 47, the terminal bronchioles are of order 5, and the 
alveoli are of order 1, giving a total of 300,153 individual 
airways leading to 150,077 alveolar (tissue) units. The equa-
tions governing the airway dimensions in the Horsfield model 
are itemized in Table 1. Each airway in the Horsfield model 
divides into two branch airways that, in general, are of 
different sizes. This asymmetrical branching pattern is deter-
dined by a connectivity parameter (\(\Delta\)) such that, for 
an airway of the \(k^{th}\) order, one branch is of order \(k - 1\), and the 
other of order \(k - 1 - \Delta k\). The values of \(\Delta k\) for each order of 
airway are specified in Table 1.

The measurements comprising Horsfield's model were made 
on lungs inflated to total lung capacity (TLC) at a pressure 
(\(P_{\text{TLC}}\)) equal to 25 cmH\(_2\)O. The dimensions at any lower 
inflation pressure are, of course, smaller because the airway 
walls are compliant. The volume of a simple compartment 
with linearly elastic walls is proportional to the transmural 
pressure, and therefore the linear dimensions change in 
proportion to the cube root of transmural pressure. Airway
walls, however, especially those of the central airways, contain considerable amounts of relatively noncompliant cartilage. By making the simplifying assumption that changes in transmural pressure stretch only the compliant portion of the wall material, the fractional change in overall linear dimension (radius or length) caused by a small change in transmural pressure is given by

$$\frac{x(P)}{x_{TLC}} = a_0 + (1 - a_0) \left(1 - \frac{P}{P_{TLC}}\right)^{1/3}$$  \hspace{1cm} (1)

where $a_0$ is the proportionate dimension at zero transmural pressure, and $x(P)$ and $x_{TLC}$ are the airway dimensions at pressures $P$ and $P_{TLC}$, respectively. This relationship provided a good fit to data reported in the literature (11, 26), as illustrated by the curves shown in Fig. 1. By assigning Horsfield’s orders to the airways in these data, we were able to fit a straight line between $a_0$ and airway order $k$

$$a_0 = 0.2 + 0.011k$$  \hspace{1cm} (2)

Impedance. Because our model was only required to simulate the impedance of the lung to small amplitude low-frequency (<6-Hz) oscillations applied at the trachea at fixed mean lung volumes, we ignored volume-dependent nonlinearities and turbulent flow effects. The series flow impedance ($Z_f$; in cmH$_2$O·l$^{-1}·$s$^{-1}$) of a single airway is, therefore, given by the linear flow equation

$$Z_f = \frac{8\mu l}{\pi r^4} + \frac{\rho l}{\pi r^2}$$  \hspace{1cm} (3)

where $r$ is the airway radius (in cm), $l$ is the airway length (cm), $\mu = 0.0019$·g·cm$^{-1}·$s$^{-1}$ is the air viscosity, $\rho = 0.00387$ g/cm$^3$ is the gas density, and the factor 0.1 converts from centimeters per grams per second units to kilograms per liter per second. Each airway also contributes a shunt impedance ($Z_s$), comprising a parallel combination of the gas compressibility and the airway wall compliance ($C_w$) and viscance. The compliance due to gas compressibility ($C_g$) is given by

$$C_g = \frac{V}{P_0}$$  \hspace{1cm} (4)

where $V$ is the volume of gas in the airway, and $P_0$ is atmospheric pressure. The airway $C_w$ can be determined by defining it as the ratio of the airway volume with resting pressure to pressure, which, from the relationship between transmural pressure and wall dimension given in Eq. 1 (arbitrarily assuming that both airway diameter and length scale in the same manner), can be expressed as

$$C_w = \frac{V_{TLC}}{P_{TLC}} \left(1 - a_0\right) \left(1 - a_0 + a_0 \left(\frac{P_{TLC}}{P}\right)^{1/3}\right)$$  \hspace{1cm} (5)

where $V_{TLC}$ is the airway volume. This relationship does not contain any explicit reference to the elastic properties of either cartilage or airway smooth muscle (ASM). The assumption is that the dynamic $C_w$ is adequately approximated by the static pressure-volume data from which the parameter $a_0$ is obtained.

The impedance of each tissue unit ($Z_{ti}$) is defined by the structural damping model, in which the real and imaginary parts of the impedance are related through a constant hysteresivity factor ($\eta$) (10). $Z_{ti}$ is therefore

$$Z_{ti} = \frac{(\eta - j)E_{ti}}{\omega}$$  \hspace{1cm} (6)

where $E_{ti}$ is the elastance of a single tissue unit and $\eta$ is the structural damping factor. We set $E_{ti}$ equal to the overall static lung elastance (set to 1.0 kPa/l for the simulations reported here), multiplied by the total number of tissue units in the model (150,077), and $\eta$ as equal to 0.15 before bronchoconstriction.

The respiratory system impedance observed at the trachea is composed of contributions from all the airways and tissue units that comprise the lung model. Because of the branching structure of the airway tree, wherein every airway connects to two smaller branch airways (until the most peripheral airways, which connect to a tissue unit instead of further branches), it is possible to implement a recursive algorithm that, starting from the trachea, traverses each branch in the tree. The input impedance ($Z_{in}$) looking into any airway segment comprises the series $Z_f$ and $Z_s$, together with a parallel combination of the two branch input impedances, $Z_{b1}$ and $Z_{b2}$. By making the simplification that $Z_s$ acts at a single point halfway along the airway length (an assumption that is valid at the low frequencies that we consider because even at 6 Hz the wavelength is much greater than the airway length),

### Table 1. Dimensions of Horsfield’s branching model of canine lung

<table>
<thead>
<tr>
<th>Order $k$</th>
<th>$\Delta$</th>
<th>Diameter, cm</th>
<th>Length, cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td>2</td>
<td>2.1</td>
<td>20.0</td>
</tr>
<tr>
<td>46</td>
<td>2</td>
<td>2.1</td>
<td>0.75</td>
</tr>
<tr>
<td>45</td>
<td>2</td>
<td>2.03</td>
<td>1.8</td>
</tr>
<tr>
<td>26, 44</td>
<td>10</td>
<td>$a_0 = 0.0585$ $- 2.87$</td>
<td>$a_0 = 0.0585$ $- 2.25$</td>
</tr>
<tr>
<td>14, 25</td>
<td>4</td>
<td>$a_0 = 0.0585$ $- 2.87$</td>
<td>$a_0 = 0.0585$ $- 2.25$</td>
</tr>
<tr>
<td>7, 13</td>
<td>4</td>
<td>$a_0 = 1.15k - 3.47$</td>
<td>$a_0 = 0.0585$ $- 2.25$</td>
</tr>
<tr>
<td>2, 6</td>
<td>0</td>
<td>$a_0 = 1.15k - 3.47$</td>
<td>$a_0 = 0.0585$ $- 2.25$</td>
</tr>
</tbody>
</table>

$k$, Order of airways; $\Delta$, connectivity parameter. Measurements were performed on a lung inflated to 25 cmH$_2$O before fixing (see text for details).
Zin becomes

$$Z_{in} = \frac{Z_f}{2} + \frac{Z_s(Z_f/2 + Z_o)}{Z_s + Z_f/2 + Z_o}$$  \hspace{1cm} (7)

where the contribution given by the branches (Zo) is simply their parallel combination

$$Z_o = \frac{Z_{b1}Z_{b2}}{Z_{b1} + Z_{b2}}$$  \hspace{1cm} (8)

To compute Zin for any particular airway, it is necessary to first compute the branch input impedances Zb1 and Zb2. These can be obtained by recursively evaluating Eq. 7 for each branch in turn. These calculations also require knowledge of their respective branch Zin, and thus the recursion process must be continued until a tissue unit is reached that contains no further branches and for which Zo = Zti. The recursion then unwinds itself and the Zin of each branch up the tree can be computed, finally providing the overall Zin at the trachea. Note that it is not possible to employ any of the computational shortcuts that can be invoked for a self-consistent tree (7, 17) because the stochastic heterogeneity we introduce destroys the self-similarity in Horsfield's branching pattern.

Bronchoconstriction. In a previous experimental study (3), a bolus of histamine was administered to the vena cava and so reached the lung periphery with little dispersion. This elicited a rapid response of contractile elements in the lung periphery. After some transit delay to reach the bronchial circulation, the histamine then presented a more diffuse profile to the central ASM, eliciting a more gradual increase in airway resistance. The magnitude of the parenchymal response was similar to that seen in tissue studies (6, 33). In our simulation model, we attempted to reproduce these features by using two time courses, Dc(t) and Dp(t) for the reactions in the central airways and peripheral tissues, respectively. Each time course was modeled as a two-exponential curve

$$D(t + t_0) = K [e^{-t_2} - e^{-t_2}]$$  \hspace{1cm} (9)

where K is a normalizing factor such that the maximum value attained by D(t) is unity, t0 is an initial delay set to 5 s, t2 represents the response rise time, and t1 is the recovery time. For Dp(t), t2 was set to 10 s and t1 to 60 s, which resulted in a peak response at about 30 s after administration of the bolus. For Dc(t), we increased t2 to 60 s, which caused the ASM bronchoconstriction to increase progressively throughout the 80-s study time. Figure 2 shows the resulting time courses.

For airways close to the periphery (orders 5 and less), a combination of the peripheral Dp(t) and central Dc(t) time courses was used to represent some degree of overlap in the regions affected by the pulmonary and bronchial circulations (20). We arbitrarily quantified this gradual overlap in the simplest way by means of a linear transition zone; thus

$$D_k(t) = m_k D_c(t) + (1 - m_k)D_p(t)$$  \hspace{1cm} (10)

where Dk(t) is bronchoconstriction time course of an airway of order k, and mk is given by

$$m_k = \begin{cases} 
1, & k \geq 6 \\
\frac{k - 2}{4}, & 6 < k < 2 \\
0, & k = 2 
\end{cases}$$  \hspace{1cm} (11)

We modeled bronchoconstriction in the periphery tissue by increasing Et and hysteresivity parameters with the Dp(t) according to

$$Et_C(t) = Et_R + D_p(t)\Delta Et_{max}$$  \hspace{1cm} (12)

and

$$\eta_C(t) = \eta_R + D_p(t)\Delta \eta_{max}$$  \hspace{1cm} (13)

where $\Delta Et_{max}$ and $\Delta \eta_{max}$ specify the changes in elastance and hysteresivity under maximal bronchoconstriction, respectively, and the subscripts C and R denote the constricted and rest values, respectively, of Et and $\eta$. For the results presented here, we set $\Delta Et_{max} = 0.6$ and $\Delta \eta_{max} = 0.15$. These values imply that under maximal bronchoconstriction the static elastance of the lung rises from 1.0 to 1.6 kPa/l, whereas central response has a rise time of 6 s and a decay time constant of 600 s (Eq. 9).

For airways close to the periphery (orders 5 and less), a combination of the peripheral Dp(t) and central Dc(t) time courses was used to represent some degree of overlap in the regions affected by the pulmonary and bronchial circulations (20). We arbitrarily quantified this gradual overlap in the simplest way by means of a linear transition zone; thus

$$D_k(t) = m_k D_c(t) + (1 - m_k)D_p(t)$$  \hspace{1cm} (10)

where Dk(t) is bronchoconstriction time course of an airway of order k, and mk is given by

$$m_k = \begin{cases} 
1, & k \geq 6 \\
\frac{k - 2}{4}, & 6 < k < 2 \\
0, & k = 2 
\end{cases}$$  \hspace{1cm} (11)

where Dk(t) is bronchoconstriction time course of an airway of order k, and mk is given by

$$c = \begin{cases} 
0.5, & k = 47 \\
0.45, & k = 45-46 \\
0.33, & k = 42-44 \\
0.2, & k = 41 \\
0.16, & k = 40 \\
0.12, & k = 12-39 \\
0, & k = 2-12 
\end{cases}$$  \hspace{1cm} (15)

The fraction c decreases from the trachea to the peripheral airways according to the empirical piecewise function (simplified from that in Ref. 12)

![Fig. 2. Simulated bronchoconstriction time course](image-url)
We made use of James's empirical relationship between airway perimeter and WA

\[ WA = \left(0.0763 + 0.9658 \pi d_{TLC}\right)^2 \]  

where \(d_{TLC}\) is the airway diameter (in cm) at TLC, taken from Horsfield's model, and WA is the cross-sectional area of the airway wall in square millimeters (19).

The parameter ASM\(\text{max}\) defines the proportional shortening of ASM in the airway wall when the bronchoconstriction time-course function \(D(t)\) equals unity. It is a simplifying parameter embodying all factors contributing to the ASM responsiveness. For the simulations reported here, we set ASM\(\text{max} = 0.3\), which is below the critical value identified by Wiggs et al. (38), where the smallest airways close completely under maximal bronchoconstriction \(D(t) = 1\). Note, however, that, when we introduce heterogeneity by stochastically varying ASM\(\text{max}\), this condition no longer holds and some airways may close completely.

Bronchoconstriction changes the airway \(C_w\) by increasing the stiffness of the ASM (29). We modeled this increasing stiffness by means of

\[ C_w = C_{w0} / (1 + \Delta C (1 - c) D(t)) \]  

where \(C_{w0}\) and \(C_{wR}\) are the constricted and rest values, respectively, of wall compliance, \(D(t)\) is the appropriate constriction time course, \((1 - c)\) is a parameter specifying how much \(C_w\) decreases with bronchoconstriction. For the results reported here, we set \(\Delta C = 1\), implying that when \(D(t) = 1\), \(C_w\) is (apart from the factor \(c\)) approximately one-half \(C_{w0}\), compatible with the results presented by Mitzner et al. (29).

Stochastic inhomogeneity. There are several parameters in our structural lung model that can be expected to vary from unit to unit within the lung. Variability in airway radius and wall thickness may be due to the presence of secretions as well as to intrinsic variability in the airway structure. The response of individual bronchi to bronchoconstricting agents may also vary, due either to intrinsic ASM factors or to circulation (i.e., drug delivery) differences. Indeed, recent studies have shown a wide degree of heterogeneity in the sensitivity of ASM to bronchoconstricting agents (4). Similarly, the responses of the tissue units can be expected to have some stochastic distribution. In this study, we are simply interested in generating heterogeneity, without regard to any detailed mechanism by which it is achieved. Therefore, we modeled the stochastic variability in the lung by applying a normally distributed random perturbation to the response parameter associated with each airway and tissue unit in the entire lung tree (i.e., the ASM\(\text{max}\) and \(\Delta C\), respectively). The SD of the perturbation ranged from 0 (deterministic) to 40% of each parameter’s nominal value.

Simulation protocol. We implemented the model in the Oberon-2 (ETH, Zurich) programming language. Simulations were performed on an IBM RS6000/390 computer. On this machine, \(\sim 7\) s of computation are required to calculate the impedance of the lung model at each simulation instant. Approximately 20 MB of memory were required to contain the complete airway tree structure.

After the protocol of the experiments reported in Ref. 3, we computed the time course of changes to the overall lung impedance for a period of 80 s after administration of a bronchoconstricting bolus. Results were calculated at 5-s time steps during the simulation period. The simulation protocol proceeded as follows.

First, the lung model was inflated to the desired operating pressure of 5 cmH\(\text{O}\) by adjusting all airway dimensions according to Eq. 1. Next, randomization factors were generated for each airway and tissue element in the lung according to the desired degree of heterogeneity. Third, for each time step of the simulation, the airways and tissue units were bronchoconstricted according to the value of the simulated bronchoconstriction time course at that instant. Finally, the lung impedance at each time step was computed by recursively following each path in the model and combining the impedances of each branch as described above.

In accordance with our earlier experimental protocol (3), the lung impedance was computed at both 1 and 6 Hz. The impedance at 1 Hz was fit to a model comprising both elastance and resistance, whereas at 6 Hz only the real part was retained. In the results that follow, we denote the lung's dynamic elastance at 1 Hz by \(E_L1\), the overall lung resistance at 1 Hz by \(R_L1\), and the resistance at 6 Hz by \(R_L6\). We take the difference \(R_L1 - R_L6\) to be an approximation to the tissue resistance at 1 Hz. From these values we define the measured hysteresis \(\eta^*\) to be

\[ \eta^* = 2\pi \frac{R_L1 - R_L6}{E_L1} \]  

To examine the variability in response obtained from different realizations of the heterogeneous lung model, we performed 10 simulations at each configuration with different stochastic randomizations, then computed the mean and SD of each set of 10 simulated signals.

RESULTS

The curves displayed in Fig. 3 show the behavior of the model with and without stochastic variability in the individual responsiveness factors. Five sets of curves are shown, corresponding to the time courses of the simulated \(R_L6\), \(E_L1\), \(R_L1 - R_L6\), and \(\eta^*\) and the percentage of tissue units that become isolated from the trachea by airway closure. In each panel, the lower solid curve corresponds to the case of zero applied heterogeneity (i.e., the deterministic Horsfield model). The upper two solid curves in each panel show the results obtained with different levels of stochastic heterogeneity, with SD equal to 20 and 40% of the nominal values, respectively. The dashed lines shown in three of the panels indicate the true tissue responses, which were obtained by combining all the \(Z_{ti}\) in parallel at each time step during the simulation. The ten different realizations of the stochastic lung model gave very similar results, with the maximum SD from the mean responses shown being only 1%.

With the larger degree of stochastic heterogeneity, the curves of \(R_L6\), \(E_L1\), and \(R_L1 - R_L6\) shown in Fig. 3 all continue to increase progressively throughout the 80-s simulation period. This is the key feature observed in a previous experimental study (3) that led us to postulate that developing heterogeneity plays an important role in the acute bronchoconstriction time course. However, our simulated curves of \(\eta^*\) in Fig. 3 also continue to increase progressively. This is in contrast to our experimental findings, in which \(\eta^*\) reached a plateau at \(\sim 25\) s.

To shed light on this discrepancy, we investigated the behavior of a simple two-branch airway model as closure is approached, first in one airway and then in
the other. The results are shown in Fig. 4, which contains the same five panels as Fig. 3. For this simulation, we kept Zti constant. The points at which the two airways close are indicated in each panel. The key finding is that airway closure is immediately preceded by a sharp peak in both RL6 and RL1, which produces a corresponding peak in h. Once closure occurs, however, the model reverts to homogeneity again and the anomalies disappear. Thus there is a critical range of heterogeneous airway narrowing that elevates h. In the complete stochastic lung model, we can expect progressively more airways to enter this range as bronchoconstriction proceeds, which would explain why the h curves shown in Fig. 3 do not reach a plateau. Note that, after both airways have closed in the simulation shown in Fig. 4, the parameter values reflect only the impedance of the central airway.

The above result suggests that our simulated h curves will reach a stable plateau if we prevent the degree of heterogeneity from ever reaching the critical range. We did this by assigning a minimum radius to each airway in the complete model together with the uppermost curves from Fig. 3 for comparison. The closure threshold mechanism produces more total airway closure, and more pronounced increases in E_{L1} and RL6, approximation to tissue resistance at 1 Hz. E_{L1}, lung's dynamic elastance at 1 Hz. h, measured hysteresivity.

DISCUSSION

Although experimental data obtained from a single port such as the trachea are insufficient to uniquely ascertain the distributed structure of the lung, it is possible to construct a distributed model of the lung on the basis of physical measurements of its structural components such as the airway dimensions described by Weibel (37) and Horsfield et al. (15). A model of lung
impedance based on these descriptions, therefore, contains many compartments that together make up the overall response. Weibel's airway-branching scheme is symmetrical, however, so only series heterogeneity (implicit in the 23 airway generations) is represented. Horsfield introduced asymmetric branching, which provides a distribution of path lengths and, consequently, some degree of both series and parallel heterogeneity. Several authors have developed models of lung impedance on the basis of one or other of these structures. For example, Pedley et al. (32) analyzed the pressures and flows that can be expected at each generation of Weibel's (37) airway tree when high-frequency oscillations are applied at the mouth. Wiggs et al. (38) similarly based their model of airway narrowing on Weibel's morphometric data. Fredberg et al. (7, 9) and Jackson et al. (17) used Horsfield's asymmetrical branching model in their simulations of the frequency dependence of airway impedance. These studies simplified the tree structure by having all airways in each equivalent generation of the model identical, thereby making the implicit assumption that any natural variability somehow averages out when the overall response is considered. However, as pointed out by Bates (2), the combined impedance of parallel branches depends not only on the mean impedance of those branches but also on their distribution about the mean.

Jackson et al. (18) utilized Horsfield's model and were able to compute a measure of ventilation inhomogeneity within the lung. They found it to be surprisingly low, probably because Zti (which were all equal) dominated the differences in path impedances. Their overall impedance showed a good correspondence with experimental data in the frequency range 5–60 Hz. Lutchen et al. (24) introduced further heterogeneity in the model by reducing the diameters of specific airway orders encompassing up to 80% of the periphery. They found that extreme levels of diameter reduction were required to change the frequency dependence of lung impedance. Hantos et al. (14) examined peripheral inhomogeneity by appending 900 parallel peripheral units to a parametric model with a single lumped element for the central airway resistance. Although they assigned widely spread random values to the peripheral units, they found that the overall effect of their inhomogeneity was negligible.

In the model presented here, we started with Horsfield's airway structure but then added heterogeneity by stochastically varying the response magnitude of each airway to a simulated bronchoconstriction time course. Without such heterogeneity (i.e., the deterministic Horsfield model), the computed response [characterized by the elastance at 1 Hz (EL1), the resistance at 6 and 1 Hz (RL6 and RL1), and the η'] closely follows the applied bronchoconstriction time course, as shown by the lower curve in each panel of Fig. 3. (Note that the value of η' calculated by means of Eq. 18 is approximately 5/6 of the true value for the deterministic case because we compute it from RL1 and RL6.) In other words, the overall response is simply a scaled version of
the response of each individual element. However, when stochastic variability is applied to the airway responses, the overall dynamic response no longer follows the (average) response of the individual elements of the lung. In particular, the apparent $Z_{ti}$ ($E_{L1}$ and $R_{L1} - R_{L6}$) rises dramatically as airways progressively close. Thus the differences among the three curves in Fig. 3 are due solely to the introduction of heterogeneity in the airway structure as bronchoconstriction proceeds. The average response across all airways in any order remains the same in each case. This result matches those of a previous experimental study (3), in which the dynamic elastance $E_{L1}$ and resistance $R_{L1} - R_{L6}$ continued to rise out to 80 s (at the largest dose of histamine) even though the elastic recoil pressure of the lung reached a plateau after ~25 s. The increase of $E_{L1}$ with bronchoconstriction is well known in the literature (27, 29, 34), and explanations of this phenomenon often involve a presumed stiffening of the lung tissue through interdependence with the airway tree (29, 35). The explanation previously postulated (3) and supported by the results shown in Figs. 3–5 is that the increases in $E_{L1}$ and $R_{L1} - R_{L6}$ are due largely to the development of severe inhomogeneity in the airway tree that progressively isolates parts of the peripheral tissue from the central airways. Indeed, as illustrated in Fig. 4, the increases in $E_{L1}$ and $R_{L1} - R_{L6}$ appear to be directly related to the proportion of terminal units that are isolated from the central airways by peripheral airway closure. This process requires no interdependence mechanism to stiffen the lung tissue, such as might be mediated by parenchymal tethering. This phenomenon is supported by the experimental data and stochastic model of Hubmayr et al. (16), who also concluded that increased dynamic impedance was caused by heterogeneous airway closure at the level of the terminal bronchioles.

The phenomenon of airway closure increases overall $E_{L1}$ by effectively removing part of the lung tissue. This can be demonstrated with a simple model containing only two compartments connected either in series or parallel; eliminate one of the compartments and the total elastance is raised to equal that of the remaining compartment (Fig. 4). However, changes in elastance tend to be unphysiologically abrupt with such simple models. Even the more complicated airway tree models such as that used by Wiggs et al. (38) demonstrate the same rapid transition in overall impedance as the point of total closure in any one airway generation is approached. In contrast, when the airway diameters are stochastically distributed across the lung, the rise in $E_{L1}$ and the decrease in $R_{L6}$ are much more reminiscent
of experimental findings (3) because the shutting down of lung regions is now more gradual as bronchoconstriction develops.

Perhaps the most interesting insight given by our simulation results is that imposing a minimum diameter that airways can narrow to, beyond which they snap completely shut, results in a time course for $h$ that resembles previous experimental observations (3). Indeed, such a closing process in vivo is to be expected in view of the liquid bridge formation that is known to rapidly occur in very narrow airways (13). This process effectively limits the degree of heterogeneity that can develop in the lung because once the critical diameter has been reached an airway closes off completely, thereby eliminating the downstream segment completely while leaving the remainder of the lung to act as a more homogeneous whole. Lutchen et al. (24) also found that there was a progressive change from homogeneous through inhomogeneous and back to homogeneous behavior in their model as an airway was progressively constricted. In our simulation we found that a limiting diameter of 0.1 mm gave quite realistic results. Increasing the limiting diameter beyond 0.1 mm resulted in too much airway closure such that $E_L$ and $R_L - R_{L6}$ rose to unrealistic values. This implicates the smaller airways as being the major site of inhomogeneity in the airway tree. Interestingly, in a previous experimental study (3) it was found that $\gamma'$ rose transiently to a large value in the two most reactive dogs when studied at a low lung volume. In view of the current modeling results, we might interpret these observations as being due to some of the larger airways being able to constrict in an extremely heterogeneous manner, while still remaining patent. By the mechanism elucidated in Fig. 4, this would produce a large increase in $\gamma'$.

Model limitations. Our model represents the structure of the lung with as much accuracy as currently available data and our computational resources permit. However, several simplifying assumptions were made that may have had an effect on the accuracy of our simulation results. Although we believe that our overall conclusions, which follow from the introduction of stochastic heterogeneity in the model, are robust, it is worth pointing out the assumptions to which our model is sensitive.

The airway wall thickness has a strong influence on the amount of airway closure induced by a particular level of bronchoconstriction. It also affects the airway $C_w$. Our values of $C_w$ are, in general, similar to those predicted by the formulas used by Suki et al. (36), which explicitly represent the wall thickness and the elastic properties of the wall tissues. Indeed, at TLC the total $C_w$ equals 3.7 ml/cmH$_2$O for both our formulations and those of Suki et al., but at a positive end-expiratory pressure of 5 cmH$_2$O the total $C_w$ under our scheme increases to 6.3 ml/cmH$_2$O. This increase in $C_w$ as the lung volume decreases accounts for the increase in slope of the airway pressure-volume relationship at low volumes.

Determining the airway wall viscoelastic behavior is problematic because it requires assumptions about the wall thickness, composition, and the effect of the interstitial tissues. Although we did experiment, including estimates of the wall viscoelastic behavior (36), it made little difference to the simulation results at the frequencies that we considered for this study. We therefore decided not to include it in our simulation.

The accurate simulation of the bronchoconstriction time course requires numerous assumptions about processes such as the dynamics of drug dispersal in the circulatory system and the dose responsiveness of the ASM and peripheral tissues. Because the purpose of this paper was to examine how heterogeneity affected the dynamic impedance of the lung, we decided to subsume all these processes into a simple time course that, in itself, matched the experimental static response of the lung to bronchoconstriction.

The form of the heterogeneity itself was chosen arbitrarily to conform to a Gaussian probability distribution function. There are almost no data in the
literature to support or refute this choice. One might argue that mechanical interdependence should induce some degree of spatial coherence in regional mechanical properties. On the other hand, secretions within an airway can affect its resistance drastically in a way that would seem to be random and uncorrelated with respect to neighboring airways. It is also possible that a skewed distribution of airway properties may be more appropriate than the symmetric Gaussian distribution employed here. The identification of these distributions from morphometric studies would therefore appear to be an important area of research for the future (see Ref. 4).

The effect of lung volume on the response to bronchoconstriction is dependent on several factors, including the relationship between pressure and airway dimension, the way in which forces of interdependence and parenchymal tethering change with inflation, and how the ASM constriction characteristics are affected by changes in airway dimension. Our model contained no interdependence mechanism, partly because we wished to demonstrate that inhomogeneous and progressive airway closure alone could account for the increase in effective dynamic impedance seen during acute bronchoconstriction. As for parenchymal tethering, several recent studies have shown how the tethering forces can modulate the ASM-constrictive forces such that the effective ASM shortening is increased at low lung volume (21, 25). Because we subsumed all the factors relating to maximal constriction into the factor ASM_max, we did not include any separate tethering mechanism in our model.

The functional relationship between pressure and airway dimension (Eq. 1) used here was chosen because of its simplicity. The use of a different formulation, such as that Lambert proposed for Weibel's model (22), would have had little bearing on the primary result of this study, which was to show how the progressive introduction of airway heterogeneity during bronchoconstriction could affect the overall lung impedance. However, a different dimension-pressure relationship could have changed the precise values of resistance and elastance that we obtained. As implemented, our simulation results were very similar to previous experimental results (3), confirming the validity of the model. Only Rint was smaller (by a factor of 4 at baseline) from all of the experimental data. We could have tried to optimize the Horsfield dimension to reduce this difference, but because the individual dogs themselves showed a wide range of responses, we decided to let the model stand on its own.

In conclusion, we have developed a computational model of the lung that embodies much of the physical structure of the lung and is able to reproduce the key features of data obtained in a previous experimental study of acute induced bronchoconstriction in dogs. Simulations with our model strongly support the notion that much of the apparent increase in Eti and resistance observed during bronchoconstriction can be attributed to the development of mechanical heterogeneity throughout the lung. However, our results also indicate that such inhomogeneities must develop to the extent that a significant proportion of the lung periphery is isolated from the central airways by peripheral airway closure before much effect on overall lung impedance is seen. We also found that, by making the airways snap shut once a critical degree of narrowing had been achieved, the time course of $\gamma$ more closely resembled the experimental.

This work was supported by the Medical Research Council of Canada and the T. Costello Memorial Research Fund. J. H. T. Bates is a Chercheur-Boursier of the Fonds de la Recherche en Santé du Quebec.

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Received 11 June 1996; accepted in final form 18 December 1996.

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