Complex airway behavior and paradoxical responses to bronchoprovocation

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Heterogeneity of airway constriction and regional ventilation in asthma are commonly studied under the paradigm that each airway’s response is independent from other airways. However, some paradoxical effects and contradictions in recent experimental and theoretical findings suggest that considering interactions among serial and parallel airways may be necessary. To examine airway behavior in a bronchial tree with 12 generations, we used an integrative model of bronchoconstriction, including for each airway the effects of pressure, tetherring, and smooth muscle forces modulated by tidal stretching during breathing. We introduced a relative smooth muscle activation factor (Tr) to simulate increasing and decreasing levels of constriction in the model and demonstrate that the apparent paradoxical experimental findings mentioned above are consistent with that network model demonstrated that, even in a virtually symmetric airway tree under uniform activation of smooth muscle, ventilation could become dramatically heterogeneous with large clusters of severely constricted peripheral airways. In the present paper we examine in detail the characteristic behavior among airways during bronchoconstriction in the model and demonstrate that the apparently paradoxical experimental findings mentioned above are fully consistent with the behavior displayed by the model during bronchoconstriction.

METHODS

We used the integrative model of bronchoconstriction previously described in detail (40). Briefly, the computational model consists of a symmetrically branching airway tree with 12 generations based on Weibel’s morphological data from the fourth to sixteenth generation of a healthy adult lung (42). As originally formulated for a single terminal bronchiol by Anafi and Wilson (4), we considered for each airway of this tree the effects of: the pressure difference between inside and outside of the airway wall, local increase of Tr in a single central airway resulted in full closure, dramatic decrease in ventilation in a group of terminal units but increased in the rest. A local increase of Tr in a single central airway resulted in full closure, while no central airway closed under global elevation of Tr. Lung volume affected the response to both local and global stimulation.

Detailed studies using high-resolution computed tomography (HRCT) imaging have confirmed substantial heterogeneity among airways in animals (16–18) and humans (14, 26, 27), but results from some of those studies are difficult to reconcile with the expected behavior of independent airways. For example, localized stimulation of individual airways with methacholine (MCh) demonstrated in dogs that normal smooth muscle is capable of causing full closure of cartilage-protected central airways (18) even in the presence of augmented parenchymal tethering forces at increased lung volumes (17). In contrast, global agonist stimulation failed to close those airways in the same animals despite delivering the agonist at 50× higher concentrations. Also, CT imaging of asthmatics challenged with agonist or cold air (27) showed only moderate average lumen reduction of conducting airways but highly heterogeneous response among airways, with a paradoxical combination of constriction and dilation. A similar paradoxical response involving central airway constriction and peripheral airway dilation was observed in rabbits during the time course of bronchoconstriction by means of synchrotron imaging. In that study, as the lung recovered from bronchoconstriction and peripheral airways reopened, conducting airways continued to constrict (9).

Clearly a combination of constriction and dilation of airways during the development of, or recovery from, bronchoconstriction is difficult to explain in terms of isolated airway behavior, and it may require consideration of airway responses depending on dynamic interactions among serial and parallel pathways, including airway-parenchyma interdependence and tidal expansion. We previously described such integrative airway behavior by a network model synthesizing current physiological knowledge of airways and lung parenchyma into a human tree geometry (40). Simulations with that network model demonstrated that, even in a virtually symmetric airway tree under uniform activation of smooth muscle, ventilation could become dramatically heterogeneous with large clusters of severely constricted peripheral airways. In the present paper we examine in detail the characteristic behavior among airways during bronchoconstriction in the model and demonstrate that the apparently paradoxical experimental findings mentioned above are fully consistent with the behavior displayed by the model during bronchoconstriction.

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the expanding tethering forces of the surrounding parenchymal tissue, and the smooth muscle forces modulated by the dynamic stretching during breathing. Interactions among these forces for each airway and the resulting distributions of pressure, flow, and volume along the airway tree were solved numerically to determine steady-state airway tree dimensions at increasing levels of smooth muscle activation. To break the computational metastability caused by the model’s imposed structural and functional symmetry, a small random perturbation in wall thickness (1% coefficient of variation) was added to all airways of the model.

Breathing cycles were simulated with constant inspiratory flow and passive exhalation to atmospheric pressure. Tidal volume (equivalent to 650 ml) and breathing frequency (12 breaths/min) were kept constant, and end-expiratory pressure (P_EE) was set at −2, 0, or 2 cmH_2O to explore the effects of changing lung volume.

The computational model was implemented in MATLAB (MathWorks, Natick, MA) with dynamic changes of pressure and flow along the airway tree calculated for time steps equivalent to 10 ms. To explore the model’s behavior at varying levels of smooth muscle activation, we introduced a relative smooth muscle activation factor (T_r) that scaled the smooth muscle tensions relative to those at maximal activation used by Anafi and Wilson (4). We conducted simulations for levels of relative activation increasing from 0.5 up to 1.0 and decreasing back to 0.5 in steps of 0.05.

Each step started with a linear transition of smooth muscle activation to the new value, followed by a constant activation period to allow the system to reach a steady state in ventilation distribution and in airway lumen throughout the bronchial tree. Relative airway radii were calculated as radii normalized by their relaxed radius. The relative ventilation of each terminal unit was calculated as the local tidal volume normalized by the corresponding tidal volume for uniform ventilation distribution. A color scale was used to visualize the ventilation of all terminal units in a square matrix, where each element corresponded to a terminal branch of a Mandelbrot-like tree structure (Fig. 1, right). The relative size of ventilation defects (VDef) was defined as the fraction of terminal units of the model with mean ventilation lower than 15% of the uniform ventilation level.

To simulate the effect of a local stimulus by an agonist in an individual airway, we first exposed the model to uniform and steady smooth muscle activation (T_r = 0.6) to establish a baseline tone and then progressively increased T_r in a single 3rd-generation airway while leaving the rest of the tree at a constant T_r. The response of the overstimulated airway was compared with others of its generation and with those of the rest of the airways of the lung for equal and greater levels of uniform activation. To simulate airway radii under static equilibration, we closed a single 3rd-generation airway by maximum activation and progressively increased T_r in all other airways from 0.4 to 1.0. The mean radius of airways distal to the closure was compared with dynamically equilibrated airway radii in another simulation without local airway stimulus.

To compare our theoretical results with experimental data of average airway responses to local and global agonist stimulation in dogs (18), we transformed the HRCT measurements of normalized mean luminal areas (relaxed airway diameters: 4.2–11.7 mm) into equivalent relative airway radii assuming a circular airway cross-section. Additionally, we assumed that the logarithm of MCh concentration scaled with T_r such that a concentration of 500 mg/ml of MCh corresponded to T_r = 1, and 10 mg/ml to T_r = 0.6. We also transformed airway lumen at baseline tone (airway diameter range: 1.5–5.5 mm) and at conditions caused by a period of apnea, which were reported in two other studies by Brown and colleagues (11, 15), to compare the measured changes in airway radii with the prediction of the model. To estimate the basal tone of the airways, we assumed that it is sufficient for our comparison to choose a T_r such that the normalized airway radius during breathing coincided with the mean airway radius of our model.

**Fig. 1.** Airway radii of all model generations and corresponding regional ventilation at increasing levels of smooth muscle activation. Airway radii are normalized by their fully relaxed size. Lines connecting the 8191 radii illustrate the branching pathways as parent-daughter connections. Line colors correspond to the colors of the schematic airway tree that shows the six upper generations of the model. The continuation of this branching pattern down to the 12th generation defines the functional relationship among terminal units within the color-coded map of regional ventilation. Note the clear separation in the 12th generation between pathways inside and outside of ventilation defects (VDefs) for relative smooth muscle activation factor (T_r) > 0.85 and the severe constriction of terminal airways. Large angles between the lines of two daughter airways indicate major difference in their response.
Changes in airway lumen during the recovery period following bronchoconstriction were estimated by assuming an exponential reduction in Tr from unity to a basal activation level. The time constant and the basal activation level (Tr = 0.6) were chosen to match the dynamic behavior of ventilation defects and the airway size measured in rabbits (9). This approximate relationship between Tr and time was used to plot the model predictions of step-by-step decreasing Tr levels at time points that correspond to the experimental data.

RESULTS

For low levels of Tr, the model exhibited uniform ventilation and homogeneous airway narrowing (Fig. 1). As Tr reached a critical level there was a clear change in behavior, with a sudden reduction in ventilation of certain terminal units. Further increments in Tr resulted in further increase of severely hypoventilated units, defined as those with a local ventilation <15% of the mean (Fig. 2). The critical transition from uniform to heterogeneous ventilation occurred at a Tr between 85% and 90% of maximal activation (0.85 ≤ Tr ≤ 0.9) for P_{EE} = 0 cmH_2O and at 0.65 ≤ Tr ≤ 0.7 for P_{EE} = −2 cmH_2O, while no transition was observed for P_{EE} ≥ 2 cmH_2O. The different P_{EE} levels had identical fractions of hypoventilated units at Tr values below the critical transitions. Substantial differences developed, however, at higher Tr values due to the differences in location of the critical transition. The dropouts in local ventilation accompanying the critical transition were not diffuse but clustered into well defined VDefs, covering an area that increased in steps with increasing Tr (Fig. 1, right).

Duality of airway response: combination of constriction and dilation. Below criticality, airway lumen reduction with increasing Tr was gradual within a generation of the three. As Tr increased above criticality, airway response became highly heterogeneous. Some airways narrowed severely, while the rest underwent small changes or dilation (Fig. 3). This combination of constriction and dilation was observed at all generations of the model, but the degree of narrowing at a given Tr was much lower in central than in peripheral airways. Indeed, closure or near-closure of airways was concentrated on peripheral airways. While Tr increased above criticality, entire groups of airways changed behavior from dilating to narrowing as they were recruited into VDef regions. As a result, as VDefs emerged in the model, the pattern of airway response along bronchial pathways was not random (Fig. 1, left). Airways...
along pathways leading to VDefes responded heterogeneously and showed bifurcating behavior between otherwise identical daughter branches. Airways along pathways leading to the rest of the lung were much more uniform and showed only a gradual central-to-peripheral lumen reduction.

Response to local activation of a central airway and bronchodilating effect of tidal expansion. Local increase of $T_r$ in a single central airway resulted in full closure even at submaximal level of smooth muscle activation ($T_r = 0.85$, Fig. 4), whereas no closure of central airways of the tree could be achieved for uniform global smooth muscle activation up to maximal levels ($T_r = 1$). For global elevation of $T_r$, average central airway radii were reduced but reached a plateau in their narrowing, so that even at activation levels above critical $T_r$, no central airway closed. Increasing $P_{EE}$ to 2 cmH$_2$O shifted the response curves for local and global stimulation toward the right (higher values of $T_r$) but did not prevent the closure of the individually stimulated central airway (Fig. 4).

These simulations of single airway challenges also demonstrate the bronchodilating effect of tidal breathing in our model. The occlusion of a single airway at the 3rd generation affected all its distal airways by stopping the tidal expansion of the smooth muscle that had the same basal tone as the ventilated airways. The dynamic equilibrium of the smooth muscle in the ventilated airways resulted in substantially larger airway radii than for the static equilibrium in the unventilated airways (Fig. 5). Furthermore, the occlusion caused a redistribution of ventilation to other airways, so that these airways further dilated compared with the mean airway radius of each generation before the single airway challenge. In these simulations with subcritical levels of basal $T_r$, the central-to-peripheral gradient in airway radii was very small and the constriction rather independent of airway generation. The mean airway radii for dynamic and for static equilibrium showed the bronchodilating effect of tidal expansion in a series of simulations with different smooth muscle activations (Fig. 6). Accordingly, the smooth muscle activation for a radius of zero in an unventilated airway would be the minimal value required for airway closure in the absence of tidal stretch.

Comparison of model predictions with CT imaging data. Our simulation results for local and global agonist stimulation are consistent with experimental data of airway responses in dogs reported by Brown and Mitzner (18), assuming the described scaling of MCh to smooth muscle activation (Fig. 6). The apnea-induced airway narrowing in dogs reported by Brown and colleagues (11, 15) was smaller than the change predicted by our model.

Time course of airway lumen during bronchoconstriction recovery. As $T_r$ starting from maximum was progressively reduced, the size of VDefes decreased, while the lumen of central airways leading to well ventilated lung regions increasingly narrowed (Fig. 7). Airways feeding VDefes showed progressive dilation during this period. As $T_r$ was further reduced, VDefes vanished and all airways of the model dilated monotonically.
DISCUSSION

We previously demonstrated that uniform activation of smooth muscle in this symmetric model of the airway tree resulted in highly heterogeneous ventilation distribution, characterized by large and contiguous VDefs (40). In this paper we explored in detail the characteristic behavior of airways within that model and obtained the following relevant results: 1) progressive activation of all airway smooth muscles in a bronchial tree led to heterogeneous response among airways, including the combination of dilation and constriction; 2) combination of peripheral airway dilation and central airway constriction was exhibited during progressive relaxation from maximal smooth muscle activation; and 3) submaximal smooth muscle activation was capable of causing full airway closure when localized to a single central airway. In contrast, maximal uniform activation of the full airway tree was incapable of bringing any central airway to closure. These results may explain a number of apparently paradoxical experimental findings as we discuss below.

It is well known that airway narrowing after bronchoprovocation causes major ventilation heterogeneity associated with the formation of large and contiguous VDefs (39–41). Although the VDef’s large size could suggest involvement of large airways, imaging with HRCT of agonist-challenged asthmatic and COPD patients has failed to demonstrate significant reductions in luminal area of airways larger than 4 mm² (10, 21, 34). Therefore, the investigators concluded that the primary cause for ventilation impairment during a bronchoconstrictive challenge was the narrowing of airways smaller than those that could be reliably assessed by HRCT.

Other HRCT studies have reported substantial heterogeneity among individual airways in the response to agonist aerosol and intravenous bronchoprovocation of animals (16) and of normal and asthmatic human subjects (14, 20, 26, 27). One of these studies (27) assessed the response of the central airways to both agonist challenge and cold air stimuli, and it reported a paradoxical combination of dilating and constricting airways that was not systematic for both stimuli. Paradoxical dilation of certain airways in response to agonist challenge had been previously identified but interpreted as the likely result of measurement errors (14). Concern about measurement errors is justified for such complex studies, but a recent study demonstrated that the heterogeneity of airway response to agonist measured with HRCT for airways of diameter >2 mm was substantially higher than the expected variability assessed from the differences between two consecutive scans at controlled lung volume and without bronchial stimuli (26). Thus, the heterogeneous response among airways, including dilation of some, appears to be a true manifestation of airway behavior that is independent of the route or type of bronchoprovocation. Further evidence for spatial and temporal heterogeneity in airway response was found in a study that used alveolar capsule oscillators to measure agonist-induced changes in bronchoconstriction (31). Structural and functional differences among individual airways and nonuniform agonist distribution are usually cited to explain the heterogeneous nature of airway response (13). However, we demonstrated recently with our integrative model of bronchoconstriction that structural or functional differences among airways or heterogeneous degree of smooth muscle activation to individual airways are not necessary to cause heterogeneous airway response (40). Indeed, we demonstrate here that a symmetric model of the airway tree subjected to uniform smooth muscle activation displays a response that includes not only the stepwise formation of VDefs but also a changing combination of dilating and constricting airways (Figs. 1 and 3).

Although the precise anatomical location of VDefs in our model depended on a minimal random perturbation in wall thickness (or any other structural or functional property) imposed on the tree for computational purposes, the resulting
pattern of airway narrowing was not random. Instead, the behavior of individual airways was systematic, with constriction of airways along pathways leading to VDefs and dilation of airways leading to well ventilated regions, a pattern suggesting a dependent response among airways of the tree (Fig. 1). The concept of airway interdependence has been traditionally used to describe local mechanical interactions between adjacent airways or between airways and parenchyma as they are expanded nonuniformly in the lung (29). In the single terminal airway model of Anafi and Wilson (4) and in our model, this local interdependence between airway and parenchyma is part of the dynamic load to which the smooth muscle is subjected during breathing. In the context of this paper, we argue that the concept of interdependence applies not only to local interactions but also to regional differences that include dynamic distribution of air flow, pressure, and tidal expansion along central-to-peripheral paths (serial) and among pathways to different regions of the lung (parallel). This means that the response of an airway to stimuli or external changes depends on other airways and vice versa.

Tidal stretch applied to a contracting smooth muscle reduces contractile force (23, 33, 36), likely as a result of disturbed myosin binding equilibrium (24, 30). Tidal stretch of an airway wall is caused by the interaction between smooth muscle, transmural pressures, and parenchymal forces during breathing (3, 4). Thus, a minimal perturbation in local or regional airway caliber that reduces airflow and regional tidal lung expansion enhances smooth muscle forces, further reducing airflow caliber. For example, the smallest difference in airflow between two parallel airways at a bifurcation results in a smaller tidal expansion of one branch. The decreasing tidal stretch in one branch increases the contractile force of its airway smooth muscle. The resulting decrease in airway lumen subsequently enhances the differences in airflow and tidal expansion, so that the positive feedback leads to dramatic changes in airway lumen, including full closure. This has a phenomenological similarity to the classic description of two soap bubbles on a Y tube, which also involves positive feedback but has a different cause.

At low levels of smooth muscle activation, the interactions within the lung are self-limiting. But as smooth muscle activation is increased above a critical level, any small perturbation can trigger the positive feedback that propagates up and down the airway tree as a phenomenon of serial interdependence. A similar but opposite phenomenon under breathing with constant tidal volume causes the dilation of airways outside of VDefs, where regional tidal volume is increased by airflow redistribution away from VDefs, and increased tidal stretching reduces smooth muscle forces and causes regional airway dilation due to parallel interdependence. Thus, for smooth muscle activation above a critical level, two complementary responses emerge: one involves the constriction of airways leading to VDefs, and the other the dilation of the rest of the airway tree. In other words, according to our model, the experimentally observed combination of airway dilation and constriction could be a manifestation of serial airway interdependence due to dynamic airway luminal instability, and of parallel interdependence due to interregional airflow redistribution. For ventilation with fixed inspiratory pressure as target instead of constant tidal volume, a local increase in resistance is not expected to cause airflow redistribution but to decrease tidal volume, which increases the size of VDefs (40). This may lead to further increase in resistance and acute ventilatory failure.

Lung volume dependence of VDefs. Airway-parenchyma tethering forces per se represent a load to the constricting smooth muscle that depends on lung volume. Evidence from studies conducted with oscillatory measurements under apneic conditions suggests that lung volume affects the heterogeneity of airway response (5) and the changes in resistance and elastance (8) during bronchoconstriction. Thus, changes in lung volume can be expected to shift the critical transition from uniform to heterogeneous states of the lung. There is no direct experimental data supporting our model’s prediction that the critical activation level in airway smooth muscle is affected by lung volume (Fig. 2A), but Ding et al. (22) demonstrated that reducing lung volume markedly increased the airway response to a contractile agonist. In that study, a fourfold increase in lung resistance was measured when normal subjects challenged with MCh were asked to reduce lung volume by only 0.5 liter. However, inspection of the published data reveals that the lung volume dependence was minimal for low MCh concentrations, but it increased rapidly at concentrations above a clear threshold for each subject (Fig. 2B). This dichotomous volume dependence at the lower volume was unexpected, because airway resistance increased monotonically with MCh concentration at the baseline volume (FRC).

Our integrative model of bronchoconstriction suggests as explanation for these results that a reduction of lung volume caused a reduction in the critical level of smooth muscle activation (Tr critical), above which VDefs were formed. If the concentration of the inhaled agonist is at FRC related to a Tr < Tr critical, the airways would be uniformly constricted but not forming VDefs (Fig. 1). As lung volume is reduced, the ensuing reduction of the critical activation level can for the same Tr result in Tr critical < Tr, triggering the formation of VDefs with clusters of severely constricted airways that increase monotonically for increasing agonist concentrations, as observed for airway resistance by Ding et al. (22).

Other models of single airway mechanics with (24, 30) and without (1) superimposed tidal breathing have predicted critical changes in airway lumen behavior during graded airway response to agonists. However, critical changes in connection with the clustering of severely constricted terminal bronchi into VDefs and the combination of dilation and constriction are unique findings of our integrative model.

Hyperreactivity of single airways. Experiments conducted in individual components of the lung (airways, tissues, or cells) are usually extrapolated qualitatively to explain overall organ behavior. That approach can only be justified if the components of the system behave independent of each other or homogeneously. This is not the case for the bronchoconstricted lung, where complex interactions among the airways are involved.

Indeed, if interdependence among airways was not important, then exposing a single airway of the tree to local smooth muscle activation should result in the same degree of narrowing as that observed when the full airway tree is uniformly exposed to the same level of activation. Quantitative CT imaging demonstrated that local agonist stimulus of a single airway (diameter > 2 mm) could cause full closure (18), while no airway closure was observed with global stimulation of the...
full airway tree by inhalation of aerosol agonist at 10–50×
greater concentrations (17). The investigators inferred that
normal smooth muscle forces were sufficient to cause airway
closure even for cartilage-protected central airways and that
parenchymal tethering forces were not enough to prevent this
effect. This also led to the speculation that the difference in
airway responses between local and global agonist challenge
was caused by a difference in the local agonist concentration;
global airway response could have been limited by the local
deposition of inhaled aerosol. Although that assertion could
still be valid, the results from our integrated model suggest that
the limited constriction of central airways to a global stimulus
could have been the result of interdependent airway behavior
and not just a limitation in agonist deposition. Indeed, our
simulations demonstrate that smooth muscle activation of a
single 3rd-generation airway in our model resulted in full
closure, even at submaximal level of smooth muscle activation
(Tr < 1, Fig. 4). In contrast, closure of these airways was avoided
when all airways of the tree were uniformly activated
even at maximal level (Tr = 1). Also consistent with experi-
mental results (17), the model showed that increasing lung
volume with PEE shifted the dose response curve of the chal-
dered tidal breathing demonstrate the relevance of flow-related
transmural pressure swings modulating the bronchodilating
effect of tidal stretch.

The central-to-peripheral differences in airway reactivity
exhibited by our model are also consistent with HRCT imaging
evidence (10, 12, 25, 27) and with theoretical models of lung
mechanics (28, 38), suggesting that most of the functional
impairment in asthma is caused by constriction of peripheral
airways. This peripheral response seems particularly paradox-
ical for cold air challenges with a substantially greater thermal
stimulus in the central airways, which led the investigators to
postulate an anatomic disconnect between the site of the
thermal stimulus and the local response of the airway tree (27).
Although more detailed simulations would be required to test
the response of the model to a centrally biased stimulus, the
central-to-peripheral difference in airway response to uniform
smooth muscle activation during dynamic conditions suggests
that serial interdependence among airways could be in part
responsible for the experimental observations.

Temporal differences in airway response. Experimental data
from a study measuring simultaneously airway luminal area
and ventilation after agonist-induced bronchoconstriction in
the rabbit showed a paradoxical increase in central airway
constriction that took place simultaneously with a dilation of
peripheral airways (9). As time progressed and VDefs re-
solved, the reduction in central airway lumen reached a pla-
teau, and the central airways began to dilate. How can a
combination of central constriction and peripheral dilation of
airways during the recovery from a bronchoconstrictive event
be explained? The authors hypothesized that the delay in
central airway response relative to that of peripheral airways
could have been caused by slow development of submucosal
edema in the central airways. Although this explanation cannot
be ruled out, there is no clear reason why such a mechanism
would not affect peripheral airways. Our model shows that as
Tr was progressively reduced from unity and VDefs decreased
in size, constriction in central airways not leading to VDefs
increased despite the reduction of Tr and started to decrease
only after the VDefs in the model had been resolved (Fig. 7).
We recognize that our model is based on human structure and
function parameters that are different from those of the mo-
nopodial airway tree of rabbits. In spite of these differences,
the similarity between model and experimental behavior sug-
gests that, as in most nonlinear complex systems (6, 7), specific
details may be less important than the type of interdependence
among components of a system.

Validation of complex models. For models based on linear
differential equations, numerous mathematical methods exist
to estimate model parameters, which allow the adjustment of
model responses to experimental data and thus the quantitative
validation of these models. No comparable general approaches
exist for nonlinear models. Nonetheless, through the use of
known physiological relationships and morphological data, it is
possible to formulate nonlinear models that may involve com-
plicated structures and large sets of parameters (more than
30,000 in our model) to simulate specific functions of lung
behavior, such as airway response during bronchoconstriction.
To validate such models that may exhibit complex behavior,
e.g., in respiratory physiology (2, 37, 40), it is essential that the
model predicts characteristic behaviors consistent with exper-
imental data, while it is less crucial that these predictions are
quantitatively exact (32). We consider the ability to predict different experimental results that had not been theoretically linked before as strong evidence of our model’s validity, although we cannot per se exclude other explanations.

We chose a symmetric airway tree for our model with a homogeneous distribution of functional and structural parameters, neglecting the natural variability of airway smooth muscle reactivity, bronchial branching structure, or agonist deposition. We did so to specifically demonstrate that the combination of dilation and constriction of airways would be possible even in a uniform and symmetric airway tree during bronchoconstriction. The specific pattern of heterogeneity in airway response in a real lung is most likely determined by the natural or pathological variability within the lung. Thus, we can speculate that structural airway heterogeneity of the system should precipitate the formation of VDefs at levels of smooth muscle activation lower than those required for a uniform system.

In summary, we have demonstrated that modeling the lung as an integrated system can explain paradoxical behaviors such as the combination of dilation and constriction of airways during the development of, or recovery from, bronchoconstriction. Furthermore, the network model shows lung volume dependence of airway obstruction and apparent lung volume dependence of airway response that had not been linked before unifies the potential mechanisms behind these observations. The modeling results that had not been theoretically quantitatively exact (32). We consider the ability to predict different experimental results that had not been theoretically linked before as strong evidence of our model’s validity, although we cannot per se exclude other explanations.

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In summary, we have demonstrated that modeling the lung as an integrated system can explain paradoxical behaviors such as the combination of dilation and constriction of airways during the development of, or recovery from, bronchoconstriction. Furthermore, the network model shows lung volume dependence of airway obstruction and apparent hyperreactivity of a locally stimulated airway compared with that resulting from global stimulation of the airway tree. The model’s ability to explain several experimental results that had not been linked before unifies the potential mechanisms behind these observations. The modeling results presented here also illustrate the relevance of serial and parallel interdependence during bronchoconstriction and suggest that accounting for those interactions may be critical for understanding the global behavior of the lung under physiological and pathological conditions.

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