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, tethering forces, 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 bronchoconstriction, including for each airway the effects of pressure, bronchoconstriction, and smooth muscle activation. At low levels of Tr, the model exhibited uniform ventilation and homogeneous airway narrowing. But as Tr reached a critical level, the airway behavior suddenly changed to a dual response with a combination of constriction and dilation. Ventilation decreased dramatically 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. Compared with imaging data for local and global stimuli, as well as for the time course of airway lumen caliber during bronchoconstriction recovery, the model predictions were similar. The results illustrate the relevance of dynamic interactions among serial and parallel pathways in airway interdependence, which may be critical for the understanding of pathological conditions in asthma.

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 bronchiole 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, ple, 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.

Heterogeneity of Airway Constriction and Regional Ventilation

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).

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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 (PEE) was set at −2, 0, or 2 cmH₂O 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 (Tᵣ) 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 (VDefs) 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 (Tᵣ = 0.6) to establish a baseline tone and then progressively increased Tᵣ in a single 3rd-generation airway while leaving the rest of the tree at a constant Tᵣ. 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 Tᵣ 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 Tᵣ such that a concentration of 500 mg/ml of MCh corresponded to Tᵣ = 1, and 10 mg/ml to Tᵣ = 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 Tᵣ 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 8,191 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 airway radii between pathways inside and outside of ventilation defects (VDefs) for relative smooth muscle activation factor (Tᵣ) = 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 $T_r$ from unity to a basal activation level. The time constant and the basal activation level ($T_r = 0.6$) were chosen to match the dynamic behavior of ventilation defects and the airway size measured in rabbits (9). This approximate relationship between $T_r$ and time was used to plot the model predictions of step-by-step decreasing $T_r$ levels at time points that correspond to the experimental data.

RESULTS

For low levels of $T_r$, the model exhibited uniform ventilation and homogeneous airway narrowing (Fig. 1). As $T_r$ reached a critical level there was a clear change in behavior, with a sudden reduction in ventilation of certain terminal units. Further increments in $T_r$ 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 $T_r$ between 85% and 90% of maximal activation ($0.85 < T_r < 0.9$) for $P_{EE} = 0$ cmH$_2$O and at $0.65 < T_r < 0.7$ for $P_{EE} = -2$ cmH$_2$O, while no transition was observed for $P_{EE} = 2$ cmH$_2$O. The different $P_{EE}$ levels had identical fractions of hypoventilated units at $T_r$ values below the critical transitions. Substantial differences developed, however, at higher $T_r$ 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 $T_r$ (Fig. 1, right).

Duality of airway response: combination of constriction and dilation. Below criticality, airway lumen reduction with increasing $T_r$ was gradual within a generation of the three. As $T_r$ 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 $T_r$ was much lower in central than in peripheral airways. Indeed, closure or near-closure of airways was concentrated on peripheral airways. While $T_r$ increased above criticality, entire groups of airways changed behavior from dilating to narrowing as they were recruited into VDef regions. As a result, VDefs emerged in the model, the pattern of airway response along bronchial pathways was not random (Fig. 1, left). Airways

![Fig. 2. Effects of smooth muscle stimulation and lung volume on responses to bronchoprovocation. A: Fraction of hypoventilated terminal units ($<15\%$ of mean ventilation) for increasing levels of smooth muscle activation and three different lung volumes in the integrative model. Hypoventilation emerged at a critical level of activation and increased above this level. Lower lung inflation (positive end-expiratory pressure $P_{EE} = -2$ cmH$_2$O) shifted the critical level to the left, while higher lung inflation ($P_{EE} = 2$ cmH$_2$O) completely prevented the onset of airway closure. B: Change in airway resistance induced by 0.5-liter reduction in lung volume below baseline volume (functional residual capacity [FRC]) redrawn from data presented by Ding et al. in normal male subjects (22). The difference in airway resistance $\Delta R_{aw}$ at the two lung volumes changed dramatically at a critical methacholine (MCh) concentration. To demonstrate this behavior we normalized the original data for each subject by its critical MCh concentration.]

![Fig. 3. Airway radii at increasing levels of smooth muscle activation. The characteristic behavior of airways at the 3rd generation is representative for central airways, while the 12th generation shows the behavior of peripheral airways. Above the critical level of smooth muscle activation ($>0.85$) emerged a combination of constriction and dilation, showing evidence of parallel airway interdependence between dilating airways located outside of VDefs and constricting airways located within VDefs (Fig. 1). The number of airways in groups of similar size visualizes the contribution of different airway behaviors to the heterogeneous response within a generation.]

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along pathways leading to VDefs 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 Tr in a single central airway resulted in full closure even at submaximal level of smooth muscle activation (Tr = 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 (Tr = 1). For global elevation of Tr, average central airway radii were reduced but reached a plateau in their narrowing, so that even at activation levels above critical Tr, no central airway closed. Increasing PEE to 2 cmH₂O shifted the response curves for local and global stimulation toward the right (higher values of Tr) 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 Tr, 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 Tr starting from maximum was progressively reduced, the size of VDefs decreased, while the lumen of central airways leading to well ventilated lung regions increasingly narrowed (Fig. 7). Airways feeding VDefs showed progressive dilation during this period. As Tr was further reduced, VDefs vanished and all airways of the model dilated monotonically.
to both agonist challenge and cold air stimuli, and it reported a
these studies (27) assessed the response of the central airways
among individual airways in the response to agonist aerosol
challenge was the narrowing of airways smaller than those that
cause for ventilation impairment during a bronchoconstrictive
21, 34). Therefore, the investigators concluded that the primary
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 find-
ings as we discuss below.

It is well known that airway narrowing after bronchoprovo-
cation causes major ventilation heterogeneity associated with
the formation of large and contiguous VDefs (39–41). Al-
though the VDef’s large size could suggest involvement of
large airways, imaging with HRCT of agonist-challenged asth-
matic 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 dem-
strated 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 forma-
tion 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) im-
posed on the tree for computational purposes, the resulting

Fig. 6. Effect of smooth muscle activation on the dynamic equilibrium of
ventilated airways (—) and on the static equilibrium of unventilated airways
( - - ). CT imaging data collected during breathing (•) and apnea (○) (11, 15) and
for global (●) and local (○) agonist stimuli (18) are superimposed using a
log-transformed MCh scale.
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 airway 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 lumen 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 apnea 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 (T_{critical}), above which VDefs were formed. If the concentration of the inhaled agonist is at FRC related to a Tr < T_{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 T_{crit} result in T_{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 (T_r < 1, Fig. 4). In contrast, closure of these airways was avoided when all airways of the tree were uniformly activated even at maximal level (T_r = 1). Also consistent with experimental results (17), the model showed that increasing lung volume with P_{EE} shifted the dose response curve of the challenged airway to the right but did not prevent its closure.

In the simulations of single airway stimulation, the rest of the airway tree was activated to a constant level (T_r = 0.6) to simulate a basal smooth muscle tone (19). Because closure of 3rd-generation airway redistributes 1/8 of the tidal volume to other regions, the result of parallel interdependence was a small relative dilation in airways with increased flow. Simulations of individual airway stimulation also illustrate the relevance of serial interdependence in our model. Airways distal to the closed branch had a constant T_r but became substantially more constricted after the closure of their parent airway (Fig. 5). Given that our model does not involve gas exchange, inspiratory-to-expiratory airway resistance asymmetry, or inertial effects, the mean level of inflation of the parenchyma subtended by an occluded airway is equal to that of the rest of the lung and thus not responsible for the increased constriction. Instead, under local conditions of apnea distal to the closed airway, the lumen of those airways is determined by the static equilibrium between smooth muscle and parenchymal forces. As such, the constriction of those airways can be interpreted as caused by the loss of dynamic parenchymal stretch and its bronchodilating effect, which is consistent with oscillatory measurements of resistance at tidal volumes between 0 and 20 ml/kg in rabbits (35). The apnea-induced airway narrowing in the model is consistent with imaging data in dogs (11, 15), except for the magnitude of the change (Fig. 6). Although this discrepancy could arise from model assumptions and parameter choices, it is also possible that the observed airway narrowing in dogs was reduced by the bronchodilating effect of hypercapnia during apnea.

The relative constriction of airways that were effectively under conditions of apnea was relatively uniform and independent of generation, which illustrates the absence of serial and parallel interdependence under static conditions. In contrast, during breathing there was a small and gradual reduction of airway lumen from central to the peripheral airways (Fig. 5). This gradient in constriction was greatly exaggerated for airways leading to VDefs, for T_r above critical levels (Fig. 1). These central-to-peripheral differences in airway behavior under 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 paradoxical 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 resolved, the reduction in central airway lumen reached a plateau, 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 T_r was progressively reduced from unity and VDefs decreased in size, constriction in central airways not leading to VDefs increased despite the reduction of T_r 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 monopodial airway tree of rabbits. In spite of these differences, the similarity between model and experimental behavior suggests 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 complicated 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 experimental 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 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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