Airway Transmural Pressures in an Airway Tree During Bronchoconstriction in Asthma

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Introduction

Asthma attacks lead to bronchoconstriction and severe breathing difficulties. However, the emergence of hypoventilated regions, referred to as ventilation defects (VDefs) [1–4], shows that severe bronchoconstriction causing VDefs is regional, and that there is much less constriction outside of VDefs than inside. The clustering of bronchoconstriction within VDefs is the result of feedback mechanisms leading to self-organized patchiness in ventilation with severe airway constriction inside of VDefs and less constriction outside [1,5]. The inhomogeneity in constriction indicates the differences in transmural pressure among the airways, but their magnitude is unknown. Tidal expansion of the lungs during breathing results in tidal changes in transmural pressure at the airways and has a strong bronchodilating effect. That means that a better understanding of both magnitude and regional differences in airway transmural pressures to prevent or recover from asthma attacks could help about 300 million people worldwide [6] that are affected by asthma. Additionally, asthma exacerbations result in the U.S. in 1.75 million emergency department visits and 456,000 hospitalizations annually [7].

The assessment of airway transmural pressure depends on the peribronchial pressure, the pressure outside of the airway wall, which cannot be directly measured in intact lungs. Mead et al. showed in an elegant study that the peribronchial pressure is approximately equal to the pleural pressure when the transpulmonary pressure is within a range that is typical for quiet breathing [8]. The relationship suggests that changes in pleural pressure during quiet tidal breathing must be closely correlated with corresponding changes in parenchymal tethering. However, the approximation that peribronchial pressure is equal to pleural pressure does not apply to hyperinflation nor to lungs with heterogeneous ventilation such as VDefs during asthma attacks. Additionally, airway narrowing during asthma attacks results in a deformation of the tissue surrounding the airway increasing the parenchymal tethering forces [9–11], and heterogeneity in airway geometry as well as asymmetry in airway branching affect bronchoconstriction [12–14]. Under these conditions, airway peribronchial pressures are different from the global average that the relationship between peribronchial and pleural pressure describes. In lungs that are not homogeneous, the transmural pressure of an airway is governed by its local environment including the pressure difference across the airway wall and the parenchymal tethering forces changing with both lung volume and airway constriction [10].

Bronchodilating effects of tidal breathing correspond at the level of the dynamic equilibrium of airway narrowing at which the counteracting forces of airway smooth muscle and its load generated by the transmural pressure are in balance [15]. Changes in the dynamic equilibrium of airway smooth muscle have been demonstrated as dilating effects of tidal stretches or forces on stimulated airway smooth muscle in tissue strips [15–18], precision cut lung slices [19], and in intact isolated lungs [20–23]. These results of tissue strips or isolated airways are representative for homogeneous airway behavior within the lungs. However, conditions in an intact airway tree are different if there is any inhomogeneity leading to differences in pressure and more complicated airflows with the tree including for example pendelluft [24–26]. In complex systems, interactions among the elements of a system such as the airways within the bronchial tree can give rise to new behaviors, referred to as emergent behaviors, that are different from the behavior of the elements in isolation [27]. Emergent phenomena are ubiquitous in biological systems [28–31] including the emergence of VDefs during asthma attacks when interactions among airways lead to self-organized clustering of severe airway constriction [1,5]. Severe regional
airway constriction results in increased regional ventilation outside of VDefs and potentially in dynamic hyperinflation, which is different from the conditions in a healthy homogeneous lung. Thus, peribronchial pressures may show substantial regional differences during asthma attacks.

The aim of this study was to estimate peak transmural pressures of the individual airways in a bronchial tree during bronchoconstriction to gain insight into the magnitude of changes and differences among airways. Aiming at a lower boundary for the range of peak transmural pressures of different possible tree configurations, a symmetric tree structure with minimal variability among airways was selected since it had the smallest VDefs compared to different degrees of asymmetry in a previous study [14], and smaller VDefs are linked to less increase in tidal expansion outside of VDefs when tidal volume is redistributed to ventilated regions. Understanding peak transmural pressures within a bronchial tree is essential for the design and interpretation of experimental studies of isolated airways or airway smooth muscle strips.

**Methods**

Assessment of transmural pressures throughout an airway tree in this study is based on a computational model of bronchoconstriction in an airway tree that has been previously described in detail [1]. Briefly, this model incorporates the Anafi and Wilson model of a single airway [9] for all the 8191 individual airways of an airway tree with 12 generations (Fig. 1). The Anafi and Wilson model described first the dynamic behavior of a single airway including a link between the airflow going through an airway and the expansion of the parenchyma surrounding the airway [9]. Also, this model incorporated the Lai-Fook model of parenchymal tethering [10], which was a previous model generation focusing on the static relationship between the narrowing of a tube-shaped anatomical structure embedded in the lung parenchyma and the increase in parenchymal tethering during the narrowing. Incorporated in the computational model of bronchoconstriction, the dynamic model of Anafi and Wilson and the static model of Lai-Fook describe the individual airways and their local interactions with the parenchyma. However, the airways are interconnected within the bronchial tree.

The airway dimensions of the tree are based on Weibel’s morphometric data for the human bronchial tree [32]. A random variation of 1% standard deviation in airway wall thickness was added as perturbation from the unstable equilibrium that a perfectly symmetric tree would have during bronchoconstriction. Airflows and pressures within the bronchial tree and the volume of terminal units are dynamic variables changing during the breathing cycle and were calculated with time steps of 10 ms. The radii of the individual airways changed from breath to breath according to smooth muscle tension and the airway’s peak transmural pressure during the preceding breathing cycle meaning \( \Delta r_k = f\left(r_{k,1}, P_{tr,peak, k,1}, T_{k,1}\right) \) where \( \Delta r_k \) is the change in radius at time-step \( k \), \( r_{k,1} \) the radius at the previous time-step, \( P_{tr,peak, k,1} \) the peak transmural pressure of the previous breath and \( T_{k,1} \) the relative airway smooth muscle tension during breath \( k \) [19]. Additionally, the model includes speed indices for the dynamics of the airway’s response to changes in its peak transmural pressure [24]. Interactions between changes in airway diameter and the airflows and pressures throughout the airway tree can lead in this model to feedback loops and self-organized behavior. For example, if the airflow through one daughter airway at a bifurcation of the tree is slightly smaller compared to the other airway, it would lead to less parenchymal tethering and lower transmural pressure, which allows more constriction of the airway further increasing airway resistance and subsequently decreasing airflow. This positive feedback leads to increasing constriction of that airway over time. A redistribution of airflow to the other daughter airway on the other hand increases parenchymal tethering and the transmural pressure, which may even result in a relative dilation of the airway [33].

The original implementation of the computational model was modified in order to save the model’s airway peak transmural pressures. The peak values of the individual airways of the tree were determined from the dynamic changes in transmural pressure during a breathing cycle using the model’s calculations with a time resolution of 10 ms. For this study, peak transmural pressures of the airways were selected at baseline during normal tidal breathing with relaxed airway smooth muscle and after 400 breaths at a steady-state of self-organized bronchoconstriction with maximum airway smooth muscle stimulation (\( T_{1} = 1 \)), tidal volume of each breath was 600 ml with 12 breaths/minute and constant airflow during inspiration at the airway opening. The model’s input at the opening of the most central airway was flow controlled during inspiration (50% of the breathing cycle) and pressure controlled during expiration using a positive end-expiratory pressure of 5 cmH2O. However, within the airway tree airflows are always distributed according to pressures differences and airway resistances. The model was compiled using MATLAB.
Compiler (MathWorks, Natick, MA), and simulation runs were performed using the Linux Cluster of Enterprise Research Infrastructure & Services at Partners Healthcare. For data analysis, relative changes in the peak transmural pressures of the airways were calculated compared to baseline values.

Ventilation of each terminal unit was calculated as the difference between minimum and maximum of the dynamic changes in volume during a breathing cycle. The mean-normalized ventilation distribution among the 4096 terminal units of the model was visualized using gray color map with 64/\sqrt{64} grid and a Mandelbrot tree structure for the location of the terminal units within the map. How closely related neighboring units of the map are within the branching hierarchy of the bronchial tree is defined by the Mandelbrot tree. Changes in peak transmural pressures and other pressures are visualized across airway generations either with a hierarchical tree of lines to illustrate the connectivity among the airways or as scatter plots with individual offsets for the data points relative to the airway generation to decrease the major overlap of data points.

Results

At baseline, all airways were relaxed, and the ventilation distribution was homogeneous. Peak transmural pressures of the airways were equal among airways of each generation of the airway tree. However, there was a central-to-peripheral gradient in transmural pressures because each airway of the bronchial tree has a resistance causing a pressure difference between its two ends when a flow goes through. In other words, all central to peripheral pathways through the airway tree had the same pressure gradient.

Bronchoconstriction led to the emergence of a heterogeneous pattern in peak transmural pressures causing differences in airway narrowing and VDefs (Fig. 2). Relative to baseline, all peak transmural pressures were increased during bronchoconstriction. However, there were strong regional differences among airways ranging from 84% increase in a central airway outside of VDefs, to only about 27% in a terminal airway inside of large region with VDefs (Figs. 2(c) and 2(d)). The airways outside of VDefs had typically an increase above 70%. But pathways leading to hypoventilated units had lower values. Peripheral airways of ventilated terminal units inside of VDefs showed much higher increases in peak transmural pressures than the airways associated with hypoventilated terminal units. Also, terminal airways of hypoventilated units in a small region with VDefs had peak transmural pressures approximately equal to terminal airways in a large region with VDefs. The central airways associated with the large region of VDefs showed only about 60–63% increase in peak transmural pressures compared to the 80–84% in the region outside of VDefs.

For further investigation of the different factors contributing to changes in peak transmural pressures, alveolar pressures and
intraluminal pressures were derived from the model and analyzed throughout the airway tree. Severe hypoventilation or airway closure in VDefs resulted in a decrease in peak alveolar pressure by about 15% relative to baseline (Fig. 3(a)). In contrast, peak alveolar pressure increased by 40% outside of VDefs, and by 30% in the better terminal units in regions with VDefs. Changes in peak alveolar pressure relative to baseline normalized by the change in transmural pressure showed contributions of alveolar pressures of up to 40% and a large variation for airways within regions with large VDefs (Fig. 3(b)). In airways outside of VDefs, increases in peak alveolar pressure had substantial and consistent contribution to the increase in peak transmural pressure.

Dynamic pressure differences between intraluminal and alveolar pressure increased during bronchoconstriction driven by the increase in airway resistance. The maximal contribution relative to total transmural pressure was 24% in a central airway inside a region with large VDefs (Fig. 4). In the airways of terminal units outside of VDefs, the intraluminal pressure made virtually no contribution to peak transmural pressure since airway resistance was relatively small so that the difference to the alveolar pressure was small. From central to peripheral airways, there was a clear decrease in the contribution of the difference between intraluminal and alveolar pressure because of the decreasing pathway resistance between the airway generation and the terminal units.

Discussion

The main findings of this study are: (1) the substantial increases in transmural pressure during bronchoconstriction, (2) the emergence of self-organized heterogeneity in airway transmural pressure associated with VDefs, (3) the effect of regional expansion on transmural pressure, and (4) the heterogeneity of intraluminal pressure within the bronchial tree during VDefs. The results show a substantial deviation of airway transmural pressure from the paradigm that pleural pressure can be used as peribronchial pressure to derive the transmural pressure. That is a fundamental difference for our understanding of the peak transmural pressures during the breathing cycles, and the difference in magnitude is relevant since it counteracts the airway smooth muscle force pulling inward (Fig. 1). Additionally, this has implications for the design and interpretation of experimental studies of isolated airways or airway smooth muscle in response to transmural pressure or smooth muscle load.

In a homogeneous lung with dilated airways, peribronchial pressure is for quiet tidal breathing less than 1 cmH2O different from pleural pressure [8] and, thus, has been assumed to be approximately equal although there is evidence that this is an oversimplification [34]. During homogeneous bronchoconstriction, one would expect contributions to an increase in peak transmural pressure from increased parenchymal tethering forces due to airway narrowing, and from both increased intraluminal pressure and dynamic hyperinflation due to increased airway resistance. Homogeneous bronchoconstriction would affect all pathways of the bronchial tree equally so that the ventilation distribution should remain homogeneous.

In contrast to homogeneous airway behavior during bronchoconstriction, imaging studies have demonstrated the emergence of VDefs in humans [1–4,35–37] and in animals [38–40]. VDefs are direct evidence for major regional differences in ventilation, airflow and parenchymal tidal expansion, which has implications for the peak transmural pressure of the airways: (1) the increase in regional tidal expansion leads to substantially higher peak transmural pressures compared to conditions with the relaxed airways, homogeneous ventilation distribution and quiet tidal breathing, and (2) increased airway resistance as well as its heterogeneity affects the intraluminal pressures in the bronchial tree.
There is a substantial increase in some airways relative to baseline conditions with dilated airway smooth muscle and a homogeneous ventilation distribution. Under the baseline conditions, the peribronchial pressure could be approximately equal to pleural pressure. But the increase in peak transmural pressure relative to the baseline cannot be generalized because several factors affect its magnitude. For example, the larger VDefs result in higher redistribution of ventilation, which increases parenchymal tidal expansion outside of VDefs affecting the peak transmural pressure of airways in that region. In other words, the order of magnitude of changes in this study is a relevant example but the exact amount depends on the specific conditions. For example, deep inspirations are highly effective in dilating airway smooth muscle, but the distribution of the parenchymal expansion during bronchoconstriction is heterogeneous so that the volume and frequency of deep breaths can affect the size of VDefs [33].

The magnitude of the increase in airway transmural pressure has major implication for the understanding of both airway and airway smooth muscle responses to tidal breathing. For experimental studies using smooth muscle strips or isolated airways, it is important to determine what amplitude of transmural pressure oscillations for isolated airways or force oscillations for airway smooth muscle strips may be typical conditions of tidal breathing and if they can either prevent the constriction of airway smooth muscle or achieve its dilation. The results of this paper show that the transmural pressure can be in some regions substantially higher than the paradigm that peribronchial pressure is approximately equal to pleural pressure suggests. Additionally, there are regions with lower peak transmural pressure. These differences are important because they reflect the heterogeneity of bronchoconstriction in an airway tree that is associated with VDefs. Computational modeling and simulation allow estimation of such differences among airways and can provide detailed insights. In fact, they are the method of choice since the peribronchial pressures of airways are not experimentally accessible for a large number of airways in different regions of the lungs, during tidal breathing and bronchoconstriction. Also, the model that was utilized here in modified form had been essential before for the demonstration of feedback mechanisms that can explain the emergence of VDefs [1]. Airway peak transmural pressure is one of the parameters of the feedback loop causing the bifurcations or divergence in airway behavior: beyond the critical point for airway stability, a small fluctuation causing a higher peak transmural pressure in one branch at an anatomical airway bifurcation would cause a slight dilation that further increases ventilation and peak transmural pressure in this airway at the next breath triggering a positive feedback [28]. In contrast, the neighboring branch would receive less ventilation leading to a positive feedback with increasing airway constriction. The feedback loop includes also peak inflation quantified by alveolar pressure and the dynamic changes in intraluminal pressure. Both contribute to the changes in peak transmural pressure as the results demonstrated.

Range, magnitude, and distribution of airway transmural pressures in a bronchial tree are affected by the configuration of the tree and by the airway geometry. For this study, an idealized symmetrically branching airway tree based on Weibel’s morphological data for the normal lung was utilized [32]. This neglects asymmetry in the branching of human airway trees as well as variations among airways others have investigated in detail using asymmetric airway trees and statistical data of the variation among airways within the bronchial tree [12, 13, 41]. However, the fundamental emergent behavior leading to VDefs occurs independent of these differences when conditions for a given tree reach the critical point beyond which positive feedback results in self-organized clustering of airway narrowing and VDefs [14]. Also, a previous study showed that a symmetric tree had compared to asymmetric tree configurations the lowest elastance [14], suggesting that VDefs were smaller and that the increase in transmural pressure in a symmetric tree may be the lower boundary for comparable different asymmetric tree configurations. An additional source of uncertainty in asymmetric tree configurations is that there are currently no morphological data including the connectivity among the individual airways throughout the airway tree, which limits our ability to determine the actual variation in impedances of different pathways from the central airway to the terminal units and its potential effect on transmural pressures.

Limitations of the study are those common for modeling in general: a model is always incomplete compared to the original. Mucus in the airways could for example further increase the obstruction of airway lumen. Also, the study utilized a single random perturbation of the model from the unstable equilibrium rather than testing different realizations of the random component. But it has been shown in previous studies that different realizations of small random variations in airway wall thickness have only a very small effect on the magnitude of VDefs so that its effect on the estimates of peak transmural pressures in the bronchial tree is expected to be negligible [14, 33]. The emergence of heterogeneity in peak transmural pressures during bronchoconstriction shows that isolated airway responses to transmural pressure oscillations cannot be extrapolated to whole organ behavior as if bronchoconstriction would be homogeneous. However, the results from computational modeling of bronchoconstriction in an airway tree may be used to investigate the effects of regional differences on airway behavior in experimental studies.

Conclusions

The results of this study suggest that bronchoconstriction leads to airway peak transmural pressures outside of VDefs substantially higher than the difference between intraluminal and pleural pressure that the paradigm of peribronchial pressure being approximately equal to pleural pressure suggested. Also, the emergence of self-organized VDefs is linked to the emergence of heterogeneity in peak transmural pressures. These differences may have consequences for airway behavior that need further investigation in the experimental studies.

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