Published in final edited form as:

Respir Physiol Neurobiol. 2013 August 15; 188(2): 94–101. doi:10.1016/j.resp.2013.06.005.

Influence of Parenchymal Heterogeneity on Airway-Parenchymal Interdependence

Baoshun Ma¹, Barbara Breen², and Jason H.T. Bates¹

¹College of Medicine, University of Vermont, Burlington, VT 05405, USA ²Auckland Bioengineering Institute, University of Auckland, Auckland, New Zealand

Abstract

To estimate the influence of parenchymal heterogeneities on airway-parenchymal interdependence, we considered a circular airway embedded within elastic parenchyma modeled as 1) a hexagonal spring network, 2) a triangular spring network, or 3) a continuum. The deformation in the parenchyma due to active airway contraction was simulated using the finite element method. Random perturbations of elastic moduli in the parenchyma did not significantly affect the overall pattern of force transmission. By contrast, when elastic moduli were increased along a path projecting radially outward from the airway, the hexagonal spring network model predicted significantly increased force along this line as the airway contracted, but this was not observed in other two models. These results indicate that tissue heterogeneities generally have minimal effect on the global nature of airway-parenchymal interdependence. However, in the exceptional circumstance of scar tissue aligned radially from the airway wall, parenchymal distortion forces may propagate much farther from the airway wall than was previously thought.

Keywords

Mechanical interdependence; lung elasticity; spring network models; continuum mechanics

1. Introduction

The pulmonary airways and the parenchyma in which they are embedded are mechanically linked via the forces of airway-parenchymal interdependence (Lai-Fook, 1979b; Mead et al., 1970; Wilson, 1972) with important functional consequences. Specifically, interdependence forces increase proportionately with transpulmonary pressure, acting to maintain patency of the airway lumen. Likewise, airway contraction distorts the nearby parenchyma, causing it to stiffen and thus increase the forces of airway-parenchymal interdependence commensurately (Lauzon et al., 1992; Mitzner et al., 1992; Smith et al., 1984). The tethering of the airways by the surrounding parenchyma thus critically affects the ability of activated airway smooth muscle to shorten, such as occurs, for example, during an asthma attack. Accordingly, being able to predict the quantitative details of airway-parenchymal

© 2013 Elsevier B.V. All rights reserved.

Corresponding author. Jason H.T. Bates, Ph.D., College of Medicine, University of Vermont, 149 Beaumont Ave., Burlington, VT. 05405, Tel: (802) 656-8912, Fax: (802) 656-8926, jason.h.bates@med.uvm.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

interdependence is crucial for understanding how airways responsiveness is affected by changes in lung volume.

Since the pioneering work of Mead et al. (Mead et al., 1970) that brought attention to the physiological importance of airway-parenchymal interdependence, there have been numerous studies of this phenomenon (Adler and Bates, 2000; Adler et al., 1998; Benjamin et al., 1974; Dandurand et al., 1993; Khan et al., 2010; Lai-Fook, 1979b; Lai-Fook and Hyatt, 1979; Lai-Fook et al., 1977a; Lai-Fook and Kallok, 1982; Ma and Bates, 2012; Noble et al., 2005; Smith et al., 1984; Wilson, 1972). All theoretical studies to date have assumed the parenchyma to be homogeneous, yet it is well known that substantial heterogeneity and anisotropy can develop in the lung parenchyma in disease (Chapman et al., 2012; Ito et al., 2004; Ito et al., 2007; Kaczka et al., 2011). Indeed, even normal parenchyma is clearly inhomogeneous (Adler et al., 1998; Ma et al., 2013). This raises the important question as to whether our understanding of the nature of airway-parenchymal interdependence, which is currently based on the assumption of parenchymal homogeneity, might change significantly if heterogeneity is taken into account.

Accordingly, the goal of the present study was to determine if regional heterogeneities in parenchymal mechanics have any important consequences for the forces of airway-parenchymal interdependence generated by airway narrowing. We performed this investigation using heterogeneous adaptations of computational models that we have investigated previously, namely a 2-dimensional circular airway embedded in homogeneous linear elastic parenchyma (Ma and Bates, 2012; Ma et al., 2013) and a 3-dimensional continuum model of a circular airway embedded in homogeneous nonlinear elastic parenchyma (Breen et al., 2012).

2. Methods

We first modeled the parenchyma as a 2-dimensional network of nonlinear springs (Ma and Bates, 2012; Ma et al., 2013). The springs were connected to each other either in a hexagonal pattern or a triangular pattern. The hexagonal spring pattern is motivated by the idealized space-filling arrangement of alveolar walls in 2 dimensions, while the triangular spring model represents a more structurally stable structure under shear. We have previously shown that slices of agarose-filled lung parenchyma behave mechanically more like a triangular network than a hexagonal one (Ma et al., 2013) despite the visual similarity of the latter to the quasi-hexagonal arrangement of alveolar walls seen on magnified sections of the lung. Given that the lung is not normally filled with agarose, it remains an open question as to how the parenchyma behaves *in situ*, so we felt it was appropriate to examine both model types in the present study.

The springs in the networks were linearly elastic, but their stiffness could be specified individually to create arbitrary degrees of elastic heterogeneity. We could thus represent, for example, the kinds of variations in regional mechanical properties that might occur in pulmonary fibrosis (Gonzalez and Ludwig, 2005). Accordingly, we investigated the effects of random variations in the stiffness of individual springs. In addition, we also modeled an extreme case of fiber stiffening, such as might result from structural remodeling, by increasing the elastic moduli of springs along a track emanating radially outward from the airway wall. The spring stiffness along this line was increased from 2 to 200 times in separate simulations. The springs were connected at their points of intersection by pin joints about which they were free to rotate with negligible friction. We reduced the zero-load length of the springs representing the walls of the airway, assuming quasi-static equilibrium, until the desired degree of airway narrowing (30% of the relaxed airway area) had been

achieved. At each step in the contraction process, the finite element (FE) method (Yang, 1986) was used to determine the equilibrium configuration of the entire network.

To explore scarring behavior in nonlinear parenchymal tissue, we constructed a FE model of a slice of lung tissue containing a cross-section of a terminal bronchiole (Breen et al., 2012). The lung slice was modeled as a three-dimensional mesh composed of finite elements that were spatially located to produce the desired geometry of the slice. Eight nodes defined each element and adjacent elements shared nodes. The nonlinear elastic behavior of the tissue was calculated at 27 ($3 \times 3 \times 3$) spatially distributed Gauss points within each element and interpolated between these points. Interpolation was accomplished using cubic Hermite basis functions in each of the three coordinate directions (Bradley et al., 1997). This enforced, at every node, continuity of all variables as well as of the first and second derivatives of the variables.

An airway was represented by a circular hole of diameter 0.4 mm centered in a slice of tissue having dimensions $3 \times 3 \times 0.2$ mm. The radius of the hole coincided with the boundary between the airway adventitia and the parenchyma, so the model did not include the airway wall itself.

The lung tissue was modeled as a compressible and nonlinearly elastic continuum with homogeneous and isotropic material properties (Fung, 1993; Kowalczyk and Kleiber, 1994; Tawhai et al., 2009). The von Mises stress

$$S_{VM} = \frac{1}{2} \sqrt{(PS_1 - PS_2)^2 + (PS_2 - PS_3)^2 + (PS_3 - PS_1)^2},$$

was obtained from the three principal x - y - z stresses PS_1 , PS_2 and PS_3 and the nonlinear strain energy density function

$$W = c e^{(aJ_1^2 + bJ_2)},$$

where J_1 and J_2 are the first and second invariants of the Green-Lagrangian finite strain tensor. The coefficients a (0.43, dimensionless), b (−0.6, dimensionless) and c (2 kPa) do not have physical meaning. Their values are set to correlate with known elastic recoil pressures for uniform volume expansions in zero gravity (Burrowes and Tawhai, 2010; Tawhai et al., 2009).

A line of scar tissue was modeled via a 100-fold increase in the coefficient c of the strain energy density function (Eq. 2) at Gauss points along a line emanating radially from the airway.

We performed our simulations from a reference state defined to have zero stress and zero strain because we are interested here in the additional parenchymal forces and displacements that are created as a result of airway contraction (note that these forces and displacements can simply be added to any that might already exist as a result of baseline transpulmonary pressure). A series of quasi-static displacements were enforced that decreased the airway diameter to approximately half its initial value. Nodes on the perimeter of the airway were forced to move stepwise to decrease the airway diameter symmetrically and the derivatives were scaled to maintain circularity. All other nodes were free to move in response with the exception of the nodes fixing the outer dimensions of the slice. Axial and rotational displacements were prevented, thus limiting the effects of the contraction to the 2-dimensional plane of the lung/airway cross-section. At each step, the Cauchy stress, which

represents the force per unit area of the deformed configuration, was calculated for every Gauss point in the FE mesh. The von Mises stress was calculated from the principal Cauchy stresses. Points nearest the fixed boundary that might introduce edge effects were excluded.

3. Results

Figure 1 shows the behavior of the hexagonal spring network model following contraction of an airway at the center for 3 different heterogeneity scenarios. When the springs representing the parenchyma were all identical the contraction led to a radially symmetric strain field (Fig. 1A, left-hand panel). The mean force (relative to a pre-contraction value of zero) in the parenchyma immediately adjacent to the airway wall showed significant dependence on radial distance from the airway wall, with the radially aligned springs coming under significant tension while the circumferentially aligned springs were less tense (Fig. 1A, right-hand panel). By about 2 diameters from the airway wall, however, all springs experienced about the same tension that remained roughly constant at 40–50% of the peak value. Close to the borders of the network, at about 6 diameters distance from the airway, spring tension fell off due to edge effects related mostly to our use of softened springs around the network border that helped to ensure numerical convergence of the model. (Accordingly, the forces in the springs connected directly to the outer boundary are not plotted in the figures.) Very similar results were obtained (Fig. 1B) when the springs in the network were given random stiffness drawn from a uniform distribution having the same mean as the uniform case with a width 15% either side of the mean. This result was also obtained when the heterogeneities were increased to encompass 40% either side of the mean.

By contrast, when the springs were returned to their original equal stiffness with the exception of a single diagonal track of springs that were stiffened by 100 fold, we found that the force along the direction of the stiffened springs was increased compared to the rest of the parenchyma by a factor of 4 to 5 (Fig. 1C). The magnitude of this concentrated force along the stiffened springs depended on how stiff these springs were compared to the remainder of the parenchymal springs. When stiffness was increased 5, 10, 50, 100 and 200-fold, the force along the stiffened springs increased by roughly 1.7, 2, 3, 4 and 5-fold, respectively, compared to the rest of the network (Fig. 2). These effects were also evident in different sized networks (i.e. different ratios of length around the outer border of the network to airway diameter), although as border length increased the magnitude of the plateau force decreased commensurately (Fig. 3). We also observed, however, that the increased force along a line of stiffened springs was sensitive to whether the springs were oriented co-linearly as opposed to simply being connected contiguously. That is, if the springs were arranged in a more zigzag pattern then force increase did not occur because the distortion of the parenchyma merely brought the springs more into alignment rather than stretching them.

A rather different picture emerged when we applied similar conditions to the triangular spring network (Fig. 4). Now the distribution of spring force (relative to a baseline force of zero) as a function of radial distance from the airway was insensitive to either of the imposed stiffness heterogeneity patterns. Furthermore, while some of the springs came under significant tension next to the airway wall, some were in significant state of compression (negative force). All spring forces, however, asymptoted toward zero with distance from the airway as opposed to settling on an elevated plateau as occurred with the hexagonal spring model shown in Fig. 1.

Figure 5A shows the continuum model with a diagonal line of stiffened tissue emanating radially from the airway wall in the lower right quadrant. Figure 5B shows results from the

continuum model with nonlinear material properties. The mean von Mises stress per element is shown as a function of radial distance from the center of the airway following airway contraction for both homogeneous tissue and with the diagonal scar shown in Fig. 5A. While the elements along the line of stiffened tissue do exhibit slightly higher stresses than the other elements, both stress distributions asymptote to zero and are sufficiently similar to allow one to conclude that, similar to the triangular spring network model shown in Fig. 4, the continuum model is insensitive to the presence of circumferentially asymmetric regions of stiffened tissue.

4. Discussion

Increased lung volume has long been known as perhaps the most potent bronchodilator (An et al., 2007), resulting in substantial amount of research into the quantitative nature of so-called airway-parenchymal interdependence beginning with the early experimental work of Mead et al (Mead et al., 1970). The most important contributions in this area, however, are almost certainly those of Lai-Fook (Adler et al., 1998; Lai-Fook, 1979b; Lai-Fook and Hyatt, 1979; Lai-Fook et al., 1978a; Lai-Fook et al., 1977a) who developed a quantitative description of how homogeneous parenchyma around an airway or blood vessel becomes distorted as the conduit changes diameter, and how this leads to an increase in the forces of airway-parenchymal interdependence. Numerous modeling studies have invoked the homogeneous parenchyma assumption to examine aspects of airway-parenchymal interdependence, with convincing results (Bates and Lauzon, 2007; Gunst et al., 1988; Lambert and Wilson, 1973; Latourelle et al., 2002). These studies, however, all assume the parenchyma to be uniform and isotropic, yet the airways in the lung are surrounded by tissue that may be quite heterogeneous, and which may include blood vessels and other airways in the immediate vicinity. Indeed, the parenchymal distortion field surrounding an airway in an explanted lung slice shows marked departures from radial symmetry (Adler et al., 1998; Ma et al., 2013), which raises the question as to how important these tissue heterogeneities are for airway-parenchymal interdependence.

The results of the present investigation build on our previous modeling studies of airway-parenchymal interdependence in which we showed that the distribution of displacements and forces within the parenchyma surrounding a contracting airway are rather different depending on whether the parenchyma is modeled as a hexagonal network of springs, a triangular network (Ma and Bates, 2012; Ma et al., 2013), or a continuum model (Breen et al., 2012). In all cases the parenchymal distortion is greatest next to the airway wall and decreases with radial distance (Figs. 1, 4 and 5). However, with the hexagonal spring network the increase in parenchymal force due to contraction levels off at a finite value at several airway diameters distance from the airway wall, and continues in this manner virtually all the way to the network boundary (Figs. 1–3). By contrast, force in the triangular spring network approaches zero with distance from the airway center and is already small by about 3–4 airway diameters (Fig. 4), similar to the predictions of the Lai-Fook theory (Lai-Fook, 1979b; Lai-Fook et al., 1977a; Lauzon et al., 1992), which is based on continuum mechanics. We attribute these differences in predicted behavior to the differences in resistance to shear exhibited by the hexagonal versus the triangular spring networks (Ma and Bates, 2012). Without the diagonal struts that form the triangular network, the hexagonal network of springs more easily undergoes shear deformation. We have previously shown that an explanted lung slice embedded in agarose behaves more like the triangular network (Ma et al., 2013).

The present study shows substantial differences between the hexagonal versus triangular spring network models (Fig. 1 vs. Fig. 4), and demonstrates a similarity between the predictions of the triangular network model and a continuum model (Fig. 4 vs. Fig. 5). This

similarity may be due to the fact that the continuum model, by its very nature, averages out the inhomogeneities, while the triangular network is more resistant to shear. In both cases, however, our results indicate that heterogeneities make little difference to the ability of an airway to narrow against the forces of airway-parenchymal interdependence. In the hexagonal parenchymal network, for example, the heterogeneities were produced by introducing random zero-mean variations in spring modulus. The elastic after-loads on the airway were thus comparable between the homogeneous and heterogeneous cases for a fixed amount of airway narrowing. Even with the stiffened line of springs, which increased the mean network modulus by about 2.6 fold, along most of the airway perimeter the outward tethering forces on the airway were the same as for the homogeneous case. For the triangular spring network we applied parenchymal heterogeneities in a similar fashion, but here we imposed the same contraction force for the various conditions, so the similar amount of airway narrowing that occurred in the homogeneous and heterogeneous cases was a direct reflection of the roughly equal opposing forces of interdependence.

It clearly remains an important open question as to how the air-filled lung behaves *in vivo*. Until that is resolved, however, we have some distinct possibilities to contemplate relative to the question of the importance of parenchymal heterogeneities. When these heterogeneities are randomly distributed on the spatial scale of an alveolar wall, the average parenchymal displacement and force as a function of distance from a contracting airway are essentially identical to the homogeneous case, regardless of which model we use to make the predictions. This indicates that natural variations in the properties of individual alveolar walls have minimal influence on stress distribution and are not likely to cause the overall nature of airway-parenchymal interdependence to depart significantly from the classic Lai-Fook theory (Lai-Fook, 1979b; Lai-Fook et al., 1977a; Lauzon et al., 1992).

Where we do see a difference, however, between model predictions and Lai-Fook theory is when the parenchymal heterogeneities are highly localized and circumferentially asymmetric (Figs. 1C, 2 and 3). We modeled an extreme version of this situation by having a contiguous line of stiffened alveolar walls propagating radially away from the airway wall in the hexagonal and triangular spring network models (Figs. 1C and 4C), such as might conceivably represent a track of fibrotic tissue or possibly a smaller vessel or airway. In this case, the hexagonal spring network model predicts a focusing of force along the stiffened tissue (Fig. 1C, 2 and 3). It must be noted, however, that this effect only occurs to a significant degree in rather contrived circumstances, when the path of fibrotic tissue has a stiffness many fold greater than the rest of the parenchyma, and when the alveolar walls it affects are close to co-linear (Figs. 1C); if the walls form a zigzag path as can occur with some orientations in a hexagonal array, the contraction of the airway merely brings the walls into alignment and does little to concentrate force along them. The constraint that springs cannot realign if they are to experience an increase in force may also explain why the forces along lines of scar tend to increase toward the border of the network (Figs. 1–3). That is, near the border the spring positions are more constrained, so in order to absorb the strain due to a contracting airway they are less able to change their orientation and so must stretch and thus bear more stress. In any case, this increase in force only occurs for rather particular configurations of stiffened springs. Furthermore, neither the triangular spring network (Fig. 4) nor the continuum model (Fig. 5) exhibits this effect to any significant degree at all. We thus conclude that, barring exceptional circumstances, calculating the effects of airway-parenchymal interdependence on airway narrowing can be done to a useful degree of accuracy by assuming the parenchyma surrounding the airway to be homogeneous. Furthermore, for a given mean level of parenchymal stiffness, regional variations in stiffness do not significantly alter the impact of airway-parenchymal interdependence on airway narrowing.

Nevertheless, to the extent that the air-filled lung *in vivo* behaves like a hexagonal network of springs, we have identified a potential situation in which significant parenchymal forces caused by a contracting airway can extend much further away from the airway than is usually thought to be the case. This mechanism could allow one contracting airway to affect the contraction of another airway located some distance away. The effect would be highly directional, of course, so probably only a single airway would be affected in this manner, but it is at least conceivable that such an effect could happen, for example, in pulmonary fibrosis where a number of normal lung units can be replaced by inextensible fibrous tissue (Gonzalez and Ludwig, 2005). On the other hand, problematic airway narrowing is not usually associated with pulmonary fibrosis, perhaps because it is effectively prevented by the large airway-parenchymal interdependence forces resulting from the increased shear modulus of fibrotic tissue. Also, as the distal lung parenchyma may often become remodeled in asthma (Ludwig, 2005), our results point to the possibility of long-range interactions between small airways during asthma attack. It remains to be seen, of course, whether these predictions play out because we remain uncertain about how real lung parenchyma behaves mechanically. Interestingly, however, structurally determined long-range force transmission has been demonstrated in cells (Blumenfeld, 2006; Hu et al., 2005; Wang and Suo, 2005).

Our study has thus revealed some possible ways in which the nature of airway-parenchymal interdependence might differ markedly from the predictions of classic Lai-Fook theory (Lai-Fook, 1979a; Lai-Fook et al., 1978b; Lai-Fook et al., 1977b), which is based on continuum mechanics and the assumption of parenchymal homogeneity. These predictions, however, are based on model calculations, and therefore are subject to the limitations inherent in these models. For example, the spring network models are 2-dimensional, and by neglecting out-of-plane forces and displacements we may have missed the inclusion of important mechanical constraints that apply in a real lung. Also, none of our models distinguished between elastic forces due to protein fibers and those due to the air-liquid interface, the latter playing a critically important role in alveolar mechanics and stability (Stamenovic, 1990; Stamenovic and Wilson, 1992). In addition, the alveolar walls in our spring network models were joined together by friction-free pin joints, while in reality macromolecules such as glycosaminoglycans offer some limited degree of rotational resistance (Cavalcante et al., 2005). Also, our simulations were initialized at a zero stress state, whereas *in vivo* the baseline stress is positive. Because scar tissue is highly nonlinear in its elastic behavior, we would expect that lung inflation would rapidly stiffen a scar, which would enhance the long-range force propagation mechanism we found in the hexagonal spring model.

Finally, despite our intriguing finding of the possibility of scar-mediated parenchymal force propagation far from a contracting airway, such conclusions remain conditional based on the current lack of certainty about how the lung actually behaves; is it more like a continuum or a hexagonal spring network? Functional studies with lung slices support the former conclusion, yet the space filling hexagonal arrangements of alveolar walls observable in thin sections make the latter conclusion compelling. Nevertheless, while this remains an important open question, the main conclusion of our study is that, in general, parenchymal heterogeneities have little influence on how the airways and the parenchyma interact. In other words, the assumption of parenchymal homogeneity is a good one in most cases.

Acknowledgments

This work was supported by NIH grants R01 HL-103405 and P30 GM-103532.

References

- Adler A, Bates JH. A micromechanical model of airway-parenchymal interdependence. *Ann Biomed Eng.* 2000; 28:309–317. [PubMed: 10784095]
- Adler A, Cowley EA, Bates JH, Eidelman DH. Airway-parenchymal interdependence after airway contraction in rat lung explants. *J Appl Physiol.* 1998; 85:231–237. [PubMed: 9655780]
- An SS, Bai TR, Bates JH, Black JL, Brown RH, Brusasco V, Chitano P, Deng L, Dowell M, Eidelman DH, Fabry B, Fairbank NJ, Ford LE, Fredberg JJ, Gerthoffer WT, Gilbert SH, Gosens R, Gunst SJ, Halayko AJ, Ingram RH, Irvin CG, James AL, Janssen LJ, King GG, Knight DA, Lauzon AM, Lakser OJ, Ludwig MS, Lutchen KR, Maksym GN, Martin JG, Mauad T, McParland BE, Mijailovich SM, Mitchell HW, Mitchell RW, Mitzner W, Murphy TM, Pare PD, Pellegrino R, Sanderson MJ, Schellenberg RR, Seow CY, Silveira PS, Smith PG, Solway J, Stephens NL, Sterk PJ, Stewart AG, Tang DD, Tepper RS, Tran T, Wang L. Airway smooth muscle dynamics: a common pathway of airway obstruction in asthma. *Eur Respir J.* 2007; 29:834–860. [PubMed: 17470619]
- Bates JH, Lauzon AM. Parenchymal tethering, airway wall stiffness, and the dynamics of bronchoconstriction. *J Appl Physiol.* 2007; 102:1912–1920. [PubMed: 17204575]
- Benjamin JJ, Murtagh PS, Proctor DF, Menkes HA, Permutt S. Pulmonary vascular interdependence in excised dog lobes. *J Appl Physiol.* 1974; 37:887–894. [PubMed: 4436220]
- Blumenfeld R. Isostaticity and controlled force transmission in the cytoskeleton: A model awaiting experimental evidence. *Biophysical Journal.* 2006; 91:1970–1983. [PubMed: 16912215]
- Bradley CP, Pullan AJ, Hunter PJ. Geometric modeling of the human torso using cubic hermite elements. *Ann Biomed Eng.* 1997; 25:96–111. [PubMed: 9124743]
- Breen BJ, Donovan GM, Sneyd J, Tawhai MH. Quantifying parenchymal tethering in a finite element simulation of a human lung slice under bronchoconstriction. *Respir Physiol Neurobiol.* 2012; 183:85–90. [PubMed: 22732325]
- Burrowes KS, Tawhai MH. Coupling of lung tissue tethering forces to fluid dynamics in the pulmonary circulation. *Intl. J. Numer. Meth. Biomed. Engng.* 2010; 26:862–875.
- Cavalcante FS, Ito S, Brewer K, Sakai H, Alencar AM, Almeida MP, Andrade JS Jr, Majumdar A, Ingenito EP, Suki B. Mechanical interactions between collagen and proteoglycans: implications for the stability of lung tissue. *J Appl Physiol.* 2005; 98:672–679. [PubMed: 15448123]
- Chapman DG, Berend N, Horlyck KR, King GG, Salome CM. Does increased baseline ventilation heterogeneity following chest wall strapping predispose to airway hyperresponsiveness? *J Appl Physiol.* 2012; 113:25–30. [PubMed: 22556397]
- Dandurand RJ, Xu LJ, Martin JG, Eidelman DH. Airway-parenchymal interdependence and bronchial responsiveness in two highly inbred rat strains. *J Appl Physiol.* 1993; 74:538–544. [PubMed: 8458768]
- Fung, YC. Chapter 2, Biomechanics: Mechanical properties of living tissue. 2nd ed.. New York: Springer-Verlag; 1993.
- Gonzalez, A.; Ludwig, MS. Structure-function correlations in pulmonary fibrosis. In: Hamid, Q.; Shannon, J.; Martin, J., editors. *Physiologic basis of respiratory disease*. Hamilton: BC Decker, Inc.; 2005. p. 77-84.
- Gunst SJ, Warner DO, Wilson TA, Hyatt RE. Parenchymal interdependence and airway response to methacholine in excised dog lobes. *J Appl Physiol.* 1988; 65:2490–2497. [PubMed: 3063709]
- Hu SH, Chen JX, Butler JP, Wang N. Prestress mediates force propagation into the nucleus. *Biochemical and Biophysical Research Communications.* 2005; 329:423–428. [PubMed: 15737604]
- Ito S, Ingenito EP, Arold SP, Parameswaran H, Tgavalekos NT, Lutchen KR, Suki B. Tissue heterogeneity in the mouse lung: effects of elastase treatment. *J Appl Physiol.* 2004; 97:204–212. [PubMed: 15020580]
- Ito S, Lutchen KR, Suki B. Effects of heterogeneities on the partitioning of airway and tissue properties in normal mice. *J Appl Physiol.* 2007; 102:859–869. [PubMed: 17138833]

- Kaczka DW, Cao K, Christensen GE, Bates JH, Simon BA. Analysis of regional mechanics in canine lung injury using forced oscillations and 3D image registration. *Ann Biomed Eng.* 2011; 39:1112–1124. [PubMed: 21132371]
- Khan MA, Ellis R, Inman MD, Bates JH, Sanderson MJ, Janssen LJ. Influence of airway wall stiffness and parenchymal tethering on the dynamics of bronchoconstriction. *Am J Physiol Lung Cell Mol Physiol.* 2010; 299:L98–L108. [PubMed: 20435686]
- Kowalczyk P, Kleiber M. Modelling and numerical analysis of stresses and strains in the human lung including tissue-gas interaction. *Eur. J. Mech, A/Solids.* 1994; 13:367–393.
- Lai-Fook SJ. A continuum mechanics analysis of pulmonary vascular interdependence in isolated dog lobes. *Journal of applied physiology.* 1979a; 46:419–429. [PubMed: 438007]
- Lai-Fook SJ. A continuum mechanics analysis of pulmonary vascular interdependence in isolated dog lobes. *J Appl Physiol.* 1979b; 46:419–429. [PubMed: 438007]
- Lai-Fook SJ, Hyatt RE. Effect of parenchyma and length changes on vessel pressure-diameter behavior in pig lungs. *J Appl Physiol.* 1979; 47:666–669. [PubMed: 511671]
- Lai-Fook SJ, Hyatt RE, Rodarte JR. Effect of parenchymal shear modulus and lung volume on bronchial pressure-diameter behavior. *J Appl Physiol.* 1978a; 44:859–868. [PubMed: 670009]
- Lai-Fook SJ, Hyatt RE, Rodarte JR. Effect of parenchymal shear modulus and lung volume on bronchial pressure-diameter behavior. *Journal of applied physiology.* 1978b; 44:859–868. [PubMed: 670009]
- Lai-Fook SJ, Hyatt RE, Rodarte JR, Wilson TA. Behavior of artificially produced holes in lung parenchyma. *J Appl Physiol.* 1977a; 43:648–655. [PubMed: 908679]
- Lai-Fook SJ, Hyatt RE, Rodarte JR, Wilson TA. Behavior of artificially produced holes in lung parenchyma. *Journal of applied physiology.* 1977b; 43:648–655. [PubMed: 908679]
- Lai-Fook SJ, Kallok MJ. Bronchial-arterial interdependence in isolated dog lung. *J Appl Physiol.* 1982; 52:1000–1007. [PubMed: 7085398]
- Lambert RK, Wilson TA. A model for the elastic properties of the lung and their effect of expiratory flow. *J Appl Physiol.* 1973; 34:34–48. [PubMed: 4697377]
- Latourelle J, Fabry B, Fredberg JJ. Dynamic equilibration of airway smooth muscle contraction during physiological loading. *J Appl Physiol.* 2002; 92:771–779. [PubMed: 11796691]
- Lauzon AM, Dechman G, Bates JH. Time course of respiratory mechanics during histamine challenge in the dog. *J Appl Physiol.* 1992; 73:2643–2647. [PubMed: 1490982]
- Ludwig, MS. Structure-function correlations in asthma. In: Hamid, Q.; Shannon, J.; Martin, J., editors. *Physiologic basis of respiratory disease.* Hamilton: BC Decker, Inc.; 2005. p. 105–113.
- Ma B, Bates JH. Continuum vs. spring network models of airway-parenchymal interdependence. *J Appl Physiol.* 2012; 113:124–129. [PubMed: 22500006]
- Ma B, Sanderson M, Bates JHT. Airway-parenchymal interdependence in the lung slice. *Respir Physiol Neurobiol.* 2013; 185:211–216. [PubMed: 23128069]
- Mead J, Takishima T, Leith D. Stress distribution in lungs: a model of pulmonary elasticity. *J Appl Physiol.* 1970; 28:596–608. [PubMed: 5442255]
- Mitzner W, Blosser S, Yager D, Wagner E. Effect of bronchial smooth muscle contraction on lung compliance. *J Appl Physiol.* 1992; 72:158–167. [PubMed: 1537710]
- Noble PB, Sharma A, McFawn PK, Mitchell HW. Airway narrowing in porcine bronchi with and without lung parenchyma. *Eur Respir J.* 2005; 26:804–811. [PubMed: 16264040]
- Smith JC, Butler JP, Hoppin FG Jr. Contribution of tree structures in the lung to lung elastic recoil. *J Appl Physiol.* 1984; 57:1422–1429. [PubMed: 6520036]
- Stamenovic D. Micromechanical foundations of pulmonary elasticity. *Physiol Rev.* 1990; 70:1117–1134. [PubMed: 2217556]
- Stamenovic D, Wilson TA. Parenchymal stability. *J Appl Physiol.* 1992; 73:596–602. [PubMed: 1399986]
- Tawhai MH, Nash MP, Lin CL, Hoffman EA. Supine and prone differences in regional lung density and pleural pressure gradients in the human lung with constant shape. *J Appl Physiol.* 2009; 107:912–920. [PubMed: 19589959]

- Wang N, Suo ZG. Long-distance propagation of forces in a cell. *Biochemical and Biophysical Research Communications*. 2005; 328:1133–1138. [PubMed: 15707995]
- Wilson TA. A continuum analysis of a two-dimensional mechanical model of the lung parenchyma. *J Appl Physiol*. 1972; 33:472–478. [PubMed: 5075845]
- Yang, TY. *Finite element structural analysis*. Englewood Cliffs, NJ: Prentice-Hall; 1986.

- Tissue forces around a contracting airway depend on how the parenchymal is modeled
- Random tissue heterogeneities do not affect airway-parenchymal interdependence
- Lines of scar tissue increase parenchymal forces leading away from a contracting airway

Figure 1.

Spring networks (left-hand panels) and forces versus radial distance from the airway wall (right-hand panels) following airway contraction in the hexagonal spring network for (A) uniform distribution of spring stiffness, (B) random distribution of stiffness (variation = 30% of mean), and (C) when stiffness is increased 100-fold along a contiguous line of springs. The widths of the springs in the left panels indicate stiffness. Forces are expressed in arbitrary units.

Figure 2.

Spring forces versus radial distance from the airway wall in the hexagonal spring network model when the stiffness of the springs along a continuous pathway from the airway wall (Fig. 1C, left-hand panel) were increased to varying degrees relative to other springs in the network. Forces are expressed in arbitrary units.

Figure 3. Spring forces versus radial distance from the airway wall in the hexagonal spring network model when the stiffness of the springs along a continuous pathway from the airway wall (Fig. 1C, left-hand panel) was increased 100-fold relative to other springs in the network, for networks that are (A) 2 and (B) 4 times larger than that in Fig. 1. Forces are expressed in arbitrary units.

Figure 4.

Spring networks (left-hand panels) and forces versus radial distance from the airway wall (right-hand panels) following airway contraction in the triangular spring network for (A) uniform distribution of spring stiffness, (B) random distribution of stiffness (variation = 30% of mean), and (C) when stiffness is increased 100-fold along a contiguous line of springs. The widths of the springs in the left panels indicate stiffness. Forces are expressed in arbitrary units.

A

B

Figure 5.

A) Finite element continuum model of lung slice with isolated airway (see text for details). The dashed line locates the modeled scar tissue. Gauss points with altered elasticity are circled in the inset. B) Von Mises stress as a function of radial distance from the airway wall for the continuum model when the parenchyma is homogeneous, and when a narrow pathway of tissue having an elastic modulus 100-fold greater than the rest of the tissue propagates away from the airway wall.