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Alveolar septal patterning during compensatory lung growth: Part II the effect of parenchymal pressure gradients

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ABSTRACT

In most mammals, compensatory lung growth occurs after the removal of one lung (pneumonectomy). Although the mechanism of alveolar growth is unknown, the patterning of complex alveolar geometry over organ-sized length scales is a central question in regenerative lung biology. Because shear forces appear capable of signaling the differentiation of important cells involved in neoalveolarization (fibroblasts and myofibroblasts), interstitial fluid mechanics provide a potential mechanism for the patterning of alveolar growth. The movement of interstitial fluid is created by two basic mechanisms: 1) the non-uniform motion of the boundary walls, and 2) parenchymal pressure gradients external to the interstitial fluid. In a previous study (Haber et al., Journal of Theoretical Biology 400: 118-128, 2016), we investigated the effects of non-uniform stretching of the primary septum (associated with its heterogeneous mechanical properties) during breathing on generating non-uniform Stokes flow in the interstitial space. In the present study, we analyzed the effect of parenchymal pressure gradients on interstitial flow. Dependent upon lung microarchitecture and physiologic conditions, parenchymal pressure gradients had a significant effect on the shear stress distribution in the interstitial space of primary septa. A dimensionless parameter δ described the ratio between the effects of a pressure gradient and the influence of non-uniform primary septal wall motion. Assuming that secondary septa are formed where shear stresses were the largest, it is shown that the geometry of the newly generated secondary septa was governed by the value of δ. For δ smaller than 0.26, the alveolus size was halved while for higher values its original size was unaltered. We conclude that the movement of interstitial fluid, governed by parenchymal pressure gradients and non-uniform primary septa wall motion, provides a plausible mechanism for the patterning of alveolar growth.

1. Introduction

In many paired organs, removal of one organ results in the “compensatory” growth of the remaining organ. In the lung, compensatory growth after the surgical removal of one lung involves an increase in lung size, weight and cell number (e.g., Gibney et al., 2011; Chamoto et al., 2012; Konerding et al., 2012). Importantly, lung growth is also characterized by an increase in the number of alveoli. In mice, more than 500,000 new alveoli form within 3 weeks after pneumonectomy (Fehrenbach et al., 2008). The mechanisms that initiate and guide neoalveolarization over organ-sized length scales are currently unknown.

There are several clues suggesting that lung movement during breathing is important to the process regulating neoalveolarization (Butler et al., 2012; Ysasi et al., 2013). The placement of inert material (e.g. wax), called "plombage", in the empty hemithorax after pneumonectomy prevents displacement and expansion of the remaining lung. Similarly, phrenic nerve transection after pneumonectomy prevents diaphragmatic contraction and the cyclic stretch of the remaining lung. Both interventions are effective an inhibiting post-pneumonectomy lung growth.

A potential mechanism for translating lung movement into regenerative signals, particularly over organ-sized length scales, is interstitial fluid flow (Rutkowski & Swartz, 2007). The mechanical forces (shear stresses) associated with interstitial flows can induce cellular differentiation. Ng et al., (2005) have shown that the shear stress associated with interstitial flow can induce the differentiation of fibroblasts into myofibroblasts–a prominent cell in the lung parenchyma (Kapanci et al., 1992) and commonly linked with both lung development (Dickie et al., 2007) and regeneration (Bennett et al., 2017).

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The movement of interstitial fluid is created by two basic mechanisms; 1) the non-uniform motion of the boundary walls, and 2) a parenchymal pressure gradient. A source of boundary wall motion is lung ventilation. Our previous work described how non-uniform motion of the walls of primary septa after pneumonectomy can generate interstitial flow and produce a non-uniform shear stress distribution (Haber et al., 2016). The direction of lymph flow and the complex interdependence of the lung parenchyma predict an interstitial pressure gradient from the subpleural alveoli to the hilum (Mead et al., 1970). Experimentally, micropuncture has been used to document a pressure gradient between the subplueural alveolar regions and the hilum of the lung (Bhattacharya et al., 1984). Although the measured gradient was reduced in situations with pulmonary edema and elevated alveolar pressures (Bhattacharya et al., 1989), the interstitial fluid gradient persisted despite extremes of edema and airway distension. The robust persistence of this longitudinal (alveolar-to-hilar) gradient suggests the potential for this gradient to participate in the specification of septal location.

In this report, we investigated the influence of parenchymal pressure gradients on interstitial fluid flow. We found that a parenchymal pressure gradient significantly modifies interstitial fluid flows and likely plays an important role in determining the size of newly-formed alveoli during compensatory growth.

2. Analysis

2.1. Geometric descriptions of the model

In this study, we adopt a geometrical model used in our previous paper and perform the analysis in line with our previous study (Haber et al., 2016). Briefly, we perceive an alveolated duct as a long cylinder of diameter D_{out} (Fig. 1). The outer boundary of this cylinder corresponds to primary septa with thickness of $2H$ (Fig. 1 right). Interstitial fluid (viscosity μ and density ρ) within the primary septa (shown in blue in the figure) is driven by a parenchymal pressure gradient exerted in the interstitial space and by the non-uniform motion of the boundary walls which was addressed in our previous paper. In the present study we will consider both the pressure gradient and non-uniform boundary motion.

The interstitial space is sandwiched between two layers of epithelium (h represents the thickness of epithelial layer) and an alveolated duct is treated as a long cylinder (Fig. 2, top) with a small thickness (H) relative to the duct outer diameter ($H << D_{out}$), the interstitial space of the primary septum was viewed as a space confined by two flat planes in the previous study. We adopt the same view here (Fig. 2 bottom). To represent a helical pattern in line elements (collagen and elastin fibers) believed to be woven at the alveolar opening (e.g., Wilson & Bachofen, 1982; Weibel, 1984) along the alveolar duct and relatively uniform size of the original alveoli, our model of the primary septum exhibits a crisscross pattern with the stiffer regions (corresponding to the sites of the collapsed secondary septa shown in red) at the edges. The analysis will be performed in a square unit cell.

2.2. The walls

We refer the reader to our previous paper (Haber et al., 2016) where a detailed description is provided how to obtain the velocity of the walls made of heterogeneous material. The primary septal walls undergo periodic stretching and contraction due to the tidal breathing and the size of the unit cell λ change periodically, namely,

$$\lambda(t) = \lambda(t+T) \tag{1}$$

where T is the breathing period. We define λ_0 as the size of the unit cell at time $t=0$ and as we have shown in our previous paper, the functional dependence of λ upon time t are determined by the stresses prevailing in the system.

We proved that the heterogeneous properties of the wall matter give rise to non-uniform wall velocity $\boldsymbol{v} = (v_x, v_y)$ that can be expressed by the real value of the following complex Fourier series along the x and y coordinates with period length λ,

$$v_x = \frac{\dot{\lambda}}{\lambda}x + \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} V_{mn}^{x} \exp\left[2i\pi\,(mx+ny)/\lambda(t)\right]$$
$$v_y = \frac{\dot{\lambda}}{\lambda}y + \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} V_{mn}^{y} \exp\left[2i\pi\,(mx+ny)/\lambda(t)\right] \tag{2}$$

The leading terms in (2) are merely velocities that are generated by the expansion and contraction of the edges of the unit cell as seen by an observer located at the unit-cell origin. We also require that $V_{00}^{x} = V_{00}^{y} = 0$ so that the velocity ay x=y =0 is zero. The constant, complex velocity coefficients V_{mn}^{x} and V_{mn}^{y} can be determined by a Fourier (complex) expansion of the velocity field at the wall, obtained, in principle, if the spatial distribution of the wall matter is known. Eq. (2) is employed as the no-slip boundary conditions that the interstitial velocity field must satisfy at the walls.

2.3. The interstitial fluid flow model

The interstitial fluid is considered incompressible and Newtonian. The layer is very thin in comparison to the layer's radius of curvature. The flow is very slow so that the Reynolds number of the flow (based on the fluid properties, the maximum stretching velocity and the layer thickness) and the Womersley number (based on the breathing frequency) are much smaller than unity.

Thus, the 3D, Stokes, quasi-steady differential equations govern the fluid pressure p and the fluid velocity field components u_x, u_y, u_z along the Cartesian coordinate system x, y, z, respectively;

$$\frac{\partial^2 u_x}{\partial x^2} + \frac{\partial^2 u_x}{\partial y^2} + \frac{\partial^2 u_x}{\partial z^2} = \frac{1}{\mu}\frac{\partial p}{\partial x}$$
$$\frac{\partial^2 u_y}{\partial x^2} + \frac{\partial^2 u_y}{\partial y^2} + \frac{\partial^2 u_y}{\partial z^2} = \frac{1}{\mu}\frac{\partial p}{\partial y}$$
$$\frac{\partial^2 u_z}{\partial x^2} + \frac{\partial^2 u_z}{\partial y^2} + \frac{\partial^2 u_z}{\partial z^2} = \frac{1}{\mu}\frac{\partial p}{\partial z}$$
$$\frac{\partial u_x}{\partial x} + \frac{\partial u_y}{\partial y} + \frac{\partial u_z}{\partial z} = 0 \tag{3}$$

Employing (2) and assuming no slip and no wall penetration, the associated boundary conditions are,

$$u_x(x,y,z=\pm H) = \frac{\dot{\lambda}x}{\lambda} + \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} V_{mn}^{x} \exp\left[2i\pi\,(mx+ny)/\lambda(t)\right]$$
$$u_y(x,y,z=\pm H) = \frac{\dot{\lambda}y}{\lambda} + \sum_{m=0}^{\infty}\sum_{n=0}^{\infty} V_{mn}^{y} \exp\left[2i\pi\,(mx+ny)/\lambda(t)\right]$$
$$u_z(x,y,z=\pm H) = \pm\dot{H} \tag{4a-c}$$

We further assume that a parenchymal pressure gradient $\Delta P/L$ exists along the axial direction of the interstitial space (In general, from the alveolar region to the hilar region (Bhattacharya et al., 1984; Aukland & Reed, 1993)). The 2D Poiseuille flow $\mathbf{u}_a$ induced by the pressure gradient alone is well known,

$$\mathbf{u}_a = -\frac{1}{2\mu}\frac{\Delta P}{L}(H^2 - z^2)\mathbf{i}_a = -\frac{\sqrt{2}}{4\mu}\frac{\Delta P}{L}(H^2 - z^2)(\mathbf{i}_x + \mathbf{i}_y) \tag{5}$$

where $\mathbf{i}_a$, $\mathbf{i}_x$, $\mathbf{i}_y$ are unit vectors along the axial direction, the x-coordinate and y coordinate, respectively. Linearity of the differential equations (3) makes it possible to superimpose the velocity components induced by the pressure gradients to those generated