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

Shimon Haber¹, Michal Weisbord¹, Steven J. Mentzer², and Akira Tsuda³

¹Faculty of Mechanical Engineering, Technion-Israel Institute of Technology, Haifa 32000, Israel

²Laboratory of Adaptive and Regenerative Biology, Brigham & Women's Hospital, Harvard Medical School, Boston MA

³Molecular and Integrative Physiological Sciences, Harvard School of Public Health, Boston, MA

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 is 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 is 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.

Correspondence: Akira Tsuda, PhD, Molecular and Integrative Physiological Sciences, Harvard School of Public Health, Boston, MA, atsuda@hsph.harvard.edu.

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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 at 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).

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 subpleural 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.

ANALYSIS

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 ($H \ll D_{out}$), 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, 1983) 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.

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,

$$\lambda(t) = \lambda(t+T) \quad [1]$$

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 $\mathbf{v} = (v_x, v_y)$ that can be expressed by the real value of the following complex Fourier series along the x and y coordinates with period length λ ,

$$\begin{aligned} v_x &= \frac{\dot{\lambda}}{\lambda} x + \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} V_{mn}^x \exp[2i\pi(mx+ny)/\lambda(t)] \\ v_y &= \frac{\dot{\lambda}}{\lambda} y + \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} V_{mn}^y \exp[2i\pi(mx+ny)/\lambda(t)] \end{aligned} \quad [2]$$

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 at $x = y = 0$ 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. Equation [2] is employed as the no-slip boundary conditions that the interstitial velocity field must satisfy at the walls.

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;

$$\begin{aligned}\frac{\partial^2 u_x}{\partial x^2} + \frac{\partial^2 u_x}{\partial y^2} + \frac{\partial^2 u_x}{\partial z^2} &= \frac{1}{\mu} \frac{\partial p}{\partial x} \\ \frac{\partial^2 u_y}{\partial x^2} + \frac{\partial^2 u_y}{\partial y^2} + \frac{\partial^2 u_y}{\partial z^2} &= \frac{1}{\mu} \frac{\partial p}{\partial y} \\ \frac{\partial^2 u_z}{\partial x^2} + \frac{\partial^2 u_z}{\partial y^2} + \frac{\partial^2 u_z}{\partial z^2} &= \frac{1}{\mu} \frac{\partial p}{\partial z} \\ \frac{\partial u_x}{\partial x} + \frac{\partial u_y}{\partial y} + \frac{\partial u_z}{\partial z} &= 0\end{aligned}\quad [3]$$

Employing [2] and assuming no slip and no wall penetration, the associated boundary conditions are,

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

We further assume that a parenchymal pressure gradient 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,

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

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 by the stretching of the walls bounding the flow field (Eqs. 17 in Haber et al 2016). Thus, the general solution for the flow and pressure fields can be expressed as the real value of the following expressions,

$$\begin{aligned} u_x &= \frac{\dot{\lambda}}{\lambda} x - \frac{\sqrt{2}}{4\mu} \frac{\Delta P}{L} (H^2 - z^2) + \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} U_{mn}^x(z) \exp[2i\pi(mx+ny)/\lambda(t)] \\ u_y &= \frac{\dot{\lambda}}{\lambda} y - \frac{\sqrt{2}}{4\mu} \frac{\Delta P}{L} (H^2 - z^2) + \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} U_{mn}^y(z) \exp[2i\pi(mx+ny)/\lambda(t)] \\ u_z &= \frac{\dot{H}}{H} z + \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} U_{mn}^z(z) \exp[2i\pi(mx+ny)/\lambda(t)] \\ p &= p_0 + (\sqrt{2}\Delta P/2L)(x+y) + \mu \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} P_{mn}(z) \exp[2i\pi(mx+ny)/\lambda(t)] \end{aligned} \quad [6]$$

Note that the terms added to the velocity field due to the pressure gradient do not change the boundary conditions [2] to be employed at the walls $z = \pm H$.

In our previous study (Haber et al., 2016), we have shown how to obtain the unknown functions of z , U_{mn}^x , U_{mn}^y , U_{mn}^z , P_{mn} accounting for symmetry of U_{mn}^x , U_{mn}^y , P_{mn} and anti-symmetry of U_{mn}^z with respect to $z=0$,

$$\begin{aligned} U_{mn}^x &= A_{mn}^x \cosh(k_{mn}z) + B_{mn}^x z k_{mn} \sinh(k_{mn}z) \\ U_{mn}^y &= A_{mn}^y \cosh(k_{mn}z) + B_{mn}^y z k_{mn} \sinh(k_{mn}z) \\ U_{mn}^z &= A_{mn}^z \sinh(k_{mn}z) + B_{mn}^z z k_{mn} \cosh(k_{mn}z) \\ P_{mn} &= A_{mn}^p \cosh(k_{mn}z) \end{aligned} \quad [7]$$

where we used the abbreviated symbols,

$$k_m = 2m\pi/\lambda, \quad k_n = 2n\pi/\lambda, \quad k_{mn} = (k_m^2 + k_n^2)^{\frac{1}{2}} \quad [8]$$

In addition, mass conservation required that

$$\frac{\dot{H}}{H} = -2 \frac{\dot{\lambda}}{\lambda} \quad [9]$$

Introduction of [7] into [3] and boundary conditions [2] yielded,

$$\begin{aligned}
A_{mn}^p &= -i \frac{2 \sinh(\beta_{mn})}{\sinh(\beta_{mn}) \cosh(\beta_{mn}) - \beta_{mn}} (k_m V_{mn}^x + k_n V_{mn}^y) \\
A_{mn}^x &= \frac{V_{mn}^x}{\cosh(\beta_{mn})} - i k_m A_{mn}^p \frac{\beta_{mn} \tanh(\beta_{mn})}{2k_{mn}^2} \\
A_{mn}^y &= \frac{V_{mn}^y}{\cosh(\beta_{mn})} - i k_n A_{mn}^p \frac{\beta_{mn} \tanh(\beta_{mn})}{2k_{mn}^2} \\
A_{mn}^z &= -A_{mn}^p \frac{\beta_{mn} \coth(\beta_{mn})}{2k_{mn}}
\end{aligned} \quad [10]$$

where

$$\beta_{mn} = k_{mn} H \quad [11]$$

Stress distribution near the walls

The maximum shear stress distribution in the interstitial fluid near the walls may play an effective role in pulmonary fibroblast differentiation (Breen 2000; Ng, Hinz & Swartz, 2005), which may result in building up new secondary septa (Dickie et al., 2007).

The stress tensor components in the interstitial liquid are,

$$\begin{aligned}
\sigma_{xx} &= -p + 2\mu \frac{\partial u_x}{\partial x}, \quad \sigma_{yy} = -p + 2\mu \frac{\partial u_y}{\partial y}, \quad \sigma_{zz} = -p + 2\mu \frac{\partial u_z}{\partial z} \\
\sigma_{xy} &= \mu \left(\frac{\partial u_x}{\partial y} + \frac{\partial u_y}{\partial x} \right), \quad \sigma_{zx} = \mu \left(\frac{\partial u_z}{\partial x} + \frac{\partial u_x}{\partial z} \right), \quad \sigma_{zy} = \mu \left(\frac{\partial u_z}{\partial y} + \frac{\partial u_y}{\partial z} \right)
\end{aligned} \quad [12]$$

Introduction of [6] into [12] at $z = H$ (where we expect the maximum value of the shear stress) yields,

$$\begin{aligned}
\sigma_{xx}|_{z=H} &= -p_0 + \mu \left(2 \frac{\dot{\lambda}}{\lambda} + \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} [-P_{mn} + 2i k_m U_{mn}^x]_{z=H} \exp[i(k_m x + k_n y)] \right), \\
\sigma_{yy}|_{z=H} &= -p_0 + \mu \left(2 \frac{\dot{\lambda}}{\lambda} + \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} [-P_{mn} + 2i k_n U_{mn}^y]_{z=H} \exp[i(k_m x + k_n y)] \right), \\
\sigma_{zz}|_{z=H} &= -p_0 + \mu \left(2 \frac{\dot{H}}{H} + \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} \left[-P_{mn} + 2 \frac{dU_{mn}^z}{dz} \right]_{z=H} \exp[i(k_m x + k_n y)] \right), \\
\sigma_{xy}|_{z=H} &= \mu \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} i [k_n U_{mn}^x + k_m U_{mn}^y]_{z=H} \exp[i(k_m x + k_n y)], \\
\sigma_{zx}|_{z=H} &= \frac{\sqrt{2}}{2} \frac{\Delta P}{L} H + \mu \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} \left[\frac{dU_{mn}^x}{dz} \right]_{z=H} \exp[i(k_m x + k_n y)], \\
\sigma_{zy}|_{z=H} &= \frac{\sqrt{2}}{2} \frac{\Delta P}{L} H + \mu \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} \left[\frac{dU_{mn}^y}{dz} \right]_{z=H} \exp[i(k_m x + k_n y)].
\end{aligned} \quad [13]$$

Only the fluid stress components σ_{zz} , σ_{zx} , σ_{zy} at $z = H$ (or $z = -H$) exert a force on the walls of the primary septa. The maximum shear traction exerted on the wall $z = H$, is at angle θ with respect to the y -axis,

$$\sigma_{z\theta} = \left(\sigma_{zx}^2 + \sigma_{zy}^2 \right)^{1/2} \Big|_{z=H \text{ (or } z=-H)} \quad \tan(\theta) = \frac{\sigma_{zx}}{\sigma_{zy}} \Big|_{z=H \text{ (or } z=-H)} \quad [14]$$

The maximum shear stress that exists in the *liquid* near the wall must be obtained from all stress components and can be evaluated at $Z = H$ following 3 steps:

- i. calculate the coefficients

$$\begin{aligned} I_1 &= \sigma_{xx} + \sigma_{yy} + \sigma_{zz}, \\ I_2 &= \sigma_{xy}^2 + \sigma_{xz}^2 + \sigma_{zy}^2 - \sigma_{xx}\sigma_{yy} - \sigma_{xx}\sigma_{zz} - \sigma_{yy}\sigma_{zz} \\ I_3 &= \sigma_{xx}\sigma_{yy}\sigma_{zz} + 2\sigma_{xy}\sigma_{xz}\sigma_{yz} - \sigma_{xx}\sigma_{yz}^2 - \sigma_{yy}\sigma_{xz}^2 - \sigma_{zz}\sigma_{yx}^2 \end{aligned} \quad [15]$$

- ii. Solve the algebraic 3rd order equation;

$$\sigma^3 - I_1\sigma^2 - I_2\sigma - I_3 = 0 \quad [16]$$

- iii. The three roots $\sigma_1, \sigma_2, \sigma_3$ are the principal stress components from which one obtains the maximum shear stress,

$$\tau_{\max} = 0.5 \max\{|\sigma_1 - \sigma_2|, |\sigma_1 - \sigma_3|, |\sigma_2 - \sigma_3|\} \quad [17]$$

RESULTS

The case of homogeneous wall materials

As shown in our previous paper (Haber et al., 2016), the wall velocity for homogeneous wall results in,

$$v_x = \frac{\dot{\sigma}}{\sigma} x, \quad v_y = \frac{\dot{\sigma}}{\sigma} y \quad [18]$$

where

$$\sigma(t) = \Delta P_0(t) \cdot R(t) / 2h, \quad [19]$$

was obtained from the known axial stress that exists in the thin walls of a pressurized cylindrical vessel, P_0 is the difference between the internal and external pressures of the vessel, R is the vessel radius and h is the wall thickness.

Since v_x at $x = \lambda/2$ equals $\dot{\lambda}/2$ and v_y at $y = \lambda/2$ equals $\dot{\lambda}/2$ we obtain that,

$$\dot{\lambda} / \lambda = \dot{\sigma} / \sigma. \quad [20]$$

The latter also defines how λ must vary with time.

It can be shown that the interstitial flow field which satisfies the foregoing boundary conditions and the Stokes equations [3] is simply,

$$\begin{aligned} u_x &= \frac{\dot{\sigma}}{\sigma} x - \frac{\sqrt{2}}{4\mu} \frac{\Delta P}{L} (H^2 - z^2), & u_y &= \frac{\dot{\sigma}}{\sigma} y - \frac{\sqrt{2}}{4\mu} \frac{\Delta P}{L} (H^2 - z^2), & u_z &= \frac{\dot{H}}{H} z, \\ p &= p_0(t) + \frac{\sqrt{2}}{2} \frac{\Delta P}{L} (x + y) \end{aligned} \quad [21]$$

and the stress tensor components prevailing in the interstitial fluid are,

$$\begin{aligned} \sigma_{xx} &= \sigma_{yy} = -p_0(t) + \frac{\sqrt{2}}{2} \frac{\Delta P}{L} (x + y) + 2\mu \frac{\dot{\sigma}}{\sigma}, \\ \sigma_{zz} &= -p_0(t) + \frac{\sqrt{2}}{2} \frac{\Delta P}{L} (x + y) + 2\mu \frac{\dot{H}}{H}, \\ \sigma_{xy} &= 0, \quad \sigma_{xz} = \sigma_{yz} = \frac{\sqrt{2}}{2} \frac{\Delta P}{L} z \end{aligned} \quad [22]$$

Consequently, the *shear* stress components that exert a shearing force on the walls are uniform everywhere and no differential contribution to forming myofibroblasts can be expected in that case.

The case of heterogeneous wall materials

Following Haber et al., 2016, we examined the most basic velocity distribution in the primary septa which satisfy the conditions that the unit-cell boundaries expand at velocity $\dot{\lambda}/2$ at $x = \lambda/2$ and $y = \lambda/2$ and vanish at the origin $x = y = 0$,

$$\begin{aligned} v_x &= \dot{\lambda} \left[\frac{x}{\lambda} + C \sin(2\pi x/\lambda) \right], \\ v_y &= \dot{\lambda} \left[\frac{y}{\lambda} + C \sin(2\pi y/\lambda) \right], & -\lambda/2 < x, y < \lambda/2 \\ v_z &= \pm \dot{H} \quad \text{at } z = \pm H \end{aligned} \quad [23a,b,c]$$

where C is a constant which depends on the heterogeneous material properties of the walls (assumed to have similar distribution in the x and y directions). Notice that various anti-symmetric functions in x and y which satisfy equations [2a,b] are feasible. Eqs. [23a,b] can be viewed as the leading term of a Fourier expansion of such functions, thereby, providing a good insight for heterogeneous cases which depend on various Young and shear moduli and Poisson coefficient.

Utilizing our previous notation, Eqs. [23a,b] can be rewritten as the real part of the complex functions,

$$\begin{aligned} v_x &= \dot{\lambda} [x/\lambda - iC \exp(2i\pi x/\lambda)], \\ v_y &= \dot{\lambda} [y/\lambda - iC \exp(2i\pi y/\lambda)] \quad -\lambda/2 < x, y < \lambda/2 \\ v_z &= \pm \dot{H} \quad \text{at} \quad z = \pm H \end{aligned} \quad [23c,d]$$

Thus, the non-vanishing Fourier coefficients in [6] are,

$$V_{1,0}^x = -iC \dot{\lambda}, \quad V_{0,1}^y = -iC \dot{\lambda}, \quad [24]$$

Hence employing [10],

$$\begin{aligned} A_{1,0}^x &= A_{0,1}^y = iC \frac{\dot{\lambda} [\beta \cosh(\beta) - \sinh(\beta)]}{[\cosh(\beta) \sinh(\beta) - \beta]}, \\ A_{1,0}^z &= A_{0,1}^z = C \frac{\dot{\lambda} \beta \cosh(\beta)}{[\cosh(\beta) \sinh(\beta) - \beta]}, \\ A_{1,0}^p &= A_{0,1}^p = -C \frac{4\pi \dot{\lambda} \sinh(\beta)}{\lambda [\sinh(\beta) \cosh(\beta) - \beta]}, \\ B_{1,0}^x &= B_{0,1}^y = -iC \frac{\dot{\lambda} \sinh(\beta)}{[\sinh(\beta) \cosh(\beta) - \beta]}, \\ B_{1,0}^z &= B_{0,1}^z = -C \frac{\dot{\lambda} \sinh(\beta)}{[\sinh(\beta) \cosh(\beta) - \beta]} \end{aligned} \quad [25]$$

where

$$\beta = 2\pi H/\lambda \quad [26]$$

Introducing [25] into [7] and considering the real part only, yields,

$$\begin{aligned} \frac{u_x}{C \dot{\lambda}} &= \frac{1}{C} \frac{x}{\lambda} + \sin(2\pi x/\lambda) \frac{[\sinh(\beta) - \beta \cosh(\beta)] \cosh(2\pi z/\lambda) + \sinh(\beta) (2\pi z/\lambda) \sinh(2\pi z/\lambda)}{\sinh(\beta) \cosh(\beta) - \beta} - \left(\frac{\sqrt{2} \Delta P H^2}{4\mu C L \dot{\lambda}} \right) \left(1 - \frac{z^2}{H^2} \right) \end{aligned} \quad [27a]$$

$$\begin{aligned} \frac{u_y}{C \dot{\lambda}} &= \frac{1}{C} \frac{y}{\lambda} + \sin(2\pi y/\lambda) \frac{[\sinh(\beta) - \beta \cosh(\beta)] \cosh(2\pi z/\lambda) + \sinh(\beta) (2\pi z/\lambda) \sinh(2\pi z/\lambda)}{\sinh(\beta) \cosh(\beta) - \beta} - \left(\frac{\sqrt{2} \Delta P H^2}{4\mu C L \dot{\lambda}} \right) \left(1 - \frac{z^2}{H^2} \right) \end{aligned} \quad [27b]$$

$$\frac{u_z}{C\dot{\lambda}} = -\frac{2}{C}\frac{z}{\lambda} + [\cos(2\pi x/\lambda) + \cos(2\pi y/\lambda)] \frac{\beta \cosh(\beta) \sinh(2\pi z/\lambda) - (2\pi z/\lambda) \sinh(\beta) \cosh(2\pi z/\lambda)}{\sinh(\beta) \cosh(\beta) - \beta}$$

[27c]

$$\frac{p-p_0(t)}{4\pi\mu(C/\beta^2)(\dot{\lambda}/\lambda)} = \left(\frac{\sqrt{2}\Delta PH^2}{4\mu CL\dot{\lambda}} \right) \left(\frac{2\pi x + 2\pi y}{\lambda} \right) - \frac{\beta^2 \sinh(\beta)}{\sinh(\beta) \cosh(\beta) - \beta} [\cos(2\pi x/\lambda) + \cos(2\pi y/\lambda)] \cosh(2\pi z/\lambda)$$

[27d]

Henceforth, we denote by δ the dimensionless parameter which consistently appears in our results. It defines the relative importance of the pressure gradient vis a vis the heterogeneity parameters of the primary septa, embedded in C , the unit-cell configuration and its kinematic behavior,

$$\delta = \frac{\sqrt{2}\Delta PH^2}{4\mu LC\dot{\lambda}} \quad [28]$$

The interstitial velocity field is illustrated in Fig. 3 for $\delta = 0.2, 1, 5$.

The dimensionless pressure [27d] in the xy plane at surface $z=H$ are depicted in Fig. 4¹ for various values of δ . The rationale for these choices of δ and in particular $\delta = 0.26$ is addressed in detail in the discussion section.

The maximum shear stress exerted on the wall at $z = \pm H$ is obtained from the hydrodynamic shear stress components,

$$\begin{aligned} \frac{[\sigma_{xz}]_{z=H}}{4\pi\mu(C/\beta)(\dot{\lambda}/\lambda)} &= \left(\frac{\sqrt{2}\Delta PH^2}{4\mu CL\dot{\lambda}} \right) + \frac{\beta \sinh^2(\beta)}{\sinh(\beta) \cosh(\beta) - \beta} \sin(2\pi x/\lambda) \\ \frac{[\sigma_{yz}]_{z=H}}{4\pi\mu(C/\beta)(\dot{\lambda}/\lambda)} &= \left(\frac{\sqrt{2}\Delta PH^2}{4\mu CL\dot{\lambda}} \right) + \frac{\beta \sinh^2(\beta)}{\sinh(\beta) \cosh(\beta) - \beta} \sin(2\pi y/\lambda) \end{aligned} \quad [29]$$

as follows [14],

¹Notice that negative dimensionless pressures were obtained. This is possible since the real pressure is obtained by adding the base pressure p_0 so the total is positive. In our previous paper (Haber et al 2016) we showed erroneously the absolute value of the dimensionless pressure.

$$\frac{[(\sigma_{\theta z})_{\max}]_{z=H}}{4\pi\mu(C/\beta)(\lambda/\lambda)} = \left\{ \begin{aligned} &\frac{\beta^2 \sinh^4(\beta)}{[\sinh(\beta)\cosh(\beta)-\beta]^2} [\sin^2(2\pi x/\lambda) + \sin^2(2\pi y/\lambda)] \\ &+ 2 \left(\frac{\sqrt{2}\Delta PH^2}{4\mu CL\lambda} \right) \frac{\beta \sinh^2(\beta)}{[\sinh(\beta)\cosh(\beta)-\beta]} [\sin(2\pi x/\lambda) + \sin(2\pi y/\lambda)] \\ &+ 2 \left(\frac{\sqrt{2}\Delta PH^2}{4\mu CL\lambda} \right)^2 \end{aligned} \right\}^{\frac{1}{2}} \quad [30]$$

The maximum dimensionless shear stresses [30] exerted on the wall at $z = H$ are depicted in Fig. 5 for various values of δ .

All the figures assume the value of $\beta = 0.1\pi$. We have not introduced the effect of changing β since it has a very small effect on the results (e.g. eq. [B.5]). For example, varying β in the range $0 < \beta < 0.335$ changes δ_{cr} by no more than 1.5%.

DISCUSSION

During tissue remodeling, the deposition of collagen and elastin fibers is essential for alveolar growth. These fibers are produced by myofibroblasts which are cells differentiated from fibroblasts (Tomasek et al., 2002; Serini & Gabbiani, 1999; Bochaton-Piallat et al. 2016). It has been reported that mechanical forces exerted by the interstitial fluid flow that surrounds fibroblasts may trigger their differentiation into myofibroblasts (e.g., Ng et al., 2005). Our goal (Haber et al., 2016 and the present study) was to predict where fibroblast differentiation is likely to occur. Utilizing the basic rules of interstitial fluid mechanic, the non-uniform shear stress distribution can be obtained and the location of maximal shear stresses can be revealed.

The interstitial (tissue) fluid must be constantly in motion to transport nutrients and waste in the interstitial space. As we have discussed in a previous paper (Haber et al. 2016), interstitial flow is traditionally viewed as flow through porous media², which can be described by Darcy's law (Bear and Corapcioglu, 1984). However, Darcy's law is a *macroscopic* representation of the flow, and the shear stress exerted by the interstitial fluid on cell surface is not considered by this law. To obtain data on shear stress distributions we need to employ a *microscopic* approach. We perceive the porous medium as a planar duct, thus, simplifying the morphology of the interstitial fluid boundaries albeit the basic physics that govern the fluid motion are kept intact.

The interstitial flow is driven either by parenchymal pressure gradients and/or the non-uniform motion of the surrounding boundary walls. As a first step, we addressed the role of non-uniform motion of the primary septal walls in generating the interstitial flow after pneumonectomy (Haber et al., 2016). In the present study, we also include the effect of a

²The application of Poiseuille flow to describe flow in porous media is well documented in the literature, in particular, when the flow-rate is sought as function of the pressure gradient (Happel and Brenner 1983). Both in Poiseuille flow and Darcy's law one assumes that the inertia terms in the Navier-Stokes equations can be neglected. In both cases, the flow-rate is proportional to the pressure gradient and a coefficient of proportionality (the permeability) can be defined. In Darcy's law the permeability, that accounts for the geometrical structure of the porous media, is normally determined experimentally. However, past investigations also adopted Poiseuille flow in various channel geometries to replace the intricate structures of porous media (e.g. Blake 1922).

parenchymal pressure gradient, which is known to be present between the alveolar region and the hilar region (Bhattacharya et al, 1984; Aukland & Reed, 1993). For instance, Lohser & Slinger (2015) reported increased lung water after pneumonectomy. One of the objectives is to investigate the relative importance of these two factors in generating the interstitial flow and, in particular, the location of maximal shear stresses in the interstitial space and on the walls.

That relative importance can be expressed by the dimensionless parameter δ (defined in Eq. 28). When $\delta \ll 1$, the importance of the non-uniform motion of the primary septal walls dominates over the parenchymal pressure gradient in generating interstitial flow and non-uniform shear stress distribution in the interstitial space, whereas when $\delta \gg 1$, the parenchymal pressure gradient becomes much more important compared to the non-uniform boundary wall motion in generating interstitial flow and the shear stress distribution is approximately uniform. It is important to state that the non-uniform motion of the primary septal walls is a necessary condition for the shear stress distribution to be non-uniform. In other words, non-uniform shear stress distribution would not be generated in the interstitial space unless the boundary wall motion is non-uniform regardless of the value of δ . When $\delta \sim 1$, the two factors are comparable; while the shear stress distribution in the interstitial space is still somewhat similarly to the one created at $\delta = 0$, the parenchymal pressure gradient would modify this pattern.

Shear Stress Pattern and δ

For $\delta = 0$, the pattern of shear stress distribution is featured with four equal maximum values at four points at $\lambda/4$ from the new unit-cell corners and high ridges that connect them (Fig. 5). Hence, the locations of the secondary septa form at $\lambda/4$ from the original unit-cell border, defining a smaller alveolar cell (See Fig. 6 red dotted line).

When $\delta > 0$ a different landscape is obtained. The peak at $x, y > 0$ (first quarter) is the highest, the two peaks at $xy < 0$, (second and fourth quarter) are somewhat lower and the peak at $x, y < 0$ (third quarter), decreases monotonously in size as δ increases (Fig. 5, 7). The ridges that connect the first quarter- and the second quarter-peaks and, similarly the first to the fourth, outline two sides of the newly formed alveolus boundaries. However, the peak in the third quarter can become lower than the ridges that connect the first to the second (and the first to the fourth). Thus, there is critical value, δ_{cr} , for which the ridges become as high as the peak at the third quarter (See Fig. 7, black dotted line). It is calculated in Appendix B.

$$\delta_{cr} = (3 - \sqrt{8})F(\beta), \quad \beta = 2\pi H/\lambda, \quad F(\beta) = \frac{\beta \sinh^2 \beta}{\sinh \beta \cosh \beta - \beta}$$

For $2H = 10^{-5}$ m and $\lambda = 10^{-4}$ m and $\beta = 0.31$, we obtain that $F(\beta) = 1.5$ is an excellent approximation. Consequently,

$$\delta_{cr} = 0.26.$$

This means that for $0 < \delta < \delta_{cr}$ we expect that a higher shear stress region (peaks and ridges) would form a new unit cell that is half the size of the original one.

For $\delta > \delta_{cr}$ the boundaries of the newly formed unit cell will connect peaks of adjacent original unit cells (see Fig. 8), possess the same size as the original ones but be shifted from their original location.

Physiological Implication

Since we predict that delta will play an important role in determining the size of newly-formed alveoli it is important to consider the value of this parameter in order to highlight why this parameter is important. As shown in Eq. 28, δ is a function of P/L , H , μ , $\dot{\lambda}$, C . H and μ are the thickness of the primary septum $2H_0$ (i.e., $2H_0$ defined as the thickness of the unit cell at time $t = 0$) and the viscosity of interstitial fluid, respectively, and here we treat them as constant ($H_0 = 5\mu\text{m}$, $\mu \approx 10^{-3} \text{ Pa}\cdot\text{s}$). The values of $\dot{\lambda}$, C , and P/L must be derived separately if the order of magnitude of δ is sought. We assume that λ changes periodically as follows, $\lambda = \lambda_0(1 + \epsilon \sin(\omega t))$ where λ_0 is the average size of alveolus ($\lambda_0 = 10^{-4}\text{m}$), thus $\dot{\lambda} = \lambda_0 \epsilon \omega = \lambda_0 \epsilon 2\pi/T$ where T is a breathing period ($T \approx 4 \text{ sec}$) and ϵ is the linear stretch. The latter is related to Tidal Volume (TV) and the Functional Residual Capacity

(FRC) via the equation, $\epsilon \approx [(FRC + TV)/FRC]^{1/3} - 1$. Since TV is approximately 500 mL, and FRC is about 40% of TLC (total Lung Capacity $\sim 6 \text{ L}$), we obtain that $\epsilon \approx 0.06$. The value of the constant C depends on the heterogeneous material properties of the walls. Although the value of the constant C is currently unknown, it is bounded and depends on the value of ϵ , namely $0 < C < (1 + \epsilon)/\epsilon \approx 17.7$. The order of magnitude of P/L can be determined if the average seepage velocity $\bar{V}$ through the interstitial duct is known. Assuming Poiseuille flow inside the interstitial duct $P/L = (3\mu\bar{V})/(2H^2)$.

Taken together, $\delta = \frac{\sqrt{2} \frac{3\mu\bar{V}}{H^2} H^2}{8\pi\mu C \lambda_0 \epsilon} = \frac{3\sqrt{2}}{8\pi} \frac{\bar{V}}{C \lambda_0 \epsilon} \approx \frac{1.12 \times 10^5 \bar{V}}{C}$. The velocity of the interstitial flow is on the order of $0.1 \sim 1 \mu\text{m/s}$ (Chary and Jain, 1989; Jain, 1999; Dafni et al., 2002), thus, $\delta \approx (0.0112 \sim 0.112)/C$ depending on the mechanical properties of the wall (C). If we assume $C = 1$ then $\delta \approx 0.0112 \sim 0.112$ which is smaller than δ_{cr} . This simple calculation with realistic values demonstrates that the non-uniform motion of the primary septal walls is more important over the parenchymal pressure gradient in generating interstitial flow and non-uniform shear stress distribution in the interstitial space for the case of $C = 1$.

Summary

Our analysis shows that the basic non-uniform pattern of shear stress distribution is created by the non-uniform cyclic motion of the primary septal walls due to the highly heterogeneous nature of wall mechanical properties. The addition of a parenchymal pressure gradient modifies this pattern substantially. The relative importance of these two mechanisms is manifested by the value of δ . High values of δ pertain to high pressure gradients and the flow is mainly controlled by their value. Low values of δ indicate that the controlling mechanism is associated with the flow generated by the expansion and contraction of inhomogeneous primary septa during breathing. A critical value of $\delta_{cr} = 0.26$

exists which determines whether the newly formed alveoli are half the size ($\delta < \delta_{cr}$) or possessing the full size of the original alveoli ($\delta > \delta_{cr}$).

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Appendix A: Maximum hydrodynamic shear stress in the liquid near the wall

Fibroblasts inside the interstitial liquid might also be affected by shear stresses. Maximum shear stresses exist in the liquid near the walls and thus will affect fibroblast that straddle the wall. To obtain the maximum shear stress one needs all 6 components of the stress tensor adjacent to the wall. Two of these components were already evaluated (Eq. [28]).

Four additional components are:

$$\begin{aligned}
\frac{[\sigma_{xx}]_{z=H}+p_0}{4\pi\mu C\lambda/\lambda} &= \frac{1}{2\pi C} + \left[1 + \frac{\sinh\beta\cosh\beta}{\sinh\beta\cosh\beta-\beta} \right] \cos\frac{2\pi x}{\lambda} \\
&+ \frac{\sinh\beta\cosh\beta}{\sinh\beta\cosh\beta-\beta} \cos\frac{2\pi y}{\lambda} - \frac{1}{\beta^2} \left(\frac{\sqrt{2}\Delta PH^2}{4\mu CL\lambda} \right) \left(\frac{2\pi x+2\pi y}{\lambda} \right) \\
\frac{[\sigma_{yy}]_{z=H}+p_0}{4\pi\mu C\lambda/\lambda} &= \frac{1}{2\pi C} + \left[1 + \frac{\sinh\beta\cosh\beta}{\sinh\beta\cosh\beta-\beta} \right] \cos\frac{2\pi y}{\lambda} \\
&+ \frac{\sinh\beta\cosh\beta}{\sinh\beta\cosh\beta-\beta} \cos\frac{2\pi x}{\lambda} - \frac{1}{\beta^2} \left(\frac{\sqrt{2}\Delta PH^2}{4\mu CL\lambda} \right) \left(\frac{2\pi x+2\pi y}{\lambda} \right) \\
\frac{[\sigma_{zz}]_{z=H}+p_0}{4\pi\mu C\lambda/\lambda} &= -\frac{1}{\pi C} + \left[\cos\frac{2\pi x}{\lambda} + \cos\frac{2\pi y}{\lambda} \right] \frac{\beta}{\sinh\beta\cosh\beta-\beta} \\
&- \frac{1}{\beta^2} \left(\frac{\sqrt{2}\Delta PH^2}{4\mu CL\lambda} \right) \left(\frac{2\pi x+2\pi y}{\lambda} \right) \\
\sigma_{xy} &= 0
\end{aligned}
\tag{A.1}$$

Calculating the principal stress tensor components and the maximum dimensionless shear stresses in the liquid adjacent to the wall (see [15–17] results in the following figures (Fig. A),

These results look almost identical to those shown in Fig. 5. Nonetheless, the values of the shear stress are higher in this case since one had to account for the normal stress components.

Figure A.
The maximum shear stress near the wall for various values of δ .

Appendix B: Critical value of δ

We need to find the maxima and minima of $F(x,y)$, (the shear stress distribution [30] squared),

$$F(X, Y) = \frac{[(\sigma_{\theta z})_{\max}]^2_{z=H}}{4\pi\mu(C/\beta)(\lambda/\lambda)} = A^2(\beta)[\sin^2(X) + \sin^2(Y)] + 2\delta A(\beta)[\sin(X) + \sin(Y)] + 2\delta^2$$

[B.1]

within the plane $-\lambda/2 < x < \lambda/2$, $-\lambda/2 < y < \lambda/2$, where

$$A(\beta) = \frac{\beta \sinh^2(\beta)}{\sinh(\beta) \cosh(\beta) - \beta}, \quad \delta = \frac{\sqrt{2}\Delta PH^2}{4\mu LC \lambda}, \quad X = \frac{2\pi x}{\lambda}, \quad Y = \frac{2\pi y}{\lambda} \quad [\text{B.2}]$$

Differentiation of F with respect to X, Y yields,

$$\begin{aligned} \frac{\partial F}{\partial X} &= 2A \cos(X) [A \sin(X) + \delta] \\ \frac{\partial F}{\partial Y} &= 2A \cos(Y) [A \sin(Y) + \delta] \end{aligned}$$

Setting the derivatives to zero yields, $\cos(X) = \cos(Y) = 0$, $\sin(X) = -\delta/A$, $\sin(Y) = -\delta/A$

Thus, the local maxima are at

$$(X, Y)_{\max} = \{(\pi/2, \pi/2), (\pi/2, -\pi/2), (-\pi/2, \pi/2), (-\pi/2, -\pi/2)\} \quad [\text{B.3}]$$

And the local maximal values of F at these locations are, respectively,

$$F_{\max} = \{2(A+\delta)^2, 2(A^2+\delta^2), 2(A^2+\delta^2), 2(A-\delta)^2\} \quad [\text{B.4}]$$

Thus, the highest maximum is at $(\pi/2, \pi/2)$, the first quarter, the second highest are at $(-\pi/2, \pi/2)$, and at $(\pi/2, -\pi/2)$, the second and fourth quarters, respectively, and the lowest maximum is at $(-\pi/2, -\pi/2)$, the third quarter.

The minimum value at the ridge between the local maxima of the first and second quarters is at $X = \arcsin(-\delta/A)$, $Y = \pi/2$. The value of F at this point is,

$$F(\text{ridge})_{\min} = (A+\delta)^2.$$

The same value is obtained at the ridge between the first and fourth quarters maxima.

The value of $\delta = \delta_{cr}$ for which the ridge's lowest point equals that of the third quarter maximum can be obtained from the following simple quadratic equation, $(A + \delta_{cr})^2 = 2(A - \delta_{cr})^2$, namely,

$$\delta_{cr} = (3 - \sqrt{8})A = (3 - \sqrt{8}) \frac{\beta \sinh^2(\beta)}{\sinh(\beta) \cosh(\beta) - \beta} \quad [\text{B.5}]$$

For $\delta > \delta_{cr}$ the lowest point on the ridge is higher than the the third quarter maximum, and vice versa. For small values of β the value of A can easily be analyzed. Utilizing the following approximations

$$\sinh(\beta) = \beta + \beta^3/6 + \beta^5/120 + \dots, \quad \cosh(\beta) = 1 + \beta^2/2 + \beta^4/24 + \dots$$

We obtain that,

$$A = \frac{3}{2} \left(1 + \frac{2\beta^2}{15} \right) + O(\beta^4)$$

Thus, for a large range of $0 < \beta < 0.335$, δ_{cr} will change by no more than 1.5%.

Highlights

- Interstitial fluid mechanics is important to understand compensatory lung growth.
- A parenchymal pressure gradient in the interstitial space is added to the analysis.
- The ratio of pressure gradient effects to the non-uniform wall motion is defined.
- Non-uniform shear stress distribution in the primary septa depends on this ratio.
- This ratio is likely to play an important role in fibroblasts' differentiation.

Figure 1.

Geometric model. The upper panels show SEM(left), its schematics (middle), and corresponding interstitial flow channels-shown in blue-of the primary septa (right) of normal rabbit alveolar duct. The lower panels show their counterparts in the case of detergent-rinsed rabbit alveolar ducts. Note that while the secondary septa appear normal in the upper panel, they collapse onto the primary septa in the case of detergent-rinsed lungs, which is very similar to the pneumonectomized case (Ysasi et al., 2015). Left and Middle panels are adapted from Bachofen et al.(1979). D_{out} and D_{in} denote the outer and inner diameter of alveolar duct, respectively; $2H$ indicates the thickness of interstitial space. In the middle and right panels, we include a representative flow direction caused by a parenchymal pressure gradient since the parenchymal pressure gradient is generally known present between the alveolar region and the hilar region (Bhattacharya et al, 1984; Aukland & Reed, 1993). (Figure is reproduced from Haber et al., 2016 with permission) [For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.]

Figure 2.

The geometrical model of a dilated primary septum with collapsed secondary septa after pneumonectomy and the definition of the unit cell. *Upper:* A dilated primary septum with collapsed secondary septa after pneumonectomy is viewed as a long cylinder. The upper view shows the location of the unit cell in the cylindrical airway. If the line elements of the acinus are woven in a helical pattern (both left-and-right-handed) in the alveolar duct, the collapsed secondary septa (shown in red) would appear as diagonal lines on the wall layers in the flat view (Wilson and Bachofen, 1982). *Lower:* Two dimensional view of the primary septum. *Inset:* The interstitial fluid of the primary septum, which is enclosed between two very close cylindrical surfaces, $2H$ apart, thus replaced with planar walls, is shown in blue. The unit cell bounded by adjacent collapsed secondary septa is our solution domain. The (x, y, z) coordinate system is embedded inside the unit cell with its origin at the center. The coordinates (x, y) are parallel to the lines formed by the secondary septa while z points along the radial direction of the alveolated airway. h ; the thickness of an epithelial wall layer.

Figure 3.

Velocity distributions for $\delta = 0.2, 1, 5$ manifesting that for $\delta = 5$ the flow is governed mainly by the pressure gradient whereas for $\delta = 0.2$ the governing mechanism is the flow induced by expansion and contraction of the inhomogeneous alveolus during breathing.

Figure 4.

The dimensionless pressure distribution at the surface ($z=H$) of the unit cell. The dimensionless pressure (eq. 27d) is shown for various values of δ . For $\delta=0$ (i.e., no pressure gradient), the pressure distribution is identical to that obtained in Haber et al. (2016). When the non-uniform primary septa wall motion dominates over pressure gradient in generating interstitial flow ($\delta < \delta_{crit}$), there are four distinct maxima at the corners of the unit cell and one minimum at its center but this topography changes as δ increases. For $\delta=10$, 1000 it is clearly shown that the pressure is governed by the flow generated by the pressure gradient. For $\delta=1000$ isobars become almost straight lines inclined at 45° with respect to the x -axis. Note that the pressure gradient is parallel to the line $x=y$.

Figure 5.

The maximum shear stress distribution exerted on the wall of the unit cell for various values of δ . For $\delta=0$ (i.e., no pressure gradient), the distribution of the dimensionless shear stress (eq. 30) is identical to that obtained in Haber et al. (2016). When the non-uniform primary septa wall motion dominates over pressure gradient in generating interstitial flow ($\delta < \delta_{crit}$), there are four distinct peaks at $\lambda/4$ from the unit-cell corners but this unique feature becomes less obvious as δ increases.. For $\delta=10, 1000$ it is clearly shown that the shear stress is governed by the flow generated by the pressure gradient. Note that the pressure gradient is parallel to the line $x=y$.

Figure 6. Iso-maximum values of shear stress exerted on the wall of the unit cell for $\delta=0$. Four equal maximum values at four points at $\lambda/4$ from the new unit-cell corners and high ridges (shown as red dotted lines)

Figure 7.

A 2D projection of the 3D shear rate topography shown in Fig. 5 for $\delta = 0.26$ that shows all four peaks. The dash line illustrates that the minimum height of the ridge between the first and second quarter peaks (highest and second highest peaks) equals the height of the peaks in the third quarter (the lowest peaks)

Figure 8.

Two panels showing 4 adjacent unit cells. The left hand side panel ($\delta=0.1$) illustrates that connecting the highest shear rate locations (4 peaks and the high ridges that connect them) outline the borders of a new square unit cell that its side is half of that of the original one. The right hand side panel ($\delta=10$) elucidates that if the third quarter peak is lower than the ridges connecting the first with the second and fourth peak, the boundaries of the new unit cell are formed by connecting peaks of adjacent unit cells.