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An investigation of the influence of cell topography on epithelial mechanical stresses during pulmonary airway reopening

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Abstract

The goal of this study is to assess the local mechanical environment of the pulmonary epithelium in a computational model of airway reopening. To this end, the boundary element method (BEM) in conjunction with lubrication theory is implemented to assess the stationary-state behavior of a semi-infinite bubble traveling through a liquid-occluded parallel plate flow chamber lined with epithelial cells. The fluid occlusion is assumed to be Newtonian and inertia is neglected. The interactions between the microgeometry of the model airway's walls and the interfacial kinematics surrounding the bubble's tip result in a complex, spatially and temporally dependent stress distribution. The walls' nonplanar topography magnifies the normal and shear stresses and stress gradients. We find that decreasing the bubble's speed serves to increase the maximum normal stress and stress gradient but decrease the maximum shear stress and stress gradient. Our results give credence to the pressure-gradient-induced epithelial damage theory recently proposed by Bilek *et al.* [J. Appl. Physiol. **94**, 770 (2003)] and Kay *et al.* [J. Appl. Physiol. **97**, 269 (2004)]. We conclude that the amplified pressure gradients found in this study may be even more detrimental to the airway's cellular epithelium during airway reopening.

I. INTRODUCTION

Respiratory distress syndrome (RDS) is a life-threatening condition that afflicts premature infants born prior to the seventh month of gestation. It is caused by an underdeveloped pulmonary system whose cells cannot yet manufacture a proper quality or quantity of lung surfactant.¹ This diminishes the surface activity of the lung lining fluid and promotes airway obstruction by liquid occlusion. High surface tension, compounded by the tiny size of the fluid-filled airways and alveoli, results in tremendous pressure requirements to open the lungs during the first breath and thereafter to maintain their patency for continued breathing.^{2–4} Current medical intervention for RDS includes mechanical ventilation and surfactant replacement therapy; however, exhaustion and lung collapse remain constant threats that too often lead to significant pulmonary impairment and infant death.⁵

Mechanical ventilation, though an indispensable life-sustaining implement, exerts excessive stresses to the walls of the airways and alveoli, causing undesirable structural and functional modifications to the pulmonary epithelium.⁶ In a recent study by Bilek *et al.*,⁷ this epithelial damage was assessed using a coupled experimental and computational model of airway reopening in which a bubble of air was forced through a liquid-occluded, cell-lined parallel plate flow chamber. Their results implicated the pressure gradient—as opposed to the more commonly touted shear stress—as being responsible for the cell membrane disruptions observed during a single reopening event. Further studies have discounted stimulus duration as a damage mechanism and provide additional evidence for the pressure gradient hypothesis.⁸

The goal of the present study is to better characterize the local mechanical stress environment of the pulmonary epithelium during airway reopening. To this end, we have

developed a computational model that expands upon that of Bilek *et al.*,⁷ in which a semi-infinite bubble of air is forced through a liquid obstructing a narrowly spaced channel with symmetrically corrugated walls (Fig. 1). Here the channel provides a two-dimensional (2D) representation of a collapsed respiratory airway, with its wall corrugations delineating the topographic variations of pulmonary epithelial cells. The occluding liquid is assumed to be Newtonian, such that its viscosity μ , density ρ , and surface tension γ are constant, and the slow viscous flow in the system is approximated by Stokes flow. Although our research is primarily concerned with the mechanics of airway reopening, it is worth noting that this system may have additional physiologic applications, such as the passage of deformable red blood cells through capillaries of varying cross-sectional area.^{9,10}

This model expands upon a number of classic fluid mechanics investigations of bubble progression through a liquid of constant surface tension and viscosity within a capillary tube. In 1935, Fairbrother and Stubbs¹¹ determined experimentally that the thickness of the film of liquid deposited in the wake of the traveling bubble front is a function of the capillary number, $Ca_U = \mu U / \gamma$, where U is the speed of bubble advancement. This dimensionless parameter, which governs the velocity of the meniscus, represents the ratio of viscous-to-interfacial stresses. Taylor¹² later carried out similar studies using liquids of higher viscosity and found that the fluid film thickness tends to be proportional to $Ca_U^{1/2}$ for $Ca_U < 0.09$ and to asymptote to a constant value at larger Ca_U . Using an asymptotic approach, Bretherton¹³ extended these investigations to $10^{-6} < Ca_U < 10^{-3}$, where he determined the thickness of the thin film and the pressure drop across the bubble's tip to be proportional to $Ca_U^{2/3}$.

Park and Homsy¹⁴ developed a theory for two-phase displacement in a Hele-Shaw cell at small Ca_U . They found asymptotic solutions for the shape of the semi-infinite bubble and the pressure drop across its interface in both the bubble cap and the thin-film regions. Reinelt and Saffman¹⁵ numerically studied this problem with a multigrid finite difference algorithm within the broader Ca_U range of $10^{-2} < Ca_U < 2.0$. Using the boundary integral technique [or boundary element method (BEM)], Martinez and Udell¹⁶ accurately predicted the interfacial shape, flow field, and pressure distribution of this system for values of Ca_U as high as 10.0. Halpern and Gaver¹⁷ also implemented BEM to compute the time-dependent shape of a semi-infinite bubble and the pressure drop across its free surface during its progression through a Hele-Shaw cell. Their results were consistent with those of Reinelt and Saffman¹⁵ for $Ca_U > 3.0$ and extended to the range $0.05 < Ca_U < 10^4$. Recently, Ghadiali and Gaver¹⁸ expanded upon this BEM analysis by adding surfactant to the system and demonstrated modifications to the flow field, mechanical stress balance, and interfacial shape as a result of the dynamic surface tension.

In the present computational model, the flat, rigid walls of a Hele-Shaw cell are overlaid with sinusoidal corrugations in order to investigate topographic effects on the flow field. A number of related investigations have examined the flow of fluids over irregular surface profiles. Stillwagon and Larson^{19,20} experimentally demonstrated that a thin fluid film develops an irregular surface profile during its spin coating on patterned substrates; they then analytically matched these results using lubrication theory. Schwartz and Weidner²¹ derived a 1D evolution equation for the surface-tension-driven leveling of a thin, Newtonian liquid layer into its minimum energy configuration, also using lubrication theory. Kalliadasis *et al.*²² extended this lubrication analysis to include the effect of an external body force on the quasisteady settling of a fluid film over “trenches” and “mounds.” Using BEM, Pozrikidis²³ observed the combined effects of gravity and capillary forces on the behavior of a thin film through examining the fluid's creeping flow along an inclined periodic wall. Mazouchi and Homsy²⁴ implemented the boundary integral technique to determine solutions

for the time-dependent Stokes flow over a nonuniform wall profile as a function of capillary number. Tsai and Miksis²⁵ also used BEM for their investigation of the deformation and snap-off of a pressure-driven finite bubble passing through a constriction in a capillary tube. Each of these studies underscore the significant contribution of topographical variations to the interfacial flow response; however, none explore the effect of a substrate's topography on the mechanical stresses exposed to that substrate's surface, which could critically influence related biological systems.

The current analysis implements BEM in conjunction with lubrication approximations to solve the Stokes equations and characterize the rigid wall's local stationary-state stress environment. We hypothesize that, within the region of the progressing bubble front, these stresses and the gradients in these stresses are significantly magnified as a consequence of the walls' topographic variations. These amplifications may damage pulmonary epithelial cells or alter their structure and function during airway reopening.

II. FORMULATION

We model the progression of an inviscid, semi-infinite bubble along a fluid-filled, corrugated horizontal channel in response to a constant fluid flow rate Q^* (Fig. 1). Because of the nonplanar wall topography, the flow field is unsteady. The liquid occlusion is assumed to be Newtonian with constant density ρ and viscosity μ , and the surfactant-free system is characterized by a constant surface tension γ . We thus ignore the physicochemical hydrodynamics that normally influence the process of airway reopening.^{18,26,27}

A. Scales

The following scales are used (* denotes dimensional quantities):

$$\begin{aligned} \mathbf{x}^* &= H\mathbf{x}, & \kappa^* &= \frac{1}{H}\kappa, & t^* &= \frac{H}{U}t = \frac{H\mu}{\gamma}t, \\ \mathbf{u}^* &= U\mathbf{u} = \frac{\gamma}{\mu}\mathbf{u}, & \tau^* &= \frac{\gamma}{H}\tau, \end{aligned} \quad (1)$$

where t^* is time and κ^* is the curvature of the free surface. The velocity scale, $U = \gamma/\mu$, is based upon the interfacial relaxation time, and stresses are scaled following a Laplace–Young pressure scale for an interface of curvature $1/H$.

B. Model domain

Our system is modeled to be symmetric about the mid-plane, so it is only necessary to analyze half the domain—we selected the lower portion. The corrugated channel wall, located at $y_{\text{bot}}^*(x^*)$, varies sinusoidally with amplitude a and wavelength λ about a mean height of $y^* = -H$:

$$y_{\text{bot}}^*(x^*) = -H + a \left[\sin\left(\frac{2\pi x^*}{\lambda}\right) \right]. \quad (2)$$

To simplify the computational analysis, these topographical variations are damped exponentially towards a flat surface far upstream and downstream of the progressing meniscus (Fig. 2). The center of the envelope that attenuates the wall's oscillations travels with the progressing bubble, such that the bubble tip is surrounded by corrugations extending significantly upstream and downstream. This attenuation has advantages for matching end conditions, and its effects on the bubble-tip region, where the analysis is primarily concerned, are negligible.

Nondimensionalization yields two governing wall geometry parameters: the dimensionless corrugation amplitude, $\varepsilon = a/H$, and wavelength, $\Lambda = \lambda/H$. The average radius of an open respiratory bronchiole in the human lung is approximately $H = 200 \mu\text{m}$.²⁸ In addition, the average values for the height $2a$ and width λ of L2 pulmonary epithelial cells are $\approx 5 \mu\text{m}$ and $50 \mu\text{m}$, respectively.⁷ This corresponds to a lower limit for the values of the geometric dimensionless parameters of $\varepsilon = 0.01$ and $\Lambda = 0.2$. Regions of collapse, where H may decrease significantly, are characterized by increased $\varepsilon = a/H$ and $\Lambda = \lambda/H$, so a range of these parameter values is explored herein.

C. Dimensionless governing equations and parameters

The dimensionless pressure P is referenced to that within the bubble, and meniscus progression occurs in response to a prescribed 2D dimensionless flow rate Q . Slow, viscous flow is assumed (Reynolds number, $\text{Re} \ll 1$), such that the governing Navier–Stokes equations may be reduced to the Stokes and continuity equations throughout the fluid domain:

$$\nabla P = \nabla^2 \mathbf{u}(\mathbf{x}, t), \quad \nabla \cdot (\mathbf{x}, t) = 0. \quad (3)$$

The bubble's shape is spatially and temporally dependent, and the interfacial stress condition is

$$\tau = \hat{\mathbf{n}} \cdot \mathbf{T} = \kappa \hat{\mathbf{n}} \text{ at } y = y_{\text{men}}(\mathbf{x}, t), \quad (4)$$

where $\hat{\mathbf{n}} = (n_x, n_y)$ is the liquid's outward-facing normal and $\mathbf{T} = -P\mathbf{I} + [\nabla \mathbf{u}(\mathbf{x}, t) + \nabla \mathbf{u}(\mathbf{x}, t)^T]$ is the viscous fluid's dimensionless stress tensor. The position $y_{\text{men}}(\mathbf{x}, t)$ delineates the interfacial shape. Marangoni and nonequilibrium normal stresses do not exist in our model, since we assume a constant surface tension.

Time stepping is accomplished using the kinematic boundary condition at the interface,

$$\frac{DY(\mathbf{x}, t)}{Dt} \cdot \hat{\mathbf{n}} = \mathbf{u}(\mathbf{x}, t) \cdot \hat{\mathbf{n}} = u_{\text{norm}}(x, y, t). \quad (5)$$

Here, $\mathbf{Y}(\mathbf{x}, t)$ defines an interfacial material point, and $u_{\text{norm}}(x, y, t)$ is the normal velocity. We maintain our system in the tip frame of reference, as described in Sec. III B.

No-slip and no-penetration apply to the viscous fluid flow at the model's rigid wall. The longitudinal velocity of the liquid far downstream of the meniscus ($x \gg 0$), where flow is assumed to be fully developed and parallel, is

$$u(x, y) = \frac{3}{2} \frac{Ca_Q}{y_{\text{bot}}^3(x)} [y^2 - y_{\text{bot}}^2(x)]. \quad (6)$$

Here, $Ca_Q = [Q^*/(2H)]/[\gamma/\mu]$ is the flow-rate-based capillary number. The values for Ca_Q examined in this study were selected to correlate to the range of flow rates used in the corresponding Bilek *et al.*⁷ experimental analysis.

D. Lubrication theory

We use lubrication theory some distance upstream of the bubble's tip to describe interfacial flow (Fig. 2). This technique significantly increases computational efficiency by allowing the truncation of the boundary element domain. The lubrication and boundary element

regions remain connected through a master spline interpolation of interfacial shape that spans the entire domain. This spline is used to calculate accurately the interfacial curvature κ which is key when implementing BEM and can be used without further approximation in the lubrication region.

In the lubrication regime

$$u(x, y, t) = -\frac{\kappa_x}{2} [y - y_{\text{bot}}(x)] [y + y_{\text{bot}}(x) - 2y_{\text{men}}(x, t)]. \quad (7)$$

The kinematic boundary condition, Eq. (5), along the air-liquid interface is

$$\frac{\partial y_{\text{men}}(x, t)}{\partial t} = v(x, y, t) - u(x, y, t) y_{\text{men},x}(x, t) = -\frac{\partial Q}{\partial x}, \quad (8)$$

so that

$$\begin{aligned} \frac{\partial y_{\text{men}}(x, t)}{\partial t} = & \frac{\kappa_{xx}}{3} [y_{\text{men}}(x, t) - y_{\text{bot}}(x)]^3 \\ & + \kappa_x [y_{\text{men}}(x, t) - y_{\text{bot}}(x)]^2 \\ & \times [y_{\text{men},x}(x, t) - y_{\text{bot},x}(x)], \end{aligned} \quad (9)$$

which is consistent with the evolution equation derived by Kalliadasis *et al.*²² This lubrication portion of the domain provides flow information that is used as boundary conditions along the surface shared by the lubrication and boundary element regions (surface *EA* of Fig. 2).

III. METHODS OF SOLUTION

Our goal is to find stationary-state solutions to the Stokes equations for the fluid flow surrounding a semi-infinite bubble that is traveling along a corrugated channel. We use the BEM to determine the time-dependent behavior of the free-surface as it passes over the wall's periodic protrusions. In addition, within the thin-film region, we incorporate lubrication approximations, which provide relevant boundary conditions, to model the flow (Fig. 2).

A. Boundary element method

We apply the BEM using the boundary integral equations²⁹ by implementing techniques described in Halpern and Gaver.¹⁷ This was accomplished by dividing our BEM domain into three-point quadratic elements, with a velocity or stress boundary condition specified in both the x and y directions at each node. Table I, which corresponds to the discretizing scheme depicted in Fig. 2, lists each of these boundary conditions.

B. Time stepping using the tip frame of reference

The analyses thus far presented have been set in the laboratory frame of reference. However, to track the behavior of the system in the neighborhood of the meniscus, it is most logical to lock kinematically the model's frame of reference to the bubble tip instead, such that

$$\begin{aligned} x|_{\text{tip}} &= x - x_{\text{tip}}, & y|_{\text{tip}} &= y, \\ u|_{\text{tip}} &= u - u_{\text{tip}}, & v|_{\text{tip}} &= v. \end{aligned} \quad (10)$$

Here, $(x|_{\text{tip}}, y|_{\text{tip}})$ and $(u|_{\text{tip}}, v|_{\text{tip}})$ refer to the x and y position and velocity in the tip frame of reference, while (x, y) and (u, v) are in the lab reference frame. The parameters x_{tip} and u_{tip} represent the tip position and velocity in the laboratory frame of reference.

To ensure that the entire system remains centered at the bubble tip, we similarly shifted the frame of reference of the kinematic boundary condition, Eq. (5). This determines the evolution equation, in the tip frame of reference, that governs the shape of the meniscus within the boundary element domain:

$$\left. \frac{DY}{Dt} \right|_{\text{tip}} = \left[(u - u_{\text{tip}}) n_x + v n_y \right] \hat{n}. \quad (11)$$

In the lubrication region, the tip-frame kinematic boundary condition is

$$\begin{aligned} \left. \frac{\partial y_{\text{men}}}{\partial t} \right|_{\text{tip}} = & \frac{\kappa_{xx}}{3} (y_{\text{men}} - y_{\text{bot}})^3 \\ & + \kappa_x \frac{\partial}{\partial x} (y_{\text{men}} - y_{\text{bot}}) \\ & \times (y_{\text{men}} - y_{\text{bot}})^2 - (u_{\text{tip}}) (n_x). \end{aligned} \quad (12)$$

Here, y_{men}/x is calculated by a second-order accurate three-point central differencing scheme, while y_{bot}/x is the derivative of the equation for the bottom wall y_{bot} , taken at each BEM node. The bubble's curvature κ and normal $\hat{n}$ and their respective derivatives are determined using a cubic spline interpolation of interfacial position that spans the entire fluid domain, as discussed in Sec. II D.

Once BEM has computed unknown velocities and stresses and lubrication theory has tabulated the velocity of the meniscus in the thin-film region, the new bubble configuration is found using the kinematic boundary condition. Time stepping is carried out using the Adams–Bashforth method (ODEPACK routine lsodes) and continues until the meniscus profile reaches stationary state, as determined by

$$\sum_i^{N_{\text{men}}} \frac{|y_i^{\text{told}} - y_i^{\text{new}}|}{N_{\text{men}}} \leq 0.0005. \quad (13)$$

Here, y_i^{told} and y_i^{new} are assessed only at those points in time when the tip of the bubble has aligned directly with the peaks of sequential wall protrusions. This protocol is thus applied to the previous and current meniscus y positions of these profiles at each of its N_{men} nodes within the boundary element domain.

IV. RESULTS

This analysis determines the behavior of a bubble of air as it forces through a liquid-occluded, cell-lined model airway using the boundary element method coupled with lubrication approximations. The temporally and spatially dependent profile of the progressing air-liquid interface continually changes to conform to the periodic pattern of the model's rigid airway walls, which in turn imparts a dynamic stress field on the cell protrusions. The current investigation is restricted to those points in time when the tip of the stationary-state bubble has aligned with one of the four distinct locations along each of the channel's periodic protuberances—the top, bottom, and upstream and downstream midheights. An example of each of the four meniscus profiles and the corresponding dimensionless normal and tangential wall stress distributions appear in Figs. 3(a)–3(c), respectively, for a set of model parameters representing a partially collapsed airway ($\varepsilon = a/H = 0.08$, $\Lambda = \lambda/H = 3.0$, and $Ca_Q = 0.01$).

This study primarily focuses on the effects of three different parameters—the cells' dimensionless height, $\varepsilon = a/H$, and width, $\Lambda = \lambda/H$, and the capillary number, $Ca_Q = [Q^*/$

$(2H)/(\gamma/\mu)$ —on normal and tangential stresses and stress gradients. The height of the cell protrusions directly impacts the extent to which the system's stress field is perturbed. This relationship is demonstrated in Figs. 4(b) and 4(c), which overlay plots of the dimensionless stress distributions in corrugated channels of different dimensionless amplitudes ($\varepsilon=0.02, 0.04, 0.08$) with those found in a flat-walled channel ($\varepsilon=0.0$). The topmost image, Fig. 4(a), shows the location of the interface with respect to the channel wall and serves to reference the stress distributions (depicted beneath) to their respective interfacial profiles. All of the results represented in Fig. 4 occur at a single snapshot in time—when the bubble tip has aligned with the top of a wall protrusion—for the case when the dimensionless corrugation wavelength and bubble speed are $\Lambda=3.0$ and $Ca_Q=0.01$. This set of plots demonstrates a trend consistent throughout the study that increasing the height of the epithelial cells with respect to channel width augments the localized variations in those stress fields. The effects of Λ and Ca_Q are discussed in Sec. V.

As shown in Fig. 4(b), the presence of wall protrusions results in a series of periodic sharp peaks and broad, shallow valleys in the dimensionless normal stress distribution induced during bubble progression. The maxima are spatially located at the highest point of the cells, where the air-liquid interface comes into close contact with the corrugated wall and its curvature is most negative. Conversely, these stresses decrease in the region of the valleys between adjacent cell protrusions, where the curvature of the bubble's profile is positive. These observations are intrinsically linked to the interfacial normal stress condition, which prescribes a magnitude to the pressure in the thin-film region that is directly related to the bubble's curvature, Eq. (4).

The dimensionless tangential stress distribution, depicted in Fig. 4(c), also assumes a periodic pattern when cell corrugations are introduced to the flow chamber walls. The changing meniscus curvature and concurrent pressure variations described above draw fluid into the trough between neighboring cells. In the thin-film region, τ_t is positively or negatively perturbed where this localized draining flow drags along the wall in the positive or negative x directions, respectively. Closer to the bubble tip, where fluid convection dominates, the magnitude and symmetry of these τ_t fluctuations are significantly reduced.

V. DISCUSSION

This study was carried out to assess the local mechanical environment of pulmonary epithelial cells during airway reopening, because, particularly within the region of the progressing bubble front, the stresses that act on an airway's walls and the gradients in these stresses may influence the structure, function, and metabolism of its cellular epithelium.⁷ Throughout the remainder of this analysis we will focus our attention solely on the maximum value of these stresses and stress gradients, which may most harm the cellular epithelium. As described in Sec. IV, the stationary-state interfacial and stress data are computed when the bubble's tip is positioned directly over the cells' top, bottom, and upstream and downstream midheights (Fig. 3); for any given set of parameters, the maximum stresses and stress gradients reported herein are chosen from the greatest of the peak values of these four different stress profiles.

A. Effect of increasing ε, Λ

The results of our analysis consistently indicate that a nonplanar airway wall topography introduces variations to the stress field exerted on that surface. This causes notable amplifications of the maximum value of the system's normal and tangential stresses and stress gradients to an extent that directly depends on the airway wall's surface geometry. Figure 5 demonstrates the relationship between the dimensionless wall corrugation wavelength Λ , and the maximum of each of these dimensionless stress components [(a)

normal stress $(\tau_n)_{\max}$, (b) normal stress gradient $(d\tau_n/dx)_{\max}$, (c) tangential stress $(\tau_t)_{\max}$, and (d) tangential stress gradient $(d\tau_t/dx)_{\max}$ for the oscillation amplitudes $\varepsilon=0.02, 0.04$, and 0.08 and $Ca_Q=0.01$. As expected, increasing ε results in an increase in the system's stresses and stress gradients. Additionally, Figs. 5(b)–5(d) show that increasing Λ reduces $(d\tau_n/dx)_{\max}$, $(\tau_t)_{\max}$, and $(d\tau_t/dx)_{\max}$. This also holds true for $(\tau_n)_{\max}$ for $\Lambda>2$ [Fig. 5(a)]. Counterintuitively, Fig. 5(a) exhibits a decrease in $(\tau_n)_{\max}$ as Λ is decreased below $\Lambda=2$. To better understand these results, the relevant scaling principles are explored in Sec. V B.

B. Scaling

1. The influence of wall curvature—Closer inspection of Fig. 5(a) reveals that, for $\Lambda>2$, $(\tau_n)_{\max}$ is inversely dependent upon Λ^2 . This relationship is more clearly presented in Fig. 6, where $(\tau_n)_{\max}$ data fall on curves of -2 slope (for larger values of Λ) when plotted in log-log format against Λ . As dictated by the interfacial stress condition, Eq. (4), $(\tau_n)_{\max}$ is directly related to the bubble's curvature. In the thin-film region, if the progressing bubble conforms to the adjacent channel wall, its maximum curvature is approximately that of the wall's protrusions:

$$(\tau_n)_{\max} \propto (\kappa_{\text{men}})_{\max} = \left(\frac{\partial^2 y_{\text{bot}}}{\partial x^2} \right)_{\max} = (2\pi)^2 \frac{\varepsilon}{\Lambda^2}, \quad (14)$$

which explains the qualitative behavior of the curves of Figs. 5(a) and 6 for $\Lambda>2$. To further examine this proposed relationship, we plot $(\tau_n)_{\max}$ against ε/Λ^2 in Fig. 7, with a curve representing Eq. (14) included as a reference, for $Ca_Q=0.01$. This figure reinforces the observation that, for larger values of Λ , Eq. (14) does faithfully predict the behavior of $(\tau_n)_{\max}$. This is important, because it shows that the geometry of the cells that line an airway's walls play a significant role in determining the maximum pressures they experience during this process of airway reopening.

2. The influence of wall slope—As depicted by Figs. 5(b)–5(d), more prominent cell protrusions—characterized by increased ε or decreased Λ —exhibit greater $(d\tau_n/dx)_{\max}$, $(\tau_t)_{\max}$, and $(d\tau_t/dx)_{\max}$. We therefore hypothesize that it is the slope of the epithelial protuberances that determines the magnification of each of these stress components and test this hypothesis in Fig. 8 by plotting (a) $(\tau_t)_{\max}$, (b) $(d\tau_t/dx)_{\max}$, and (c) $(d\tau_n/dx)_{\max}$ as a function of the corrugation slope parameter, ε/Λ , for $Ca_Q=0.01$. In each of these graphs, the data collapse to nearly a single relationship, supporting the proposed slope dependency. It is also important to note that even a small increase in ε/Λ elicits a notable increase in the values of $(\tau_t)_{\max}$, $(d\tau_t/dx)_{\max}$, and $(d\tau_n/dx)_{\max}$ that are exerted on those cells, which may have significant physiologic implications during airway reopening.

C. Effects of increasing Ca_Q

1. An explanation for the $(\tau_n)_{\max}$ behavior—As noted in Sec. V B, the $(\tau_n)_{\max}$ scaling analysis is no longer relevant at smaller corrugation wavelengths, $\Lambda<2$. We hypothesize that this is the case because, when $Ca_Q=0.01$, the bubble fails to conform to the topography of the channel walls, instead slipping over the walls nearly unaffected by their more tightly packed protuberances. This results in a relatively level thin film characterized by a considerably diminished curvature and a commensurately reduced $(\tau_n)_{\max}$.

To test this hypothesis, we investigated $(\tau_n)_{\max} \psi Ca_Q$ for $\varepsilon/\Lambda^2=0.01$ (Fig. 9). Theoretically, as described by Eq. (14), $(\tau_n)_{\max}$ approaches $(2\pi)^2 \varepsilon/\Lambda^2$ if the surface of the bubble conforms to the channel wall (when $Ca_Q=0.00$). However, Fig. 9 demonstrates that increasing Ca_Q decreases $(\tau_n)_{\max}$ significantly below this theoretical value—a consequence of thicker fluid films with flatter interfacial profiles—until $(\tau_n)_{\max}$ approaches a geometry

dependent, Ca_Q -insensitive value. This reduction is most dramatic when $\Lambda=1$ and becomes less precipitous as Λ steps up in value and the interface can more easily settle into the epithelial landscape.

To further explore this hypothesis, we relate the theoretical film thickness $(1-\beta)$, which has been determined by Bretherton¹³ to be

$$1 - \beta = 1.337 Ca_U^{2/3}, \quad (15)$$

to the height of the wall protrusions (2ϵ). For a given wall shape, we seek the critical capillary number, $(Ca_Q)_{crit}$, above which the liquid film is too thick for the wall's corrugations to sufficiently deform the bubble. We estimate that this will occur when the film thickness exceeds the protuberance amplitude, $(1-\beta) > 2\epsilon$.

Applying the relationship $Ca_Q = \beta Ca_U$ and assuming that the corresponding film thickness is $\approx 2\epsilon$:

$$(Ca_Q)_{crit} = \left(\frac{2\epsilon}{1.337} \right)^{3/2} (1 - 2\epsilon). \quad (16)$$

Values of $(Ca_Q)_{crit}$ are tabulated in Table II for $\epsilon/\Lambda^2=0.01$. These data explain why $(\tau_n)_{max}$ fails to follow the expected ϵ/Λ^2 scaling when $Ca_Q=0.01$ and $\Lambda=1$ in Figs. 5(a), 6, and 7: the spacing between neighboring epithelial cell protrusions is too small and the thickness of the trailing film too large for the interface to properly respond to the wall's protrusions.

2. A mechanism for cell trauma—Bilek *et al.*⁷ recently found, in a complementary experimental model of airway reopening, that trauma to pulmonary epithelial cells increases with decreasing bubble progression velocity. They coupled this investigation with a computational analysis that matches our own for the limiting case of a flat channel wall topography ($\epsilon=0.00$). The system was designed to identify the behavior of the airway's maximum reopening shear stress, shear stress gradient, and normal stress gradient in an effort to pinpoint that component of the airway's stresses which is most responsible for the observed cell damage. Through the present study, we hope to expand on that analysis by determining the influence of an epithelial cell layer on the model airway's reopening stress environment.

As discussed in Sec. V C 1, increasing the reopening bubble's dimensionless speed Ca_Q results in the thickening of the thin-film region. This can significantly influence the overall reopening stress cycle, and the presence of the nonplanar epithelial layer only serves to augment these effects. One final set of computational experiments examines the behavior of $(\tau_t)_{max}$, $(d\tau_t/dx)_{max}$, and $(d\tau_n/dx)_{max}$ while Ca_Q is varied and the maximum wall topographic curvature is fixed at a constant value of $\epsilon/\Lambda^2=0.01$. Figure 10 presents these results and contrasts them against those obtained in the Bilek *et al.*⁷ study for flat channel walls ($\epsilon/\Lambda^2=0.00$). Figure 10 reveals a monotonic increase in the system's (a) $(\tau_t)_{max}$ and (b) $(d\tau_t/dx)_{max}$ over the range of Ca_Q tested. In terms of cell damage, Bilek *et al.*⁷ discounted these stress components as possible modes of injury, because they both tend to decrease at slower bubble speeds (smaller Ca_Q), where epithelial membrane damage is greatest. Figures 10(a) and 10(b) demonstrate that although our $(\tau_t)_{max}$ and $(d\tau_t/dx)_{max}$ results are amplified over those obtained in the flat-walled channel, this magnification becomes less significant at the low Ca_Q where experiments were conducted; so these results are consistent with the hypothesis of Bilek *et al.*⁷

Figure 10(c) depicts $(d\tau_n/dx)_{\max}$ as a function of Ca_Q . This reopening stress component increases in with decreasing Ca_Q , and it was therefore singled out in the Bilek study⁷ to possibly induce the observed cell damage at lower bubble velocities. Our analysis, by exhibiting the same $(d\tau_n/dx)_{\max}$ behavior, reinforces this hypothesis. Interestingly, the amplification of this stress component by the nonplanar channel wall topography persists as Ca_Q is decreased. This occurs because the thin film conforms to the wall at low Ca_Q , as demonstrated in Fig. 9. Thus, the impact of the normal stress gradient could potentially be far more substantial than that predicted in the Bilek study,⁷ even at lower reopening bubble speeds.

D. Model limitations

Our model is based upon a number of assumptions that limit its direct applicability to airway reopening in infants with RDS. However, its results do reveal interesting mechanical phenomena that contribute to the current body of knowledge surrounding this disease. In addition, it provides an opportunity for further expansion and development into a more physiologically realistic system.

The most apparent of these limitations pertains to the two-dimensional, symmetric geometry of our system in which the airway is modeled as a set of parallel, planar (but cell-corrugated) plates. The true cross-sectional area of a respiratory airway becomes increasingly complex as it approaches a more-collapsed state. In addition, we assign a periodic, sinusoidal pattern to the airway's epithelial topography; however, micrographs of the airways clearly demonstrate nonuniform cell shapes and distributions.⁷

Throughout the framework of our model, the airway wall and its lining epithelial cells are assumed to be rigid structures. In reality, both are highly elastic and deform in response to applied pressures and shear stresses. Collapsed airway walls peel apart as an air bubble forces through, which induces large-scale modifications of the occluding fluid's flow field and of the airway's mechanical environment.⁴ On a smaller scale, "a dynamic wave of stresses is imparted on the airway tissues"⁷ in the region of the progressing meniscus that likely cause a variety of structural changes in their lining cells. These complex airway and epithelial deformations certainly interact with the reopening stress field.

In our system, the surface tension of the occluding fluid is assumed to be constant—in reality, lung fluid contains pulmonary surfactant, which is highly surface active and causes considerable, dynamic changes in the bubble's interfacial stresses.^{18,30,31} This, in turn, has a significant stabilizing impact on the overall mechanical environment of the airways as they are reopened.^{3,27} Our occluding fluid is also characterized by constant viscosity μ . However, pulmonary lining fluid is most likely non-Newtonian and may instead exhibit viscoelastic properties, especially in the upper airways.³²

Airflow in the real lung is unstable and pulsatile, and inertia may be important during airway reopening. Additionally, in our system, although the bubble pushes forward at a constant flow rate ($Q^* = \int u^* dy^*$), the bubble's speed is not constant and may become relatively large as the flow chamber wall clearance decreases and also as Ca_Q increases. This results in an increase in inertia and thus the Reynolds number Re , and the Stokes flow hypothesis may not always be valid. However, the studies of Hazel and Heil³³ indicate that for moderate Re , a system's qualitative behavior remains similar to the Stokes flow limit.

VI. CONCLUSIONS

The primary objective of this study was to assess the local mechanical environment of pulmonary epithelial cells during airway reopening in newborns with RDS. Our

computational investigation focused on the relationship between the microgeometry of the respiratory airway walls and the interfacial kinematics surrounding the tip of a semi-infinite bubble as it clears a liquid-occluded airway. We hypothesize that, within this region, the airway wall stresses and stress gradients that result from the displacement of the lung fluid by the progressing meniscus may influence the structure, function, and integrity of the pulmonary epithelium.

Within our cell-corrugated system, the stationary-state meniscus profile continually evolves as it travels along the model airway, which in turn produces a complex, spatially and temporally dependent reopening stress distribution. Upstream of the bubble tip, the curvature of the air-liquid interface directly influences the pressures that are exerted on the airway's cells. In the regions where the bubble comes into close contact with the top of a protruding epithelial cell, its curvature ($\kappa - \epsilon/\Lambda^2$) is most negative and results in a notable elevation in dimensionless normal stress. Conversely, this stress is reduced in the valleys between adjacent cell corrugations, where the curvature in the bubble's profile is positive.

The pressure difference induced by cell topography locally drives the occluding fluid from higher to lower elevations of the epithelial cell. This imparts additional shear stresses onto the cell surfaces, which perturbs the reopening shear stress field. Because flow along the left-hand (upstream) side of each cell valley is in the direction of the bubble's progression, the resulting dimensionless shear stress is positive; similar logic dictates that, along the right-hand (downstream) side of a valley, it is negative. Clearly, the more pronounced these cell protrusions are (increasing ϵ/Λ), the larger will be the localized fluctuations in the system's pressures and shear stresses, and the greater the maximum of these stresses and their gradients.

The behavior of our system's reopening stresses and stress gradients is also dependent upon the dimensionless speed of bubble progression Ca_Q . As demonstrated by our results, decreasing Ca_Q , which decreases the thickness of the thin-fluid film, increases $(\tau_n)_{\max}$ and $(d\tau_n/dx)_{\max}$. On the other hand, $(\tau_t)_{\max}$ and $(d\tau_t/dx)_{\max}$ tend to decrease with Ca_Q . Qualitatively, the behavior of each of these maximum stress components agrees with that found in the complementary Bilek *et al.*⁷ analysis, in which $d\tau_n/dx$ was determined to be responsible for the epithelial damage observed during a reopening event. Quantitatively, we found that accounting for the nonplanar cell topography of the flow chamber walls consistently amplifies the values of each stress component. Thus $d\tau_n/dx$ is likely to be even more detrimental to the epithelial layer during airway reopening than previous studies^{7,8} have indicated.

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FIG. 1.

A semi-infinite air bubble progressing with constant flow rate Q^* along a parallel plate flow chamber whose rigid walls are corrugated by epithelial cells. The fluid occlusion is characterized by a constant viscosity μ , density ρ , and surface tension γ .

FIG. 2.

Two-dimensional model geometry. Due to the system's symmetry, we need only to analyze half of the domain. Nodes *A* through *E* circumscribe the BEM domain. Lubrication theory is implemented further upstream of the bubble's tip in the thin-film region.

FIG. 3.

Progressing (a) bubble profiles, and corresponding dimensionless (b) normal and (c) shear stress distributions. Results are presented in their dimensionless forms with $\varepsilon=0.08$, $\Lambda=3.0$, and $Ca_Q=0.01$. The curves are drawn when the bubble's tip has aligned with the upstream midheight (light gray line), valley (medium gray line), downstream midheight (dark gray line), or apex (black line) of the wall's epithelial protrusions.

FIG. 4.

Dimensionless (b) normal and (c) shear stress profiles when the bubble's tip has aligned with the apex of a channel wall protrusion, depicted in (a). Here, $\epsilon=0.00$ (gray line), 0.02 (.....), 0.04 (--), and 0.08 (—); $\Lambda=3.0$; and $Ca_Q=0.01$.

FIG. 5.

Maximum dimensionless (a) normal stress, (b) normal stress gradient, (c) shear stress, and (d) shear stress gradient as a function of corrugation wavelength Λ for $\epsilon=0.00$ (circle), 0.02 (square), 0.04 (triangle), and 0.08 (diamond) and $Ca_Q=0.01$.

FIG. 6. Maximum dimensionless normal stress as a function of corrugation wavelength Λ for $\epsilon=0.02$ (square), 0.04 (triangle), and 0.08 (diamond) and $Ca_Q=0.01$. For $\Lambda>2$, these log-log curves, which exhibit a slope of -2 , demonstrate an inverse $(\tau_n)_{\max}-\Lambda^2$ relationship.

FIG. 7.

Maximum dimensionless normal stress as a function of the corrugation curvature parameter ϵ/Λ^2 for $\Lambda=1$ (circle), 2 (square), 3 (triangle), and 4 (diamond) and $Ca_Q=0.01$. As Λ increases above $\Lambda=1$, the $(\tau_n)_{\max}$ data tend toward the wall corrugation's maximum curvature (gray line), Eq. (14).

FIG. 8.

Maximum dimensionless (a) shear stress, (b) shear stress gradient, and (c) normal stress gradient as a function of the corrugation slope parameter ε/Λ for $\Lambda=1$ (circle), 2 (square), 3 (triangle), and 4 (diamond) and $Ca_Q=0.01$.

FIG. 9. Maximum dimensionless normal stress as a function of Ca_Q for $\epsilon/\Lambda^2=0.01$ with $\Lambda=1$ (circle), 2 (square), and 3 (triangle).

FIG. 10.

Maximum dimensionless (a) shear stress, (b) shear stress gradient, and (c) normal stress gradient as a function of Ca_Q for $\epsilon/\Lambda^2=0.01$ with $\Lambda=1$ (circle), 2 (square), and 3 (triangle). The behavior of our results, though quantitatively amplified, agree with that in work by Bilek *et al.* (Ref. 7), whose computational flow chamber system was characterized by flat wall topography (gray line). Notice that $(d\tau_n/dx)_{\max}$ is the only of these stress components to consistently increase with decreasing Ca_Q .

TABLE I

Boundary conditions (BCs) at each node of the BEM domain (see Fig. 2) must be specified in the x and y directions. Each surface ($AB, BC, \dots, EA$) is composed of multiple face nodes (all nodes along that surface but the corner nodes) and two corner nodes. Corner nodes are defined by different sets of x - and y -directed BCs at the two surfaces they adjoin.

Nodes	BC (x component)	BC (y component)
Face AB	$u=0$	$v=0$
Corner A	$u=0$	$v=0$
Corner B	$\tau_x = \frac{3CaQ}{y_{\text{bot}}^2}$	$v=0$
Face BC	$u = \frac{3}{2} \frac{CaQ}{y_{\text{bot}}^3} (y^2 - y_{\text{bot}}^2)$	$v=0$
Corner B	$u = \frac{3}{2} \frac{CaQ}{y_{\text{bot}}^3} (y^2 - y_{\text{bot}}^2)$	$\tau_y = \frac{3CaQ}{y_{\text{bot}}^2}$
Corner C	$u = \frac{3}{2} \frac{CaQ}{y_{\text{bot}}^3} (y^2 - y_{\text{bot}}^2)$	$\tau_y=0$
Face CD	$\tau_x=0$	$v=0$
Corner C	$\tau_x=0$	$v=0$
Corner D	$\tau_x=0$	$v=0$
Face DE	$\tau_x = \kappa n_x$	$\tau_y = \kappa n_y$
Corner D	$\tau_x = \kappa n_x$	$\tau_y = \kappa n_y$
Corner E	$\tau_x = \kappa n_x$	$\tau_y = \kappa n_y$
Face EA	$u = -\frac{\kappa_x}{2} (y - y_{\text{bot}}) (y + y_{\text{bot}} - 2y_{\text{men}})$	$\tau_y = -\frac{u}{y} = \kappa_x (y - y_{\text{men}})$
Corner E	$u = -\frac{\kappa_x}{2} (y - y_{\text{bot}}) (y + y_{\text{bot}} - 2y_{\text{men}})$	$\tau_y = -\frac{u}{y} = \kappa_x (y - y_{\text{men}})$
Corner A	$\tau_x = \kappa n_x$	$\tau_y = -\frac{u}{y} = \kappa_x (y - y_{\text{men}})$

TABLE II

The critical capillary number $(Ca_Q)_{\text{crit}}$ as a function of wall corrugation amplitude ϵ when the corrugation curvature parameter is $\epsilon/\Lambda^2=0.01$.

Λ	ϵ	$(Ca_Q)_{\text{crit}}$
1	0.01	0.0018
2	0.04	0.013
3	0.09	0.041
4	0.16	0.080