Computational Analysis of Microbubble Flows in Bifurcating Airways: Role of Gravity, Inertia, and Surface Tension

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Although mechanical ventilation is a life-saving therapy for patients with severe lung disorders, the microbubble flows generated during ventilation generate hydrodynamic stresses, including pressure and shear stress gradients, which damage the pulmonary epithelium. In this study, we used computational fluid dynamics to investigate how gravity, inertia, and surface tension influence both microbubble flow patterns in bifurcating airways and the magnitude/distribution of hydrodynamic stresses on the airway wall. Direct interface tracking and finite element techniques were used to simulate bubble propagation in a two-dimensional (2D) liquid-filled bifurcating airway. Computational solutions of the full incompressible Navier–Stokes equation were used to investigate how inertia, gravity, and surface tension forces as characterized by the Reynolds (Re), Bond (Bo), and Capillary (Ca) numbers influence pressure and shear stress gradients at the airway wall. Gravity had a significant impact on flow patterns and hydrodynamic stress magnitudes where $Bo > 1$ led to dramatic changes in bubble shape and increased pressure and shear stress gradients in the upper daughter airway. Interestingly, increased pressure gradients near the bifurcation point (i.e., carina) were only elevated during asymmetric bubble splitting. Although changes in pressure gradient magnitudes were generally more sensitive to Ca , under large Re conditions, both Re and Ca significantly altered the pressure gradient magnitude. We conclude that inertia, gravity, and surface tension can all have a significant impact on microbubble flow patterns and hydrodynamic stresses in bifurcating airways. [DOI: 10.1115/1.4028097]

Keywords: microbubble flows, bifurcating airways, gravity, inertia, surface tension

1 Introduction

The lung contains a network of bifurcating airways which allows for efficient oxygen/carbon dioxide transport to pulmonary alveoli. However, during the acute respiratory distress syndrome (ARDS), bacterial/viral infections lead to disruption of the alveolar–capillary barrier and fluid-occlusion of pulmonary airways [1–3]. This severely compromises gas transport within the lung and results in severe hypoxia and high mortality rates [4]. Although mechanical ventilation is the standard of care for ARDS patients, the mechanical forces generated during ventilation can exacerbate the existing lung injury, a condition referred to as ventilator-induced lung injury [5]. These mechanical forces may include over-distension of lung epithelial cells [6], high transmural pressures [7], and surface tension forces during cyclic airway reopening [8,9]. In addition to causing cell necrosis and barrier disruption, these mechanical forces can also activate pro-inflammatory signaling [5,10]. Although recent improvements in ventilation strategies such as low tidal volume ventilation have reduced mortality rates, ARDS currently causes the same number of deaths in the US as breast cancer and prostate cancer combined [11] and developing improved ventilator strategies is a major public health challenge.

During ventilation, the cyclic closure and reopening of fluid-filled pulmonary airways leads to microbubble flows which are a significant source of cellular injury and inflammation [2,10]. The

physics of microbubble flows has been studied for many decades. For example, Bretherton [12] used lubrication theory to investigate bubble motion in a liquid filled tube and found that film thickness and pressure drop across the air–liquid interface was proportional to $Ca^{2/3}$ for $Ca \ll 1$ where Ca is a dimensionless bubble velocity that represents the ratio of viscous to surface tension forces. More recently, investigators have used computational techniques to characterize the hydrodynamic stresses associated microbubble flows. For example, Halpern and Gaver [13] used the boundary element method (BEM) to simulate semi-infinite bubble propagation in a rigid 2D channel and Gaver et al. [14] extended this analysis to a flexible airway/channel. Heil [15] investigated bubble motion in a three-dimensional (3D) flexible channel and Ghadiali et al. [16,17] investigated the effects of surfactant transport and Marangoni stresses on microbubble flows. Recently, Smith and Gaver have characterized the hydrodynamic stress field surrounding an oscillating microbubble [18].

In addition to computational studies, experimental techniques have been used to investigate how the hydrodynamic stresses generated during microbubble flows influence cell injury. Using a combination of in vitro experiments and boundary element simulations, Gaver and colleagues [8,19] demonstrated that spatial gradient in pressure is the primary cause of cell necrosis during microbubble flow. Subsequently, Yalcin et al. confirmed this finding and demonstrated that type II epithelial cells are more susceptible to microbubble injury [9]. In a separate study, these authors also demonstrated that changes in the cell's biophysical properties can be used to prevent cellular necrosis and detachment during microbubble flows [20]. In support of this concept, Dailey and Ghadiali [21,22] have recently used imaged-based computational

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techniques to investigate how changes in cellular mechanics and morphology may be used to prevent cell injury and deformation. Naire and Jensen [23] also used theoretical models to show that the elastic modulus of the epithelial layer plays a key role in determining cell deformation during microbubble flows.

Although these previous studies have investigated the mechanisms responsible for cell injury during microbubble flows, they only simulated bubble propagation in straight airways and did not account for the bifurcating geometry of pulmonary airways. Previous studies have demonstrated that numerous factors including roll angle, bifurcation angle, bubble volume, surface tension, inertia, and gravity can all influence the fluid dynamics of microbubble or liquid-plug propagation in bifurcating airways [24–26]. In addition, numerical and experimental studies have investigated how downstream boundary conditions, gas/liquid flow rates and surfactants influence the splitting ratio and breakup of microbubbles in a bifurcating channel [27–29]. Recently, Calderon et al. [30] used the BEM to numerically simulate pressure driven propagation of a semi-infinite bubble through a bifurcating blood vessel. These authors demonstrated that bubble splitting was function of driving pressure and that bubble propagation could impart large shear stress on the vessel wall. This study was primarily interested in microbubble flows through the microvasculature and therefore did not consider inertial or gravity effects and only investigated larger Capillary numbers (i.e., $Ca > 10^{-2}$). However, in the pulmonary system, the Capillary number can be very small ($Ca < 10^{-4}$) and the dimensionless variables relating inertial to viscous forces (the Reynolds number, Re) and gravity to surface tension forces (the Bond number, Bo) are often not negligible ($Re > 100$ and $Bo > 1$) [31]. Finally, although the Calderon study focused on bubble splitting and wall shear stress, experimental studies [8,9] have clearly demonstrated that the magnitude of pressure gradients at the airway wall is the primary determinate of cell injury. Therefore, the goal of this study is to numerically investigate the effect of gravity, inertia, and surface tension on microbubble flows in a bifurcating airway. We are specifically interested in how these factors influence pressure gradients at the airway wall in order to understand how airway bifurcations may influence cell injury patterns. To achieve this goal, we have developed a computational model of microbubble propagation in a fluid-filled bifurcating airway which solves the full incompressible Navier–Stokes equations using a finite element technique. This technique can simulate a wide range of Ca , Re , and Bo and a sensitivity analysis was used to determine the relative importance of these parameters on pressure gradients during microbubble flows.

2 Model

2.1 Geometric Model of the Bifurcating Airway. Although the bifurcating geometry of pulmonary airways is irregular and potentially asymmetric, in this study we used a simplified airway bifurcation model as shown in Fig. 1. We specified a symmetric branching angle between the parent and daughter airways of $\theta_1 = \theta_2 = 32.5$ deg and used smooth transitions between the parent and the upper/lower daughter airways as well as a curved middle interior wall (carina). Although we are only interested in the microbubble dynamics at the leading or diverging bifurcation, we added a trailing/converging bifurcation to avoid the arbitrary specification of impedance or pressure conditions within the daughter airways. Rather, this model allows us to simulate microbubble propagation by applying equivalent flow rates to the inlet and outlet. In addition to general flow patterns, we are particularly interested characterizing the pressure gradient at the three wall locations indicated by the red lines in Fig. 1 (i.e., the upper daughter, lower daughter, and the middle interior airway walls). For initial bubble shape conditions, we used an elliptical bubble with a minor/major axis of 0.0008 m and 0.002 m, respectively. At $t = 0$ the leading tip of the bubble was initially located at 0.0022 m from the carina of the bifurcation.

2.2 Dimensionless Governing Equations and Variables. In this study, we simulated microbubble propagation in a bifurcating airway filled with an incompressible, Newtonian fluid with constant density and viscosity. The COMSOL 3.5 (Boston, MA) finite element package was used to solve the momentum balance and continuity equations governing fluid flow

$$\rho \left(\frac{\partial \vec{u}'}{\partial t'} + (\vec{u}' \cdot \nabla') \vec{u}' \right) = -\nabla' p' + \mu \nabla' \cdot \left(\nabla' \vec{u}' + (\nabla' \vec{u}')^T \right) + \rho \vec{g} \quad (1)$$

$$\nabla' \cdot \vec{u}' = 0 \quad (2)$$

where ρ is the density, $\vec{u}'$ is the fluid velocity vector, p' is the pressure, μ is the dynamic viscosity, and $\vec{g}$ is the acceleration due to gravity. Given the following velocity, pressure, time, and spatial scales:

$$\vec{u} = \frac{\vec{u}'}{U}, \quad p = \frac{p'}{\rho U^2}, \quad \frac{\partial}{\partial t} = \frac{R}{U} \frac{\partial}{\partial t'}, \quad \nabla = R \nabla'$$

Fig. 1 Schematic view of microbubble propagation in a two-generation bifurcating airway. Curved lines indicate locations for hydrodynamic stress evaluation and represent the upper, lower, and middle interior airway walls.

Eq. (1) can be rewritten in nondimensional form as

$$\frac{\partial \vec{u}}{\partial t} + (\vec{u} \cdot \nabla) \vec{u} = \nabla \cdot \boldsymbol{\sigma} + \frac{\text{Bo}}{\text{Re} \cdot \text{Ca}} \quad (3)$$

where

$$\text{Re} = \frac{\rho U R}{\mu}, \quad \text{Ca} = \frac{\mu U}{\gamma}, \quad \text{Bo} = \frac{\rho g R^2}{\gamma}, \quad \text{and} \quad (4)$$

$$\boldsymbol{\sigma} = -p + \frac{1}{\text{Re}} \left(\nabla \vec{u} + (\nabla \vec{u})^T \right)$$

Here R is the upstream airway radius, U is the mean upstream fluid velocity, γ is the air–liquid surface tension, and $\boldsymbol{\sigma}$ is the fluid stress tensor. Re represents the ratio of inertial and viscous forces, Ca represents the ratio of viscous to surface tension forces, and Bo represents the ratio of gravity to surface tension forces.

2.3 Boundary Conditions. There are three types of boundaries in the model domain. Channel/airway walls are modeled with no-slip conditions, a parabolic velocity profile with a mean velocity of U was specified at the inlet and outlet such that the inlet and outlet flow rate are equivalent and the air–liquid interface is modeled as a free surface boundary with a surface tension γ . As with previous studies [16], we do not solve for airflow within the bubble given the negligible viscosity and density of air. In this model, surface tension forces enter through the following free surface boundary condition at the air–liquid interface:

$$\boldsymbol{\sigma} \cdot \vec{n} = -P_a \vec{n} + \frac{\Gamma \gamma}{\text{Re} \cdot \text{Ca}} \vec{n} \quad (5)$$

where $\vec{n}$ is the outward unit normal from fluid to air, P_a is the air pressure, and Γ is the curvature defined as $\Gamma = -\nabla \cdot \vec{n}$.

2.4 Weak Form Boundary Term. In the current study, we used weak formulations in COMSOL to specify the boundary conditions at the air–liquid interface. Weak formulations are derived by multiplying Eq. (3), with a test function, $\vec{v}$, and then integrating over the spatial domain, Ω

$$\int_{\Omega} \vec{v} \left[-\frac{\text{Bo}}{\text{Re} \cdot \text{Ca}} + \left(\frac{\partial \vec{u}}{\partial t} + (\vec{u} \cdot \nabla) \vec{u} \right) \right] d\Omega = \int_{\Omega} \vec{v} (\nabla \cdot \boldsymbol{\sigma}) d\Omega \quad (6)$$

Integrating the divergence of stress term by parts yields

$$\begin{aligned} \int_{\Omega} \vec{v} \left[-\frac{\text{Bo}}{\text{Re} \cdot \text{Ca}} + \left(\frac{\partial \vec{u}}{\partial t} + (\vec{u} \cdot \nabla) \vec{u} \right) \right] d\Omega + \int_{\Omega} \nabla \vec{v} \cdot \boldsymbol{\sigma} d\Omega \\ = \int_S \vec{v} (\boldsymbol{\sigma} \cdot \vec{n}) dS \end{aligned} \quad (7)$$

where S surface domain bounding Ω and the right hand side of Eq. (7) represents boundary conditions. Equation (5) can be used to rewrite the free-surface boundary components of the right hand side of Eq. (7) as

$$\int_S \vec{v} (\boldsymbol{\sigma} \cdot \vec{n}) dS = - \int_S \vec{v} P_a \vec{n} dS + \frac{1}{\text{Re} \cdot \text{Ca}} \int_S \vec{v} \Gamma \gamma \vec{n} dS \quad (8)$$

The surface divergence theorem [32] is used to rewrite the last term of Eq. (8)

$$\int_S \vec{v} \Gamma \gamma \vec{n} dS = \int_S \gamma \nabla_s \vec{v} dS - \int_c \vec{v} \gamma \vec{n}_s dc \quad (9)$$

where ∇_s represents the gradient operator tangent to the surface, c is the contour bounding the free surface, and $\vec{n}_s$ is the outward unit

binormal. Although the integral $\int_c \vec{v} \gamma \vec{n}_s dc$ must be included when considering a dynamic contact line, in this study this integral is equal to zero since we simulate bubble propagation with no contact line. Setting a reference pressure of $P_a = 0$, Eq. (8) becomes

$$\int_S \vec{v} (\boldsymbol{\sigma} \cdot \vec{n}) dS = \frac{1}{\text{Re} \cdot \text{Ca}} \int_S \gamma \nabla_s \vec{v} dS \quad (10)$$

Equation (10) represents the weak form of the boundary condition in Eq. (5) which can be directly inputted as “weak constraints” on the air–liquid interface. This method has significant advantages compared to traditional methods that require expensive calculations of interface curvature at each time step [16,17]. In addition to efficient implementation of complex interface conditions, the weak form of the boundary condition is general and can also be used to solve 3D free surface flow problems. Finally, we use the arbitrary Lagrangian–Eulerian moving mesh application mode to satisfy kinetic boundary conditions at the air–liquid interface. Although we implement Winslow smoothing to maintain well-shaped elements, a dynamic remeshing algorithm was used to ensure accurate solutions.

2.5 Fluid Properties and Baseline Values. In this study we seek to capture the range of Re , Ca , and Bo values that may exist in the human lung during ventilation. We specifically focus on the magnitude of Re , Ca , and Bo that exists between the small conducting bronchioles (i.e., generation 10) and the respiratory bronchioles (generation 19), since this is the likely site for cellular injury [9]. For normal breathing conditions (i.e., 500 ml tidal volume and 12 breaths per minute) and the range of total cross-sectional area in this region ($8\text{--}1000 \text{ cm}^2$) [33] the expected range of reopening velocities is $0.1 \text{ cm/s} < U < 12.6 \text{ cm/s}$. Using the range of airway radius in this region ($0.025 \text{ cm} < R < 0.1 \text{ cm}$), the density and viscosity of water (1 g/cm^3 and 1 cP) and an air–liquid surface tension of 72 dyn/cm yields

$$0.25 < \text{Re} < 125; \quad 1.4 \times 10^{-5} < \text{Ca} < 1.7 \times 10^{-3} \\ 8.5 \times 10^{-3} < \text{Bo} < 0.136$$

However, mucus fluid within the pulmonary system may have a viscosity that is $\sim 50\times$ greater than the viscosity of water [34] and assuming a fluid viscosity of 47 cP yields

$$0.005 < \text{Re} < 2.66; \quad 6.5 \times 10^{-4} < \text{Ca} < 0.082 \\ 8.5 \times 10^{-3} < \text{Bo} < 0.136$$

Finally, we note that the surface tension of normal lung fluid may be much lower than 72 dyn/cm [3] and this would lead to larger Ca and Bo values. To capture this wide range of dimensionless parameters we assume baseline conditions of $\text{Re} = 2.66$, $\text{Ca} = 0.082$, and $\text{Bo} = 0.136$ which corresponds to airway reopening in a 10th generation airway with a fluid viscosity of 47 cP . We then perform independent parameter variation studies about these conditions to investigate the effect of larger Re values, larger and smaller Ca values and larger and smaller Bo values.

2.6 Numerical Considerations

2.6.1 Remeshing Algorithm Due to large deformation of fluid elements during bubble flow, a remeshing procedure [35] was implemented to insure accurate calculations. In this procedure we tracked the triangular mesh quality parameter q

$$q = \frac{4\sqrt{3}a}{h_1^2 + h_2^2 + h_3^2} \quad (11)$$

where a is the mesh area, h_1 , h_2 , and h_3 are the side lengths of the triangle and q can vary from 0 to 1 with $q=0$ representing a

collapsed element and $q=1$ representing an equilateral triangle. The minimum q at each time step was checked and $q=0.1$ was used as a stop condition. A new geometry was created from the deformed mesh at the last stop point and remeshed. A restart function was then used to continue simulations of bubble propagation. We note that simulations at smaller Ca values required frequent remeshing due to rapid deformation of elements in the thin film.

2.6.2 Mesh Independence Study. The finite element model was meshed with three-node Lagrange quadratic triangular elements. The mesh density was specified by checking two different measures of mass conservation. Since the inlet and outlet flow rates are equivalent, if there is no change in bubble volume, i.e., no net flow into or out of the bubble, the sum of the flow rate in upper and lower daughter airways should be equivalent to the inlet/outlet flow rate. We therefore calculated the bubble volume change and compared the sum of the upper and lower daughter airway flow rates with the inlet flow rate to determine if we have an adequate mesh size. A mesh independence study was conducted to determine the appropriate mesh density where one simulation at a small Capillary number ($Ca=0.0008$) was meshed with different number of finite elements. A small Capillary number simulation was used since there will be more numerical instabilities in the thin film for these simulations. Results indicate that an average mesh density of $\sim 100,000$ elements is sufficient to obtain a bubble volume change $<0.8\%$ and a combined flow rate in the upper and lower daughter airway that is $<1.19\%$ different than the inlet flow rate. We also investigated how mesh density influenced the maximum pressure gradient and shear stress gradient and found that a mesh density of 100,000 elements produced pressure gradients and shear stress gradients that were within 1% of the values produced using 175,000 elements.

2.6.3 Method Validation. In this study, we used finite element methods and a weak form boundary term at the air–liquid

interface to simulate bubble propagation in a 2D airway bifurcation. To ensure the accuracy of this method, we first simulated the well-studied problem of bubble propagation in a 2D channel and compared our finite element solution with Bretherton's asymptotic predictions at very low Ca values [12] and boundary element solutions at large Ca values [13]. As described in the Appendix, our finite element method was able to accurately capture these known solutions at low and high Ca simultaneously. Therefore, this finite element technique is an efficient and accurate way to simulate moving air–liquid interfaces over a wide range of Ca values.

3 Results and Discussion

Previous research [8,19] indicates that spatial gradients in pressure during bubble propagation is the major factor responsible for cell injury during airway reopening. In addition, Yalcin et al. [9] reported a statistically significant correlation between cell death during bubble propagation and spatial gradients in shear stress. However, we note that this correlation with shear stress gradients was weaker than the correlation with pressure gradients. Therefore, in this study we seek to understand how different biophysical forces, i.e., gravity, inertia, and surface tension, influence the pressure and shear stress gradients in a bifurcating airway during bubble propagation. We conducted several simulations by independently varying Bo , Re , and Ca from baseline conditions and characterized how these parameters influence pressure and shear stress gradients. We also conducted a sensitivity analysis to determine the relative importance of gravity, inertia, and surface tension forces on the pressure gradient response. This sensitivity analysis was conducted at baseline conditions as well as at higher/lower Re conditions.

3.1 Effects of Gravity. The influence of gravity on pressure and shear stress gradients was investigated by conducting simulations with $Bo=0.068, 0.136, 0.68$, and 1.36 while maintaining a

Fig. 2 Comparison of bubble shapes during propagation with fixed $Ca = 0.082$ and $Re = 2.66$ and varying Bond numbers: (a) $Bo = 0.068$, ($t = 0, 0.005, 0.01, 0.015, 0.02, 0.03, 0.048$ s) (b) $Bo = 0.136$ ($t = 0, 0.005, 0.01, 0.015, 0.02, 0.03, 0.05$ s), (c) $Bo = 0.68$ ($t = 0, 0.005, 0.01, 0.015, 0.02, 0.03, 0.045$ s), and (d) $Bo = 1.36$ ($t = 0, 0.005, 0.01, 0.015, 0.02, 0.03, 0.04$ s)

constant $Ca = 0.082$ and $Re = 2.66$. Figure 2 shows bubble shape profiles during propagation into the leading bifurcation for different values of Bo . At low Bo values (Figs. 2(a) and 2(b)) we observed a symmetric bubble shape and even bubble penetration into the bifurcation. However, at higher Bo (Figs. 2(c) and 2(d)) we observe an asymmetric bubble shape with a larger fraction of the bubble moving into the upper daughter airway due to buoyancy. As shown in Figs. 3(a) and 3(b), we also investigated how gravity influences the velocity and pressure within the fluid surrounding the bubble. Although symmetric velocity and pressure fields were observed at low Bo values, uneven bubble penetration at larger Bo led to larger pressures in the upper daughter airway. We also observed large pressures in the thin film between the bubble and middle interior wall during symmetric bubble penetration. At larger Bo , large pressures were also observed in the thin film along the upper daughter airway wall. Therefore, buoyancy effects at large Bo lead not only to asymmetric penetration of the bubble into the bifurcation but also to an increased pressure along the upper daughter airway wall.

We also investigated how gravity influences both pressure and shear stress gradients along the upper and lower daughter airway wall. In Figs. 4(a) and 4(b), we plot the pressure gradient as a function of position along the upper (Fig. 4(a)) and lower (Fig. 4(b)) daughter airway walls as defined by the curved lines in Fig. 1. These pressure gradient plots represent a “snapshot” in time where the bubble has partially penetrated into the bifurcation as shown in Fig. 3. The pressure gradient is relatively low near the parent airway (arc length equal to zero) and there is a rapid increase in the pressure gradient and a peak in the pressure gradient as you approach the daughter airway (larger arc length). For the upper daughter airway, increasing Bo causes an increase in the peak pressure gradient while in the lower daughter airway, increasing Bo results in a decrease in peak pressure gradient. Similar patterns were observed for the shear stress gradient (Figs. 4(c) and 4(d)) and we note that the shear stress gradient magnitudes are significantly lower than pressure gradient magnitudes.

Therefore, larger Bo leads to increased bubble penetration into the upper daughter airway and this asymmetric flow can significantly increase gradients in pressure and shear stress at the airway wall.

Although previous investigations indicate that altered airflow patterns near the carina of an airway bifurcation lead to increased particle deposition in this region [36], it is not known if microbubble propagation through an airway bifurcation leads to increased cell injury near the carina. Since cell injury has been most directly correlated with the pressure gradient magnitude [8,9], we compared the maximum pressure gradient along the upper and lower airway walls with the maximum pressure gradient along the middle interior wall (carina) for the conditions shown in Figs. 2 and 3. As shown in Fig. 5, at low values of Bo where there is a nearly symmetric bubble penetration, the maximum pressure gradient magnitude is similar at all three locations (top airway, lower airway, and middle interior walls) with the top airway experiencing a slightly larger pressure gradient. For a moderate Bo (0.68) the top airway still experiences a slightly larger pressure gradient than the middle interior wall. However, at $Bo > 1$ where there is significant asymmetries in bubble penetration, the middle interior wall experiences a larger pressure gradient magnitude than the top airway. This indicates that asymmetric bubble penetrations might lead to more cell injury at the carina.

3.2 Effects of Inertia. We investigated the influence of inertia on pressure and shear stress gradients by conducting several simulations at different values of Re (i.e., $Re = 2.66, 26.6, 53.2$, and 133) while maintaining a constant $Ca = 0.082$ and $Bo = 0.136$. As shown in Fig. 6, increasing inertial forces resulted in elevated pressure gradients and shear stress gradients in both the upper and lower airway walls. We note that pressure gradients increase dramatically by ~ 4 to 5 fold when $Re > 50$. Under these conditions, the increase in pressure/shear stress gradients was similar in both the upper and lower daughter airways since the baseline Bo number was small enough that the bubble experienced even penetration at all Re numbers. However, based on the results

Fig. 3 Velocity fields and pressure distribution within the fluid during bubble propagation with fixed $Ca = 0.082$ and $Re = 2.66$ and varying Bond numbers: (a) $Bo = 0.068$ ($t = 0.048$ s), (b) $Bo = 0.136$ ($t = 0.05$ s), (c) $Bo = 0.68$ ($t = 0.045$ s), and (d) $Bo = 1.36$ ($t = 0.04$ s)

Fig. 4 Pressure and shear stress gradients along the upper and lower daughter airway wall as a function of Bond number. Data were obtained for different Bond numbers at fixed $Ca = 0.082$ and $Re = 2.66$ at $t = 0.04$ s. (a) Pressure gradients in the upper daughter airway, (b) pressure gradients in the lower daughter airway, (c) shear stress gradients in upper daughter airway, and (d) shear stress gradients in lower daughter airway.

Fig. 5 Maximum pressure gradients along the upper, lower, and middle interior walls as a function of Bo . At low Bo , maximum pressure gradient is comparable on the upper, lower, and middle interior walls while at higher Bo , maximum pressure gradient is higher on the upper and middle interior wall.

in Fig. 4, uneven bubble splitting at high Bo might alter the influence of inertial forces on pressure/shear stress gradients. Therefore, as shown in Fig. 7, we conducted additional simulations in which we fixed $Ca = 0.082$, varied both Bo and Re and monitored the maximum pressure gradient on the upper and lower daughter airway walls. For a given value of Bo , increasing Re always leads to an increase in pressure gradients in both the upper and lower daughter airways. Consistent with Fig. 4, for a given Re ,

increasing Bo resulted in a larger pressure gradient in the upper airway and a lower pressure gradient in the lower airway. From Fig. 7, we note that for a given Bo , changing Re has a larger effect on pressure gradients at high Re values where there is a sharp rise in pressure gradients for $Re > 30-80$.

3.3 Effects of Surface Tension. Although it is well established that surface tension forces can significantly influence the hydrodynamics of bubble flow in straight channels [8,9], less information is available about how surface tension influences hydrodynamic stresses during microbubble propagation in an airway bifurcation. In this study we investigated the effect of surface tension by varying Ca (i.e., $Ca = 0.82, 0.082, 0.008, 0.0008$) while maintaining a constant $Re = 2.66$ and $Bo = 0.136$. Simulation results indicate that the bubble shape changed dramatically with Capillary number. Specifically, at lower Ca , the bubble was more circular and filled the airway bifurcation such that fluid film between the bubble and airway wall was extremely thin. Conversely, at larger Ca , the bubble was more elongated and exhibited a thicker film thickness within the bifurcation. In addition to changes in bubble shape, we were particularly interested in how varying Ca would influence pressure and shear stress gradients on the upper and lower airway wall. As shown in Fig. 8, decreasing Ca which corresponds to an increase in surface tension forces resulted in a very large increase in both the pressure and shear stress gradients on the upper and lower airway walls. Although this increase occurs on both the upper and lower airway walls, it is noteworthy that even though bubble penetration into the bifurcation at this Bo value (0.136) appears to be even, the maximum pressure gradient and shear stress gradient at a given Ca value is always larger in the upper airway. This is due to the fact that gravitational forces are not eliminated (i.e., Bo is not zero) and this data indicates that even at small values of Bo , there can be

Fig. 6 Pressure and shear stress gradients along the upper and lower daughter airway wall as a function of Reynolds number. Data was obtained for different Reynolds numbers at fixed $Ca = 0.082$ and $Bo = 0.136$. (a) Pressure gradients in the upper daughter airway, (b) pressure gradients in the lower daughter airway, (c) shear stress gradients in upper daughter airway, and (d) shear stress gradients in lower daughter airway.

Fig. 7 Maximum pressure gradient calculations at fixed Capillary number ($Ca = 0.082$) by varying Bond numbers ($Bo = 0.068$, $Bo = 0.136$, $Bo = 0.68$, $Bo = 1.36$) and Reynolds numbers ($Re = 2.66$, $Re = 26.6$, $Re = 53.2$, $Re = 133$) for (a) upper daughter airway and (b) lower daughter airway wall

heterogeneous distributions in pressure/shear stress gradient within the bifurcation.

To further analyze the effect of varying Ca at different Bo values, we conducted additional simulations where we fixed $Re = 0.082$, varied both Bo and Ca and monitored the maximum pressure gradient in the upper and lower daughter airway walls. As shown in Fig. 9, for a given value of Bo , decreasing Ca lead to a large increase in the maximum pressure gradient in the upper daughter airway. A similar increase in pressure gradients with decreasing Ca was observed in the lower daughter airway for low values of Bo (0.068 or 0.136). However, at larger Bo values (>0.68), the increase in pressure gradient with decreasing Ca was not as dramatic in the lower daughter airway. Consistent with data

in Fig. 4, increasing Bo resulted in larger pressure gradients in the upper daughter airway as compared to the lower daughter airway. However, it is interesting to note that for a given Ca value, increasing the Bo number only had a modest effect on pressure gradients in the upper daughter airway but had a more significant effect on pressure gradients in the lower daughter airway. Therefore, the effect of Bo on pressure gradients during bubble propagation in an airway bifurcation is strongly dependent on the Ca value.

3.4 Discussion. It is now well recognized that the mechanical forces generated during the artificial ventilation of patients with

Fig. 8 Pressure and shear stress gradients along the upper and lower daughter airway walls as a function of Capillary number. Data were obtained for different Capillary numbers at fixed $Re = 2.66$ and $Bo = 0.136$. (a) Pressure gradients in the upper daughter airway, (b) pressure gradients in the lower daughter airway, (c) shear stress gradients in upper daughter airway, and (d) shear stress gradients in lower daughter airway.

Fig. 9 Maximum pressure gradient calculations at fixed Reynolds number ($Re = 2.66$) by varying Bond numbers ($Bo = 0.068$, $Bo = 0.136$, $Bo = 0.68$, $Bo = 1.36$) and Capillary numbers ($Ca = 0.82$, $Ca = 0.082$, $Ca = 0.008$, $Ca = 0.0008$) for (a) upper daughter airway and (b) lower daughter airway

ARDS can exacerbate lung injury. As described in several recent review articles [37,38], the heterogeneous nature of lung injury results in different types of mechanical forces being exerted to the airway/alveolar epithelium [39,40] including stretching forces and surface tension forces during interfacial flows [3,41]. Although previous studies have been able to mitigate cellular injury during interfacial flows by altering cellular mechanics [20,42], these studies did not account for the effect of airway bifurcations on cellular injury. Recently, several investigators have developed numerical models of microbubble dynamics in bifurcating blood vessels [24,25,30,43]. However, the focus of those previous studies was bubble lodging and occlusion of the tumor microvasculature and those studies did not characterize how microbubble flows

alters the hydrodynamic stresses responsible for cellular injury. The goal of this study was to use computational techniques to investigate how gravity, inertia, and surface tension forces alter the distributions and magnitudes of hydrodynamic stresses in airway bifurcations during microbubble flows.

In this study, finite element techniques were used to simulate a wide range of Bond numbers (Bo) which represents the ratio of gravity to surface tension forces. As shown in Figs. 2 and 3, when Bo is large, gravity forces dominate inertial and surface tension forces and this leads to buoyancy driven motion of the microbubble into the upper daughter airway. Buoyancy driven bubble motion into the upper daughter airway is consistent with previous experimental results [26,44] and results in a thinning of the fluid

film separating the bubble from the upper daughter airway wall. Consistent with previous studies that demonstrated a direct correlation between film thickness and pressure gradients [3], bubble movement into the upper airway results in larger pressure gradients on the upper daughter airway wall as compared to the lower daughter airway wall (Fig. 4). Since large pressure gradients have been shown to be the major factor responsible for cell injury, the implication of these results is that airways in the gravity independent lung regions may be more susceptible to interfacial flows and cell injury during mechanical ventilation.

A significant advantage of the finite element simulation of microbubble flows is the ability to simulate a wide range of inertial forces as characterized by the Reynolds number (Re). As described in Sec. 2.5, Re values have a wide range in the pulmonary system (i.e., $0.05 < \text{Re} < 125$) and although previous studies have simulated bubble propagation for finite Re values [15,45,46], to our knowledge the effect of inertia on microbubble propagation in an airway bifurcation has not been evaluated. As shown in Figs. 6 and 7, increasing Re leads to a significant increase in pressure gradients on both the upper and lower daughter airway walls. This result is consistent with previous studies which report that the inclusion of fluid inertia increases the pressure required to propagate a finger of air in a 3D channel [46]. It is also clear from Fig. 7 that the primary effect of larger Bo values, i.e., increased pressure gradients in the upper daughter airway and decreased pressure gradients in the lower daughter airway, is modulated by the presence of large inertial forces. Specifically, we observed smaller changes in pressure gradients with Bo at large Re values. Therefore, inertial forces can significantly affect the pressure gradients exerted on epithelial cells during microbubble flows in airway bifurcations. Our simulations also indicate that previous studies which assumed Stokes Flow conditions in bifurcating geometries [30] might underestimate the fluid stresses exerted at airway walls and the pressures required to drive microbubble flows.

Most previous computational studies of microbubble flows could only simulate moderate Capillary numbers of $\text{Ca} > 0.01$ [13,16,17]. However, the range of Ca in the lung can vary over several orders of magnitude ($1 \times 10^{-5} < \text{Ca} < 0.1$). In addition, several of the in vitro experiments used to simulate cellular injury during airway reopening typically utilize bubble propagation velocities that result in $\text{Ca} \ll 1 \times 10^{-3}$ [8,9]. As a result, to correlate the cell death measured in vitro with the hydrodynamic stresses generated during microbubble flows, previous investigators had to extrapolate computational data obtained at larger Ca values to the low Ca conditions used in experiments [8,9]. As demonstrated in the Appendix, one major advantage of the finite element method used in this study is that it can seamlessly simulate a wide range of Ca values in one simulation package.

Therefore, this finite element technique could be used to more accurately and directly analyze cellular responses to hydrodynamic stresses at appropriate in vitro experimental conditions.

In this study, we investigated how varying Ca over a wide range influences pressure/shear stress gradient magnitudes and as shown in Figs. 8 and 9, at low values of Bo (i.e., negligible gravity forces) pressure gradients in both the upper and lower daughter airway are a strong inverse function of Ca and this data is consistent with previous studies [8,9,19]. Interestingly, for $\text{Ca} < 0.01$, increases in Bo lead to a significant reduction in the maximum pressure gradients in the lower daughter airway. This indicates that uneven bubble penetration into the bifurcation may protect the epithelial cells in the lower gravity dependent airway from microbubble-induced injury. Future experimental studies that expose epithelial cells to microbubble flows in a bifurcating airway could be used to test the computational prediction of less cell injury in gravity dependent airways.

Although inertia, gravity, and surface tension forces clearly influence the distribution and magnitudes of pressure gradients during microbubble flows in a bifurcating airway, the relative importance of these parameters might vary under different conditions. We have therefore conducted a sensitivity analysis with the data in Figs. 7 and 9 to determine the relative importance of Re, Ca, and Bo under both baseline conditions and under larger/smaller Re conditions. For this analysis, we calculated a log-scale derivative-based sensitivity value [47]

$$\alpha = \frac{\partial[\log(y)]}{\partial[\log(x)]} = \frac{x}{y} \frac{\partial y}{\partial x} \quad (12)$$

where α is the sensitivity value, dy/dx is the local slope of the resultant variable versus parameter curve, y represents the resultant variable (i.e., maximum pressure gradient), and x represents the parameter of interest (i.e., Bo, Ca, or Re). Although standard procedure is to only calculate α at baseline conditions (i.e., $\text{Re} = 2.66$, $\text{Ca} = 0.082$, and $\text{Bo} = 0.136$), we are also interested in how larger/smaller Re values alters the sensitivity of pressure gradient to a given parameter. Therefore, as shown in Fig. 10, we calculated the sensitivity of pressure gradients to changes in Ca, Bo, and Re as a function of Re. For all conditions we observed that $\alpha \sim 1$ for Ca indicating that changes in Ca produce nearly linear changes in the pressure gradient magnitude. Interestingly, data in Figs. 10(a) and 10(b) indicate that under high Reynolds number conditions, pressure gradient magnitudes are equally sensitivity to changes in Ca and Re. Specifically, at low Re, the sensitivity of pressure gradients to Ca is largest while at larger Re values, the sensitivity of pressure gradients to Re is nearly equal to the sensitivity of

Fig. 10 Sensitivity of maximum pressure gradient to changes in Re, Ca, and Bo for different baseline values of Re. (a) Represents data from the upper daughter airway and (b) represents data from the lower daughter airway.

pressure gradients to Ca . We conclude that under a majority of conditions studied, pressure gradient magnitudes are determined by the Ca value and thus surface tension forces dominate the response in this system. However, in the larger conducting airways, where Re values are larger, pressure gradient values are equally affected by changes in Ca and Re . As a result, both surface tension and inertia forces are important under these conditions. Finally, we note that although the sensitivity of pressure gradient magnitudes to changes in Bo are not as large as sensitivities to Re and Ca , it is clear from Figs. 3 and 4 that gravity alters the penetration of the microbubble and that this asymmetric penetration significantly influences the distribution of pressure gradients in airway bifurcations.

In addition to elucidating the role of inertia, surface tension and gravity on the pressure gradients generated by microbubble flows in bifurcating airways, our model has made several computational predictions that could be tested in future experimental studies. First, as shown in Fig. 5, at low Bond numbers where the microbubble penetrates evenly between the upper and lower daughter airway, the maximum pressure gradients on the upper, lower, and middle interior walls are comparable. Therefore, under these conditions we would not expect to observe significant differences in cell injury between cells cultured on the upper or lower airway walls. However, at higher Bo values, the upper airway wall and the middle interior wall experience larger pressure gradients and under these conditions we would expect to observe significant differences in cell injury between cells cultured on the upper or lower airway walls as well as the highest degree of cell injury at the carina. We note that although this 2D model, which would correspond to an extruded 3D model in vitro, might be difficult to fabricate, planar in vitro models using custom designed flow gaskets [9,20] could be employed and compared with appropriate 3D computational models.

3.5 Model Limitations. In this study, we made several simplifying assumptions to achieve a tractable simulation of microbubble propagation in a fluid-filled bifurcating airway. First, we used a 2D channel geometry while airways in vivo have a complex 3D geometry. In addition, we assumed a two-generation symmetric airway shape while airways in vivo can exhibit bifurcating asymmetries [48]. This study also assumed that the free surface has a constant surface tension. However, the presence of pulmonary surfactant can generate complex spatial and temporal distributions of surface tension along the interface [16]. Finally, our model did not include any cells on the airway wall or the effects of airway compliance. Previous computational studies indicate that airway wall tension can significantly affect the transient pressures during reopening [49] and an experimental study from our lab indicates that changes in airway wall compliance can significantly alter the amount of cellular injury [50]. Therefore, future models of microbubble flows in airway bifurcations should be

enhanced to include fluid–structure interactions between the bubble and compliant airway wall. Given that the major utility of these types of computational models is their ability to help interpret experimental data, we suggest that future studies first focus on conducting in vitro studies that investigate cell injury during airway reopening in a bifurcating geometry and in silico studies that extend the current model to 3D so that it accurately captures the geometry used in in vitro experiments. Future studies could then use image-based finite element modeling techniques [51,52] to develop computational models of airway reopening in more realistic geometries.

4 Conclusions

In this study, we developed a 2D computational fluid dynamic model of microbubble propagation in a bifurcating airway and used this model to investigate the influence of inertia, gravity, and surface tension forces on the hydrodynamic stresses generated during microbubble propagation in bifurcating airways. Results indicate that pressure gradient magnitudes were similar along the upper, lower, and middle interior airway walls during symmetric bubble propagation. In contrast, asymmetric bubble propagation into the bifurcation lead to larger pressure gradients along the middle interior (carina) and upper airway walls. Since the carina experiences the largest pressure gradient during asymmetric bifurcations when $Bo > 1$, this computational model predicts that there will be more cell injury at this location under these conditions. Under most conditions studied, changing Ca had the greatest impact on pressure gradient values indicating the importance of surface tension forces in this system. However, at large values of Re (i.e., $Re > 50$) inertial forces significantly impacted the magnitude of pressure gradients and we conclude that both inertia and surface tension forces are important factors in determining the pressure gradients that develop during the reopening of airway bifurcations. This study has therefore provided important new information about the fluid mechanics of microbubble propagation in bifurcating airways and has provided a computational technique for effectively simulating interfacial flows in respiratory airways with complex geometries.

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Appendix: Straight Airway Model Verification

Before applying the current numerical algorithm to bubble propagation in a bifurcating airway, it was first used to simulate bubble propagation in a straight 2D fluid-filled channel (see Fig. 11(a)) to compare with previous results. For this model, a

Fig. 11 (a) Velocity field and bubble shape during propagation in a straight 2D channel. Solid line is the initial bubble shape. (b) Comparison of the dimensionless film thickness obtained with current finite element technique (triangles) with Bretherton's asymptotic predictions (dashed line) and BEM simulations (solid line).

no-slip boundary condition was applied on channel walls and parabolic velocity profiles with a mean velocity of U were applied at the upstream and downstream boundaries. The weak form of the free surface boundary condition, Eq. (10), was applied on the air-liquid interface. The advantage of this model is that it can efficiently simulate a wide range of Ca values, including very small Ca values. Starting with an elliptical bubble shape (see grey line in Fig. 11(a)), the bubble converges to a steady state shape and this convergence is aided by our remeshing algorithm. To validate our computational technique, we calculated the film thickness between the bubble and channel wall and compared this value with both Bretherton's asymptotic predictions [12] and BEM solutions [13] (see Fig. 11(b)). The comparisons between our simulation results and Bretherton's predictions at low Capillary numbers were all within 0.12% relative error. In addition, the comparisons with the BEM solutions at higher Capillary numbers were all within 0.15% relative error. As a result, our finite element method is able to accurately and efficiently simulate a wide range of Ca values in one software package.

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