Bolus dispersal through the lungs in surfactant replacement therapy

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Espinosa, F. F., and R. D. Kamm. Bolus dispersal through the lungs in surfactant replacement therapy. J. Appl. Physiol. 86(1): 391–410, 1999.—A model is presented of surfactant replacement therapy. An instilled bolus is pushed into the lungs on the first inspiration, coating the airways with a layer of surfactant and depositing some in the alveoli. Layer thickness depends on the capillary number ($\mu U/\gamma$, where $\mu$, $U$, and $\gamma$ are bolus viscosity, advancing meniscus velocity, and surface tension, respectively). Larger capillary number leads to thicker layers, reducing alveolar delivery. Subsequently, surface tension gradients sweep surfactant into alveoli not receiving surfactant during the first inspiration. The effects on spreading of sorption kinetics, bolus viscosity, initial layer thickness, initial penetration of surfactant, gravity, and shear stress are examined. Sorption nearly eliminates surface tension gradients in central airways but produces a sharp transition at the leading edge of the exogenous layer. Local thinning of the liquid layer results, trapping 95% of the surfactant in the airways. Gravity and ventilation augment transport somewhat. Transport to the periphery takes 4–170 s for the leading edge but considerably longer for the bulk of the surfactant. The model demonstrates how the various physical parameters governing surfactant distribution might alter the response to surfactant replacement therapy.

Surface tension; airway liquid; modeling; respiratory distress syndrome; surfactant replacement therapy (SRT) is the standard treatment for premature neonates suffering from surfactant insufficiency of prematurity. Response is rapid, and complications such as cyanosis and bradycardia are minimal (45). Recent animal experiments have also shown that surfactant treatments are beneficial in some neonatal inflammatory lung diseases such as meconium aspiration (39) and some types of pneumonia (21). Surfactant has also been examined as a spreading agent for drug delivery (32). In view of the rapidly expanding role of surfactant instillation, it is increasingly important to understand the process by which a bolus of surfactant is dispersed through the lungs. Yet a comprehensive model or framework does not exist for describing how a surfactant bolus placed into the trachea is transported out to the periphery.1

Recent modeling efforts have focused on transient spreading of localized surfactant monolayers by surface tension gradients. Profiles of liquid layer thickness and surfactant concentration have been reported, with the time for surfactant to reach the lung periphery predicted. In general, surface tension gradients induced by a nonuniform distribution of surfactant at the air-liquid interface drive liquid from regions of low surface tension to regions of high surface tension. The resulting flows cause liquid to accumulate at the leading edge of the monolayer with simultaneous thinning of the liquid layer at the deposition site. For a fixed amount of insoluble surfactant deposited over an initially surfactant-free interface, the spatial extent of the monolayer grows as follows: $t^1$ for a droplet (11), $t^2$ for a strip (9, 24), and $t^3$ for a front (1), where $t$ is time.

Other studies have examined the case in which the surface-active agent is soluble in the liquid layer, primarily in the context of pulmonary drug delivery. For example, it has been shown that when the airway wall is a perfect absorber of the surfactant as it diffuses across the layer, axial gradients in surface tension decrease and the spreading rate is reduced (18). With no absorption at the wall, disturbances in the liquid layer increase, but spreading rates are not significantly altered from the insoluble situation (25). When a drug is modeled as a passive solute in the liquid layer, surface tension gradients sweep it along at one-half the surface velocity (27).

The time for surfactant to spread to the periphery has been estimated in two separate studies with seemingly contradictory results. Espinosa et al. (9), extrapolating from their findings in a single-tube model, estimated that surfactant could reach the periphery in as little as 12 s. Jensen et al. (26), using a model that accounted for real airway geometry, estimated the transit time from the trachea to airway generation 16 to be 15 min. Jensen et al. attributed the difference between their prediction and that of Espinosa et al. to the effects of surfactant dilution associated with the rapid increase in surface area in the direction of the periphery. Although these effects certainly influence transport rates, much of the difference is attributable to different values used for the liquid layer viscosity and thickness in the respective calculations. The viscosity ($\mu$) used by Espinosa et al., $\mu = 0.01 \text{g} \cdot \text{s}^{-1} \cdot \text{cm}^{-1}$, was a factor of 10 lower than that of Jensen et al. When this lower value is used in the model of Jensen et al., the transit time is reduced from 15 to 1.5 min. Additionally, the thickness of the endogenous liquid layer was taken to be a uniform 10-µm layer in the model of Espinosa et al. but varied between 2 µm in the trachea and 0.2 µm at generation 16 in the calculations of Jensen et al. Because spreading time is inversely proportional to liquid layer thickness, this further contributes to the difference in predicted times. Last, Espinosa et al. modeled a finite amount of insoluble surfactant, leading to a decrease in surfactant concentration as the monolayer spread toward regions of...
higher surface tension. In contrast, Jensen et al. held surface concentration fixed at the trachea, essentially approximating a source of surfactant that maintained a surface tension gradient along the airway tree. This would reduce transit times; however, a direct comparison of the two predictions cannot easily be made. The effect of dilution, therefore, is difficult to discern but appears to be smaller than initially believed. Clearly, the choice of values for the physical variables can have a profound effect on the transit times predicted.

The behavior of these models is dramatically influenced, however, by the presence of endogenous surfactant; the accumulation of liquid at the leading edge is reduced (9, 24), and spreading rates diminish (15).

Thus previous studies (9, 11, 18, 24–27) have extensively examined the general character of surfactant-driven flow, with application to spreading in the lungs. Yet certain aspects present in SRT have not been addressed. The exchange of material between the liquid layer and the epithelium has been considered in the context of drug delivery (18, 25, 27); the effects on surfactant delivery of surfactant exchange between the liquid deposited in the airways during SRT and the air-liquid interface has not. Additionally, effects such as gravity and shear stress from airflow in a whole lung geometry have not been previously considered. Furthermore, these earlier models consider transport of surfactant through the lung as occurring only over endogenous liquid layers. They do not address the clinical setting of how an exogenous surfactant originating in the trachea and main stem bronchi is pushed through the airways with the following inspiration. No consideration has been given to how this aspect of SRT determines the quantity of surfactant reaching the periphery or the amount of surfactant remaining in the airways. This comprehensive model for examining exogenous surfactant transport through the lungs is developed in the context of SRT.

CURRENT PROCEDURE FOR SRT

The most common protocol calls for instilling surfactant at 100 mg/kg body wt suspended in saline at 4 ml/kg body wt into the lungs for the treatment of neonatal respiratory distress syndrome (RDS). This is carried out by injecting four quarter-dose aliquots of 1 ml/kg each into the trachea, with the neonate positioned in one of four orientations for each quarter-dose: head up, left or right lateral, and head down, left or right lateral. The infant is hand ventilated for 30 s between each aliquot at a rate of 30 breaths/min, with tidal volumes near 7–9 ml/kg. After treatment and hand ventilation, the neonate is returned to the ventilator (40). Variations of this procedure have been used clinically as well (46). In the instance that a meniscus occludes the trachea and main stem bronchi (7), initial dispersal of the surfactant through the lungs relies solely on the positive pressure from the hand ventilator. Otherwise, surfactant is likely to deposit in the dependent lung according to gravity (3). No studies have addressed how the first inspiration affects distribution of a meniscus in the airways.

CONCEPTUAL MODEL AND OBJECTIVE

A comprehensive framework is proposed that addresses how a surfactant bolus that fills the bronchi and trachea (6, 7) is dispersed through the lungs. Conceptually, the distribution process is modeled as follows.

Phase 1

After bolus instillation (Fig. 1A), surfactant is distributed through the airway network as the bolus is

Fig. 1. Conceptual model of surfactant dispersal into diseased lungs (from Ref. 6). A: surfactant is instilled, here depicted as a meniscus in trachea. B: phase 1, where bolus is initially pushed into periphery. C: continued spreading and recruitment during phase 2, as surface tension gradient sweeps surfactant distally during recruitment.
advanced distally by the ensuing inspiration. As the bolus advances, it coats the airway walls with a thin layer of surfactant suspension, the thickness depending on the bolus properties (viscosity and surface tension) and the rate at which it is convected distally. Because of the heterogeneity of the lung in RDS, the initial distribution of surfactant will likely be nonuniform: the regions with higher compliance will receive a greater fraction of surfactant during the initial inspiration (Fig. 1B).

Phase 2

The liquid layer left behind in the airways by the advancing bolus during phase 1 provides the "reservoir" of surfactant that can potentially be delivered to terminal units not initially reached. Regions of the lung that lack endogenous surfactant (and, therefore, are less compliant) have a lower probability of being reached during phase 1. It is assumed that, although the expansion of these regions is impaired as a result of, e.g., the lack of surfactant, they are nonetheless patent with a continuous layer of liquid on the walls. Along those pathways, surface tension gradients exist that will draw the exogenous surfactant distally to locations where the surface tension remains high, thereby recruiting additional alveoli (Fig. 1C).

To examine this framework of surfactant dispersal, independent models for phases 1 and 2 are developed. The model for phase 1 applies experimental results obtained for a viscous liquid being purged by air from a single capillary tube to a branching lung geometry by using a Weibel morphometric model (43). Liquid layer profiles along the airway tree and the volume of the liquid initially left in the airways and that deposited in the periphery (past generation 14) are presented for different bolus viscosities and inspiration rates. The liquid layer profile established during phase 1 provides the "initial condition" for spreading during phase 2. Phase 2 is examined in a theoretical model similar to those described earlier (9, 11, 18, 24–26) but with the additional capability of simulating surfactant exchange from the bulk liquid to the interface.

Time-dependent evolution equations for liquid layer thickness, surfactant surface concentration, and surfactant bulk concentration are solved in a symmetric Weibel geometry. Effects on transport of sorpton kinetics, liquid viscosity, initial liquid layer thickness, initial surfactant penetration into the lungs, gravity, and shear stress due to airflow are considered. Profiles of liquid layer thickness and surfactant concentration are presented, and the amount of surfactant carried to the periphery as a function of time is computed.

MODEL DEVELOPMENT

Bolus Convection I into the Lungs

The simulation is based on the assumption that the injected surfactant bolus forms a plug in the central airways when first introduced into the lungs. The conditions under which this occurs are examined in a separate study (7). This section describes the model developed for how the bolus of surfactant initially filling the trachea and major bronchi is distributed along the airways on inspiration (phase 1). Published experimental results revealing the factors that control this phase of the dispersal process are employed.

The advance of a surfactant bolus by the first inspiration is modeled using experimental results for displacement of a viscous liquid in a small tube by a finger of air (Fig. 2). The liquid has a surface tension γ; the meniscus advances with velocity U inside a uniform capillary tube of radius R∞. The radius of the air-liquid interface for the liquid left behind is R0. After passage of the meniscus, the fraction of the cross section occupied by the liquid coating the tube wall

\[ m = 1 - \frac{\pi R_0^2}{\pi R_c^2} \]  

(1)

can be expressed as a function of the capillary number (Ca = μU/γ), a ratio of viscous effects to surface tension effects. The conditions that determine the functional relationship between Eq. 1 and Ca have been the focus of investigation since 1935. This problem was initially formulated to examine the motion of an air bubble through a small, liquid-filled capillary tube (2, 10, 41) and has more recently found relevance in tertiary oil recovery (33, 37, 38).

As a brief review, the experimental results of Fairbrother and Stubbs (10) indicate that m ~ Ca^\frac{2}{3} for 10^{-4} < Ca < 10^{-2}. Taylor (41) later confirmed and extended this finding to Ca ~ 10^{-3}. For larger Ca, m tapers off more rapidly than Ca^\frac{2}{3}, asymptotically approaching m = 0.56 near Ca = 2 (41). These findings (as Ca approaches 0) are in conflict with the theoretical prediction of Bretherton (2), who found that the fraction of liquid lining the tube scaled as Ca^\frac{2}{3}, indicating that less liquid should remain in the tube than was found experimentally. Bretherton's experimental results were in good agreement with m ~ Ca^\frac{2}{3} for Ca > 10^{-4} but gave thicker liquid layers for smaller Ca, where his analysis should have been more accurate. He speculated that the presence of contaminants in the experiments might support a shear stress at the air-liquid interface and thereby explain this difference. After reanalyzing the problem by treating the interface as rigid, the limiting case with surface impurities present, Bretherton found that m actually decreased or slightly increased (39).
increased and, therefore, discounted the effects of surface-active agents. Schwartz et al. (38) reexamined this problem and observed a bubble length-to-diameter ratio (L/D) dependence. Short bubbles with L/D < 15 were in good agreement with the results of Bretherton, whereas long ones (L/D > 25) were more aligned with the experiments of Fairbrother and Stubbs (10) for 10^-5 < Ca < 10^-3. Ratulowski and Chang (37) showed that surfactants can generate surface tension gradients that increase m by a maximum of 4^\text{th} over the result of Bretherton at small Ca (Ca ∝ 10^-6). This difference diminishes as Ca increases, with their theory giving m ∝ Ca^0 for larger Ca (Ca > 10^-4).

In this work the experimental findings of Fairbrother and Stubbs (10) and Taylor (41) are used to model phase 1 of surfactant dispersal on the basis that 1) the finger of air that advances the bolus distally can essentially be considered as a bubble of infinite length as it passes through the airways; 2) the extension of results of Fairbrother and Stubbs and those of Taylor from a single tube to a bifurcating network of airways was found to be approximately valid in an in vitro experiment (35); and 3) only Taylor provides results for large Ca, allowing treatment of the intermediate airways where Ca can approach 1.

Therefore, the fraction of liquid lining the airways will be described by the experimental results of Fairbrother and Stubbs (10) and Taylor (41). The two regimens for small and large Ca can be captured by the following expressions

\[ m = \begin{cases} Ca^{0.5} & 0 \leq Ca \leq 0.09 \\ 0.56[1 - \exp(-2.89Ca^{0.55})] & 0.09 < Ca \end{cases} \tag{2} \]

where the latter is similar to that used by Halpern and Gaver (17). These results are used in a symmetric Weibel geometry (43) that is scaled down for a neonate (22).

By computing the local bolus Ca along the airway tree, the fraction of liquid lining the airway walls for a given generation can be estimated from Eq. 2. With viscosity being a property of the bolus, only the local velocity and surface tension of the advancing meniscus need to be determined. This is accomplished by assuming a steady flow rate (V̇) at the trachea and dividing it by the total cross-sectional luminal area at the site of the meniscus, \( \pi r_h^2 \), where \( n \) is the airway generation number. Letting \( R_1 = R_2 (1 - m) \) from Eq. 1, the local Ca is

\[ Ca = \frac{\mu V}{\gamma \pi R_h^2 (1 - m) 2^n} \tag{3} \]

For example, depending on the flow rate at the trachea, the viscosity of the surfactant bolus, and the surface tension, the Ca can range from ~1.5 in the trachea (V = 10 ml/s, \( \mu = 0.8 \text{ g} \cdot \text{s}^{-1} \cdot \text{cm}^{-1}, \gamma = 37 \text{ dyn/cm} \)) to 10^-4 in generation 14 (V = 2 ml/s, \( \mu = 0.01 \text{ g} \cdot \text{s}^{-1} \cdot \text{cm}^{-1}, \gamma = 22 \text{ dyn/cm} \)). Here the value of surface tension was estimated using a dynamic surface tension model for lung surfactant (36). For a given flow rate at the trachea, the area expansion rate at the meniscus was related to the area cycling rate in the dynamic surface tension model. In this manner the dynamic surface tension was determined throughout the airway tree and used in Eq. 3.

Once m is known, R can be calculated and the liquid layer thickness (h) can be determined. Because the deposited liquid lining is much thicker than the initial endogenous liquid layer, the former is assumed to consist entirely of instilled liquid. The volume of liquid lining the airways is calculated by integrating the liquid layer thickness along the airway tree. With use of this volume and the assumption of an initial bolus volume, the net volume reaching the periphery during the first inspiration can be estimated. The volume of liquid left coating the airways is presented in RESULTS for different values of viscosity and flow rate.

**Recruitment Model**

Regions in the lung not receiving surfactant during the initial passage of the bolus (phase 1) must rely on surface tension gradients to deliver exogenous surfactant (phase 2). Phase 2 can be viewed as transporting surfactant to surfactant-deficient, low-compliant regions of the lung. The action of phase 1 leaves exogenous surfactant coating the airways through generation \( n \) with a nonzero endogenous surfactant concentration distal to this location. This initial condition is shown in Fig. 3.

A summary of the governing equations that describe transport in a symmetric Weibel geometry is detailed in the APPENDIX. They consist of 1) a force balance between pressure gradients, surface tension gradients, airflow shear stress, wall shear stress, and gravity, where pressure in the liquid is determined from Laplace's law, 2) conservation of surfactant, relating temporal changes in liquid layer thickness to the net flux of liquid along the airway tree, 3) conservation of surfactant, relating temporal changes in surface and bulk concentrations to the longitudinal gradient in surfactant flux at the surface and in the bulk and to the exchange rate at the air-liquid interface due to sorption, 4) a sorption model that simulates surfactant exchange between the interfacial tension and the bulk, 5) an equation of state, relating surface concentration to surface tension, 6) a model for applied shear stress at the air-liquid interface, valid for airflow through an airway network (4), and 7) a ventilation function that provides symmetric and asymmetric patterns with respect to inspiration and expiration times.

In this model, several assumptions are made. 1) Inertial effects in the liquid layer are neglected, because the Reynolds number (Re), a ratio of inertial to viscous forces, is much less than 1. That is

\[ Re = \frac{\rho u h_0}{\mu L_0} = \frac{\rho \gamma_{max} h_0^2}{\mu L_0^2} \ll 1 \tag{4} \]

where \( \rho \) is density, \( u \) is the characteristic liquid velocity along the airways, \( \gamma_{max} \) is the maximum surface tension, \( h_0 \) is the reference liquid layer thickness, and \( L_0 \) is the length of the airway tree for a neonate [approxi-
...liquid layer thickness, \( h \), surfactant surface concentration (\( \Gamma \)), bulk concentration (\( c \)), axial position along the airway tree (\( x \)), and time scales are scaled by the respective reference quantities \( h_0 \), \( \Gamma_{\text{ref}} \), \( c_{\text{ref}} \), \( L_0 \), and \( \tau_0 \). \( L_0 \) and \( \tau_0 \) are the total length of the neonatal conducting airways and desorption time scale, respectively.

From this scaling, six dimensionless parameters are obtained. Two describe sorption: \( \tau_A/\tau_D = k_2/k_1 \), a ratio of surfactant adsorption to desorption time, and \( \tau_C/\tau_D \), a ratio of viscous spreading to desorption time. Here \( \tau_A = 1/k_1 \), \( \tau_D = 1/k_2 \), and \( \tau_C = \mu L_0^2 / h_0 \gamma_{\text{max}} \), where \( k_1 \) and \( k_2 \) are the adsorption and desorption constants, respectively. The importance of gravity with respect to surfactant spreading is examined through the Bond number (\( Bo = \rho g h_0 L_0 / \gamma_{\text{max}} \), where \( \rho \) is gravity). For a given tidal volume and breathing period, the effect of shear stress from airflow is measured by \( f \), a ratio of the time for inspiration to the time for a complete breath. Last, two parameters enter from the initial conditions on the liquid layer thickness and surfactant concentration distributions (Fig. 3). \( h_{\text{bol}} = h_0 \) is the maximum liquid layer thickness in the trachea resulting from the initial dispersal process, and \( n_{\text{bol}} \) is the airway generation through which the surfactant has initially penetrated, providing a means of examining heterogeneities in the lungs.

Together, \( \tau_A/\tau_D \), \( \tau_C/\tau_D \), \( h_{\text{bol}} \), \( n_{\text{bol}} \), \( n_{\text{bol}} \), \( Bo \), and \( f \) comprise the set of parameters that characterize the process of recruitment. As described earlier, the initial profile for the liquid layer thickness was obtained from the bolus dispersal model (phase 1), with an arbitrary distribution for the exogenous bulk concentration assigned. The surface concentration is initially assumed to be in equilibrium with the bulk.

**RESULTS**

The simulations examine how a bolus occluding the trachea and main stem bronchi reaches the periphery during SRT. The two models developed explore different phases of the transport process and are joined to provide a comprehensive picture of surfactant dispersal. First, a family of curves examining the effects of viscosity and ventilatory flow rate on liquid layer thickness (\( h_0 \)), Ca, meniscus surface tension (\( \gamma^* \)), liquid layer thickness-to-airway radius (\( h/R \)), and accumulated volume (\( V_{\text{acc}} \)) vs. distance along the airway tree are plotted. These results in phase 1 are employed as an initial condition for phase 2. Transient simulations provide time evolution profiles of liquid layer thickness, surfactant surface concentration, and surfactant bulk concentration. Effects of surfactant bulk concentration, liquid layer viscosity, initial liquid layer thickness, initial extent of the monolayer, gravity, and shear stress from airflow are presented. Transit times and percentage of surfactant transported to the periphery are reported.

**Phase 1: Bolus Dispersal**

Profiles of \( h_0 \), \( Ca \), \( \gamma^* \), \( h/R \), and \( V_{\text{acc}} \) along the airway tree (Fig. 4) were calculated for \( V = 7 \text{ ml/s} \) with \( \mu = 0.01, 0.1, 0.2, 0.4 \), and \( 0.8 \text{ g·s}^{-1}·\text{cm}^{-1} \). The accumulated
volume is the cumulative amount of liquid left in the airways as the bolus is pushed from the trachea completely through the last conducting airway (generation 14). In general, increasing viscosity or flow rate (all else being equal) increases Ca (Eq. 2), which leads to a larger fraction of liquid being left on the airway walls.

The liquid layer thickness in the intermediate airways ranges from approximately $h/h_0 = 12$ for $\mu = 0.01$.
variation exists for the different values of viscosity, and the bolus has passed (in ~ 0.02 s, results not shown), returning the surface tension to 22 dyn/cm.

$h/R_c$ increases as flow rate and viscosity increase, reducing the lumen of the airways (Fig. 4D). This is likely to lead to airway obstruction by liquid bridging, which can occur when the volume of liquid lining a cylindrical tube is $> 5.6R_c^2$ (31). For an airway, this requires $\pi(R_c^2 - R_i^2)L_a > 5.6R_c^2$, where $L_a$ is the length of an airway and $L_a \approx 6R_c$. Letting $R_i = R_c - h$ and solving for $h/R_c$, airway closure can occur for $h/R_c > 0.16$.

Surface tension of the meniscus front as it passes through each generation is plotted in Fig. 4C. Little variation exists for the different values of viscosity, with the results for $\mu = 0.1$ g·s$^{-1}$·cm$^{-1}$ only plotted for clarity. The rapid area expansion at the meniscus momentarily decreases the surface concentration of surfactant, raising the surface tension to ~37 dyn/cm through generation 8 and dropping off to 25 dyn/cm in generation 14. However, surfactant is rapidly adsorbed into the interface along the entire network once the bolus has passed (in ~ 0.02 s, results not shown), returning the surface tension to 22 dyn/cm.

As mentioned earlier, when $h/R_c > 0.16$, airway obstruction by liquid bridging is likely to occur (31). This instability has been studied by several research groups (19, 20, 29, 30, 34) and is certain to play a role in transport (see discussion), but it is not the subject of this analysis. Hence, to study transport by surface tension gradients, stable liquid layers that would not lead to liquid bridging ($h/R_c < 0.16$) were chosen. Therefore, the liquid layer resulting when $V = 0.28$ ml/s and $\mu = 0.1$ g·s$^{-1}$·cm$^{-1}$ from phase 1 was chosen as the initial condition for the recruitment model. Although this flow rate is quite small (an order of magnitude smaller than those clinically used), it is only the initial inspiration rate for delivering the surfactant and not the ventilatory rate used in the course of treatment. Once phase 1 is completed, standard ventilatory support can be resumed. Alternatively, a stable liquid layer similar to this one could result under current clinical conditions where ventilation rate is much higher ($V = 7$ ml/s). In this case, occlusion by liquid bridging and reopening of the airways occurs over several given breaths. Each time occlusion occurs, the applied ventilation drives the menisci into the lungs. In this manner, liquid is carried distally, and the liquid layer thins until a stable liquid lining results. The physics of this process are not addressed here; rather, we have chosen conditions that provide a stable liquid layer to systematically study transport after a stable layer is established.

In Fig. 4E, plots of accumulated volume along the airways provide a measure of the volume of liquid left behind in the conducting airways with $V = 7$ ml/s. For example, the curve for a surfactant with $\mu = 0.1$ g·s$^{-1}$·cm$^{-1}$ reveals that a little more than 0.75 ml of suspension would coat generations 1-14. Conversely, the volume immediately deposited in the periphery (distal to generation 14) for a given bolus volume can be computed using these same results. For example, using the illustration just presented, if one starts with a bolus volume of 1.5 ml at the trachea, a little more than 0.5 ml immediately reaches the periphery ($V = 7$ ml/s). A family of curves for the total volume of liquid lining the airways ($V_A$) as a function of ventilation rate is plotted for different viscosities in Fig. 5. Thus, by knowing the viscosity of the surfactant instillation and the ventilation rate, the volume of liquid left in the airways or reaching the alveoli after the initial inspiration can be predicted. Controlling the volume of liquid left in the airways has clinical significance (see discussion).
The temporal character of transport is analyzed by tracking the extent to which 50, 75, 95, and 100% of the exogenous surfactant mass penetrates into the lungs. Trajectories of $x/L_0$ vs. $t/\tau_v$ are given for each fraction of surfactant tracked, where $x/L_0$ is the axial location along the airway tree. $x/L_0$ is determined by integrating along the surface and bulk concentrations of surfactant, starting at the trachea and proceeding distally. Once a particular percentage of exogenous surfactant has been “recovered,” the value of $x/L_0$ is noted. Recovering 100% of the exogenous surfactant mass corresponds to tracking the leading edge of the exogenous surfactant layer. This process is described by

$$\int_0^{x/L_0} (c^*+h^* \beta + G^*)W^* \, dx = f_{exo} M_{exo}^* + M_{fendo}^*$$

where the asterisk denotes dimensionless quantities defined in the APPENDIX. $\beta = \Gamma_{ref}/\Gamma_{ref} h_0$, $W^*$ is the total airway circumference along the airway tree, $f_{exo}$ is the fraction of exogenous surfactant to be tracked, $M_{exo}^*$ is the total exogenous surfactant mass, and $M_{fendo}^*$ is the endogenous surfactant mass associated with a given fraction of exogenous surfactant. A specific fraction of exogenous mass is tracked by evaluating the integral until it equals the expression on the right for given values of $f_{exo}$, $M_{exo}^*$, and $M_{fendo}^*$.

Evolution profiles of $h/h_0$, $\lambda/\lambda_{ref}$, and $c/c_{ref}$ vs. $x/L_0$ illustrate how the liquid layer deforms and how the surfactant distributes in time. These results along with the temporal trajectories are used to characterize and evaluate the recruitment process. Effects of sorption, liquid layer viscosity and thickness, initial exogenous penetration, gravity, and shear stress due to ventilation are now examined.

Sorption. The exogenous surfactant used clinically is highly concentrated [25 mg/ml (40)] and rapidly absorbs to the air-liquid interface. However, to provide a comparison of the present model to previous models, an insoluble surfactant is initially considered, where the surfactant in the bulk does not adsorb. Plots of $h/h_0$, $\lambda/\lambda_{ref}$, and surface tension are presented in Fig. 6 for $t/\tau_v = 0, 0.1, 0.2, \text{ and } 0.3$, where $\tau_v = 142 \text{ s}$. Parameter values are $H_{bol} = 8$, $n_{bol} = 4$, $Bo = 0$, and $f = 0$. The initial condition is shown as a solid line. Qualitatively, an upwelling of liquid is generated at the leading edge of the monolayer as spreading begins (Fig. 6A). The diffuse, rather than sharp, front of this wave is characteristic of transport when an endogenous surfactant is present (9, 24). Behind the crest, the liquid thins rapidly to a local minimum in thickness before rising again in the direction of the trachea. The liquid layer over the entire domain is pulled distally by the action of surface tension gradients, with the thickness in the trachea falling as time progresses. Figure 6B shows the interfacial concentration decreasing as the insoluble surfactant spreads into the lung. Gradients in surface concentration and, correspondingly, surface tension are established over the entire domain and diminish as time proceeds (Fig. 6C). A small increase in the distal surface concentration is observed as surfactant reaches the periphery. These results are similar to others in the literature for an insoluble surfactant (9, 11, 24).

Different percentages of exogenous surfactant are tracked in Fig. 7. The leading edge of the exogenous mass (100%) rapidly travels into the lungs, reaching a plateau between generations 10 and 12 by $t/\tau_v = 0.3$ (43 s). Twenty-five percent lies between generations 4 and 12, with 50% remaining in the trachea. The trajectories for 50, 75, and 95% have not reached a plateau, signifyng that surface tension gradients (surfactant gradients) are still present (Fig. 6C).

Effects of sorption are now considered for a concentration similar to that used in SRT [c = 10 mg/ml (40)] with $\beta = 0.03$, $\tau_v/\tau_0 = 10^{-2}$, and $\tau_v/\tau_0 = 2.38$ ($\mu = 0.1 \text{ g} \cdot \text{s}^{-1} \cdot \text{cm}^{-1}$). The overall character of the liquid layer changes significantly (Fig. 8). The steep leading edge is steeper, and dramatic thinning extends up the airway tree over several generations. A detail of the leading edge highlights this thinning of the liquid layer (Fig. 8B). Transport of liquid from the trachea is also noticeably reduced. This can be explained on the basis of Fig. 9A, showing that, rather than decrease, the surface concentration remains nearly constant behind the leading edge. This results in a near-zero surface tension gradient through the intermediate airways (Fig. 9B).

Profiles of $\lambda/\lambda_{ref}$ become almost stationary. Because concentration gradients (and, therefore, surface tension gradients) remain fixed, liquid is continually pumped distally from the same airways. The absence of gradients in the more central airways means that the liquid pumped from the small airways is not replenished and the liquid layer continues to thin. In Fig. 9C, the bulk concentration is shown with similar stationary profiles.

Because gradients are reduced over a large extent of the domain compared with the case of an insoluble surfactant, 95% of the surfactant mass travels no further than generation 2 during the first 40 s (Fig. 10). The bulk of the surfactant is therefore essentially trapped in the central airways and prevented from reaching the periphery by the thinned liquid layer in generations 6–10. However, the leading edge preceding the crest in Fig. 8 has nearly propagated to the periphery in the same time. For comparison, tra-
jectories for a more dilute bulk concentration \( (c = 1 \text{ mg/ml}, \tau_A/\tau_D = 10^{-2}, \text{ and } \beta = 0.3) \) are also plotted in Fig. 10. Here, all portions are carried more deeply into the lungs, with the leading edge reaching the periphery. Although a lower concentration spreads more rapidly, the total amount of surfactant transported is less.

In summary, sorption brings surfactant into the air-liquid interface, keeping surface tension constant and low behind the leading edge. A steep, linear gradient connects this surfactant-rich region with the surfactant-deficient liquid layer ahead of the leading edge, resulting in strong pumping and severe thinning over these airways.

Viscosity. The dynamic viscosity of an exogenous surfactant bolus is controlled by many factors such as lipid concentration and temperature. To examine the effect of viscosity, transport is examined for a higher viscosity \( (\mu = 0.01 \text{ g·s}^{-1}·\text{cm}^{-1}) \). The simulation parameters are \( \tau_A/\tau_D = 10^{-3}, \tau_v/\tau_D = 0.238, H_{bol} = 8, n_{bol} = 4, \text{Bo} = 0, f = 0, \text{ and } \tau_v = 572 \text{ s.} \) As is evident from Fig. 11A, liquid layer thinning is even more accentuated and extends further up the airway tree (generation 4). The gradient in surface tension becomes situated over the thinned region and continues to slowly pump fluid from this location (Fig. 11B). The net effect is a dramatic reduction in the rate at which surfactant is transported toward the periphery. Profiles in \( T/T_{ref} \) are essentially stationary (Fig. 11B), with 95% of the surfactant “trapped” behind generation 3 (Fig. 12). For further comparison, trajectories for a lower viscosity are also plotted in Fig. 12 (\( \mu = 0.01 \text{ g·s}^{-1}·\text{cm}^{-1}, \tau_v/\tau_D = 0.238, \tau_v = 142 \text{ s.} \) In this case the leading edge propagates to the periphery in \(< 2 \text{ s}, \) with 5% residing between generations 5 and 14.

Fig. 7. Trajectories for different percentages of exogenous surfactant mass along airway tree \((x/L_0)\) vs. time \((t/v)\) for an insoluble surfactant. Generation numbers \((1–14)\) are shown along right axis. \( \tau_v = 142 \text{ s.} \)

Fig. 6. Insoluble surfactant. Evolution profiles of liquid layer thickness \((h/h_0), T/T_{ref}, \text{ and } g^* \) vs. \( x/L_0 \). \( \beta = 0.03, \tau_A/\tau_D = 1, \tau_v/\tau_D = 0, H_{bol} = 8, n_{bol} = 4, \text{Bo} = 0, f = 0; h_0 = 10^{-3} \text{ cm, and } \tau_v = 142 \text{ s.} \) Spreading occurs from left to right. Generation numbers \((1–14)\) are shown along top of plots. Profiles for \( t/v = 0, 0.1, 0.2, \text{ and } 0.3. \) \( \tau_v, \text{ viscous spreading; } \tau_A/\tau_D, \text{ ratio of surfactant adsorption to desorption time; } \tau_v/\tau_D, \text{ ratio of viscous spreading to desorption time; } \text{Bo, Bond number; } f \text{ ratio of time for inspiration to time for a complete breath; } t, \text{ time.} \)
Liquid layer thickness. To mitigate the barrier produced by localized thinning, it might be desirable to increase the initial liquid layer thickness as, for example, by pushing the initial bolus into the lung more rapidly. Changing overall liquid layer thickness is examined for $H_{bol} = 26$, with $\tau_A/T_D = 10^{-3}$, $\tau_v/T_D = 2.38$, $H_{bol} = 8$, $n_{bol} = 4$, $Bo = 0$, $f = 0$, $h_0 = 10^{-3}$ cm, and $\tau_v = 142$ s. Generation numbers (1-14) are shown along top of plots. Profiles for $t/v = 0, 0.1, 0.2, and 0.3$.

**Fig. 8.** Effect of sorption. Evolution profiles of liquid layer thickness (A) and details at leading edge (B) vs. $x/L_0$. $\beta = 0.03$, $\tau_A/T_D = 10^{-3}$, $\tau_v/T_D = 2.38$, $H_{bol} = 8$, $n_{bol} = 4$, $Bo = 0$, $f = 0$, and $\tau_v = 142$ s. Generation numbers (1-14) are shown along top of plots.

Extent of initial monolayer. One means of assessing how heterogeneity in the lungs affects transit time is to

**Fig. 9.** Effect of sorption. Evolution profiles of $\Gamma/\Gamma_{ref}$, $\gamma^*$, and bulk concentration ($\alpha/c_{bol}$) vs. $x/L_0$. $\beta = 0.03$, $\tau_A/T_D = 10^{-3}$, $\tau_v/T_D = 2.38$, $H_{bol} = 8$, $n_{bol} = 4$, $Bo = 0$, $f = 0$, $h_0 = 10^{-3}$ cm, and $\tau_v = 142$ s. Generation numbers (1-14) are shown along top of plots. Profiles for $t/v = 0, 0.1, 0.2, and 0.3$. 

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as the surfactant is swept back and forth asymmetrically in time. The effect in the periphery is observed for the case in which the inspiratory phase is short, and the expiratory phase is long (not shown). However, for a reduced viscosity, \( \mu = 0.01 \, \text{g} \cdot \text{s}^{-1} \cdot \text{cm}^{-1} \) (\( \tau_v/\tau_D = 10^{-3} \), \( \tau_L/\tau_D = 2.38 \)), some effects are apparent for the case in which the inspiratory phase is reduced relative to the expiratory phase (\( f = 0.25 \)). These trajectories are presented in Fig. 19 along with results for \( f = 0 \) for comparison. The influence of shear stress is mainly confined to the intermediate airways, where the asymmetry in the flow pattern is readily evident as the surfactant is swept back and forth asymmetrically in time.

Shear stress from airflow. Shear stress from airflow was examined for asymmetric ventilation, reasoning (see Discussion) that asymmetric flow patterns may have a net effect on transport due to nonlinearities in the relationship between shear stress and flow rate. No effect was observed for \( \mu = 0.1 \, \text{g} \cdot \text{s}^{-1} \cdot \text{cm}^{-1} \) (\( \tau_v/\tau_D = 2.38 \), not shown).

The effect of gravity is examined here in the maximized inflow region of the lungs with respect to gravity. Orientation of the infant is thought to favor the dependent region of the lungs with respect to gravity. The effect of gravity is examined here in the maximized situation in which gravity acts along the axis of each airway. The \( \text{Bo} \) for this simulation is 0.15, with \( \tau_{v}/\tau_D = 10^{-3} \), \( \tau_{l}/\tau_D = 2.38 \), \( H_{bol} = 8 \), \( n_{bol} = 8 \), \( \text{Bo} = 0 \), \( f = 0 \), and \( \tau_v = 142 \, \text{s} \). The major outcome of this simulation is that the leading edge of the instilled surfactant, and therefore the gradient in surface tension, is placed over an increasingly thinner liquid layer as \( n_{bol} \) increases (not shown). This results in a diminished upwelling of the liquid at the leading edge and more significant thinning in the distal airways. With a shorter distance to travel, transit time of the leading edge to the periphery decreases (Fig. 15), but the amount of surfactant trapped in the intermediate airways increases (compare with reference curves).

Gravity. Orientation of the infant is thought to influence the distribution of surfactant, favoring the dependent region of the lungs with respect to gravity. The effect of gravity is examined here in the maximized situation in which gravity acts along the axis of each airway. The \( \text{Bo} \) for this simulation is 0.15, with \( \tau_{v}/\tau_D = 10^{-3} \), \( \tau_{l}/\tau_D = 2.38 \), \( H_{bol} = 8 \), \( n_{bol} = 4 \), \( \text{Bo} = 0 \), \( f = 0 \), and \( \tau_v = 142 \, \text{s} \). Figure 16 illustrates the gravitational effects on the liquid layer, whereas Fig. 17 presents concentration data. As shown in Fig. 16, a steep front appears at the leading edge, consistent with earlier results. However, rather than remain stagnant, the liquid in the trachea and intermediate airways flows toward the periphery, propelled by gravity. The slope of the progressing film sharpens into a “kinematic shock.” As time proceeds (Fig. 16), a second wave structure forms further upstream. Flow continues down into the distal airways, with the liquid layer in the proximal airways stabilizing, changing little between \( \tau_{v} = 0.15 \) and 0.2 (Fig. 16B). Gravity has significantly augmented the surfactant transport in the airways, with one-half of the mass residing between generations 6 and 14 (Fig. 18); however, the effect of gravity is not as pronounced at the leading edge, where the liquid layer is much thinner.

Shear stress from airflow. Shear stress from airflow was examined for asymmetric ventilation, reasoning (see Discussion) that asymmetric flow patterns may have a net effect on transport due to nonlinearities in the relationship between shear stress and flow rate. No effect was observed for \( \mu = 0.1 \, \text{g} \cdot \text{s}^{-1} \cdot \text{cm}^{-1} \) (\( \tau_v/\tau_D = 2.38 \), not shown). However, for a reduced viscosity, \( \mu = 0.01 \, \text{g} \cdot \text{s}^{-1} \cdot \text{cm}^{-1} \) (\( \tau_v/\tau_D = 10^{-3} \), \( \tau_L/\tau_D = 2.38 \)), some effects are apparent for the case in which the inspiratory phase is reduced relative to the expiratory phase (\( f = 0.25 \)). These trajectories are presented in Fig. 19 along with results for \( f = 0 \) for comparison. The influence of shear stress is mainly confined to the intermediate airways, where the asymmetry in the flow pattern is readily evident as the surfactant is swept back and forth asymmetrically in time.

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minimal, since the level of shear stress diminishes as the flow velocity drops due to the enormous increase in cross-sectional area.

**DISCUSSION**

A thorough understanding of how surfactant is delivered to different regions of the lungs is becoming more important inasmuch as SRT is now the standard treatment for RDS and may have an expanding role in treating other inflammatory lung diseases (21, 39). To this end, we developed a comprehensive model for studying the dispersal of a surfactant bolus through the lungs. Conceptually, this process is modeled as having two distinct phases. Phase 1 examines the dispersal of a bolus that initially fills the trachea and bronchi. Depending on bolus parameters and the rate of the first inspiration, some fraction of the bolus may be immediately deposited in the alveolar zone, with the remaining portion left lining the conducting airways. This dispersal mode may be the most important, yet the least examined to date.

Phase 2 then occurs, which represents recruitment of air spaces that did not receive surfactant during the first inspiration. This is primarily accomplished by the action of surface tension gradients, which sweep surfactant left in the airways during phase 1 into surfactant-deficient regions. Thus the surfactant that remains in the airways as the bolus is convected through the airway tree becomes the reservoir from which the remaining surfactant-deficient alveoli draw exogenous surfactant. This process constitutes bolus dispersal through the lungs. In the following discussion the physical properties governing distribution of surfactant are examined.
The initial advancement of the bolus through the airways will significantly impact efficacy of treatment. The factors governing deposition are the viscosity and surface tension of the bolus and the volume flow rate at which the first inspiration is given. Together, these variables form a dimensionless parameter known as the capillary number (Ca = \( \mu V/\gamma A \)), where \( A \) is the total cross-sectional area of the lumen at a given generation in the airway tree. In general, the results show that for larger Ca, i.e., high viscosity or fast inspiration, a larger fraction of the bolus is left coating the airways rather than being deposited in alveoli. This is summarized in Fig. 5, showing that as the flow rate and viscosity are increased, the total volume of liquid left lining the airways increases. If the amount of surfactant to be deposited in the alveolar zone is to be maximized (minimal airway deposition), the bolus should be pushed into the lungs at small Ca. For example, if a 1-ml bolus with a viscosity of \( \mu = 0.1 \) \( \text{g} \cdot \text{s}^{-1} \cdot \text{cm}^{-1} \) is inspired at \( V = 2.5 \) and 10 ml/s, twice the amount of surfactant (0.5 ml) is deposited in the alveoli at the lower flow rate (small Ca) of 2.5 ml/s (Fig. 5).

This ability to control initial bolus dispersal has significant clinical implications for SRT. Because SRT can be administered in multiple doses, the clinical objective of each dose could be different and controlled accordingly. For example, consider a two-dose treatment...
ment schedule where the strategy of the first dose would be to maximize alveolar deposition. This would deliver surfactant to open and partially open acinar regions, helping to immediately stabilize these functional end units. This could be accomplished by advancing the bolus with a slow inspiration, using a low-viscosity surfactant formulation or a combination of both (i.e., small Ca). Next, the clinical objective might be to recruit surfactant-deficient terminal units. This could be achieved by providing a surfactant reservoir in the airways leading up to these units from which to draw surfactant. This is accomplished by depositing a larger fraction of the bolus in the conducting airways than in patent alveoli by advancing the bolus at large Ca. Surface tension gradients can then further distribute surfactant to these untreated alveoli (phase 2). In summary, the bolus should be of low viscosity and/or be advanced slowly to maximize deposition in the periphery and of high viscosity and/or advanced rapidly to maximize deposition along the conducting airways.

The fraction deposited in the periphery will clearly depend on the volume of the instilled bolus. For example, if a single dose on the order of 1 ml with \( V = 7-10 \text{ ml/s} \) were administered, Fig. 5 predicts that 80–100% of the bolus would deposit in the airways. In support of this prediction, Winter et al. (44) reported that up to 80% of the surfactant given to fetal rabbits deposited in the conducting airways, speculating that the bolus volume was a factor contributing to the lack of alveolar deposition. Others have stated that 80–90% of a surfactant bolus reaches the alveoli (16). This could occur when large or multiple boluses are used with a larger fraction actually reaching the periphery. For example, if a bolus volume of 4 ml was administered as a single bolus [recommended total volume for a 1-kg neonate (40)] with \( \mu = 0.1 \text{ g·s}^{-1}·\text{cm}^{-1} \) and \( V = 7 \text{ ml/s} \) (approximately the flow rate given clinically, i.e., 7 ml tidal volume over 1 s of inspiration), Fig. 5 predicts that ~0.8 ml will remain in the preacinar airways, with 80% of the surfactant bolus (3.2 ml) immediately depositing in the alveolar zone. This could also occur in the clinical case of four separate aliquots; i.e., one aliquot completely lines the airways with the other three to likely reach the periphery. This is supported by the findings of Gilliard et al. (14), who observed better distribution through the periphery for larger bolus volumes than for smaller volumes.

Before we turn our attention to phase 2 (recruitment), some comments addressing our model in the context of the lung are provided. As described in Model Development, the fraction of liquid left lining the airways was determined from the works of Fairbrother and Stubbs (10) and Taylor (41). These results were chosen for the present model because they were in reasonable agreement with experiments performed in a laboratory airway model (35). However, these past studies were performed in rigid capillary tubes, whereas the pulmonary airways are flexible and may be partially collapsed in disease (19). Given et al. (12) examined the role of flexibility on the liquid layer thickness in a flexible-walled channel. They found that at small Ca (<0.3) the fraction of liquid remaining in a flexible channel was similar to the rigid capillary results. Interestingly, as Ca increased, the fraction of liquid left coating the walls decreased, resulting in a thinner liquid layer than the rigid capillary results used here. This suggests that where Ca is large in the first number of generations, the liquid layer might be thinner than predicted here. This might prevent occlusion and liquid bridging from occurring, allowing more surfactant to be transported distally. The presence of cartilage in these first generations increases airway stiffness, however, reducing the influence of airway compliance. The actual situation is likely to lie somewhere between rigid and flexible extremes. However, once an airway has opened, it will appear to be locally rigid to a passing bolus.

The process of airway reopening to present an approximate rigid section as the bolus passes through and applicability of using the results of Fairbrother and Stubbs (10) and Taylor (41) in the lung can be envisioned as follows. The advancing bolus will occlude the airways over several diameters, with the leading edge pushing air initially in the lungs ahead of it. As the bolus is pushed distally, the pressure in the lungs increases, and collapsed airways will begin to reopen. By the time the trailing edge of the bolus arrives, it is likely that the passing meniscus will travel through patent airways. This is supported by the literature, where reopening times of compliantly collapsed airways in RDS have been estimated to be <0.1 s (12). This is a factor of 10 shorter than inspiratory times of 0.1 s. Thus the airways will likely have time to reopen before the traveling menisci passes. Additionally, as the bolus proceeds distally, the bolus volume decreases. This brings the leading and trailing menisci into closer proximity, which could alter deposition (38). However, a detailed analysis is beyond the scope of this model.

Fig. 19. Trajectories for different percentages of exogenous surfactant mass along airway tree (x(t)/0 vs. time (t/0)). Effect of ventilation: solid lines, \( f = 0.25 \) (tidal volume = 6.6 ml, \( \tau_p = 2 \text{ s}, \tau_v = 14.2 \text{ s} \); dashed lines, \( f = 0 \). Generation numbers (1–14) are shown along right axis.
Phase 2: Recruitment

After the bolus has been pushed into the lungs on the first breath, a fraction of exogenous surfactant coats the airway walls, with the remainder deposited in favorable end units (i.e., those alveoli with a higher compliance). For air spaces not treated by this initial stage of distribution, the only source of exogenous surfactants is the portion left behind in the proximal airways by the passing bolus. With the assumption that surface tension is higher in the untreated air spaces, this reservoir of surfactant will be swept distally into these regions by surface tension gradients. Thus additional alveoli continue to be recruited after the bolus is initially advanced through the airways. This transport by surface tension gradients was examined in a symmetric lung model and is idealized as proceeding through a patent airway tree. Effects of sorption, bolus viscosity, initial liquid layer thickness, initial monolayer length, gravity, and shear stress from airflow on recruitment and transit times to the periphery were presented above.

In SRT, highly concentrated surfactant bolii of ~25 mg/ml are instilled into the trachea and bronchi. After being advanced through the lungs by the first inspiration, an equilibrium surfactant surface concentration forms with respect to the surfactant bulk concentration. As spreading ensues, the local concentrations of the bulk and surface are altered by convection and interfacial exchange. The exchange of a soluble surfactant between the bulk and the interface was captured by using a kinetic sorption model for surfactant in the limit of sorption-controlled transfer. Previous studies do not account for this type of exchange, treating the surfactant at the interface as insoluble or soluble in a liquid layer that is initially surfactant free. In the spreading of a finite mass of insoluble surfactant, surface concentration at the deposition site decreases with time as the surfactant is swept distally by surface tension gradients that exist along the airway tree. In contrast, surfactant adsorption keeps surface concentration (and surface tension) uniform along most of the exogenous liquid layer. More importantly, adsorption maintains a large surface tension gradient at the leading edge of the monolayer, where the exogenous surfactant concentration undergoes a transition to the endogenous concentration. This large gradient helps propagate the leading edge into the periphery; however, it is accompanied by severe thinning of the liquid layer (generations 6–12 in Fig. 8A), which impedes further spreading. Adsorption also abolishes surface tension gradients within the more central airways that might otherwise drive flow along the airway tree, leaving a majority of the exogenous surfactant trapped behind the leading edge of the monolayer. The net result is that although the leading edge may penetrate more deeply into the lungs, much of the surfactant reservoir remains in the conducting airways. All other parameters were examined in conjunction with the effects of sorption.

Increasing the viscosity of the bolus not only increases transport times as a result of a larger viscous resistance in the liquid layer but also affects the physics of spreading by interacting with the sorption time scale. This interplay is readily understood as an extension to the previous comments on surfactant adsorption. As the viscous time scale increases with respect to the sorption time scale, more time is available for surfactant to adsorb onto the air-liquid interface, keeping surface concentration high. The net result is that the surface tension gradient at the leading edge becomes nearly stationary after an initial advancement (Fig. 11B), with strong focal pumping and thinning of liquid over a greater number of airway generations than previously observed (Fig. 11A).

Reducing the viscous stresses that retard flow is an obvious approach for reducing transit times to the periphery. Increasing the liquid layer thickness (e.g., by rapidly advancing the bolus through the lungs) at first appears to accomplish this, since the leading edge propagates more rapidly into the periphery. Yet 95% of the exogenous surfactant deposited in the conducting airways during phase 1 remains proximal to generation 5 after 40 s.

Pulmonary disease is typically heterogeneous, which will lead to varying degrees of penetration of exogenous surfactant during phase 1; transit times to the periphery will thus vary as well. To examine this effect, the leading edge of the exogenous surfactant was positioned in different generations through the symmetric lung geometry. Clearly, transit time is reduced when the monolayer initially penetrates further into the periphery. As observed in Fig. 15, spreading time decreases from 40 to 28 s as the leading edge is moved from generation 4 to generation 10. Additionally, because the exogenous layer extends deeper into the lungs, an overall greater percentage of surfactant is placed distally. However, as observed in all these cases, sorption prevents significant gradients in surface tension from forming in the more central airways, hindering the transport of a majority of surfactant toward the periphery. Indeed, the dominant feature in all these results is the effective barrier to distal transport of surfactant produced by the drastic thinning of the peripheral airway’s liquid layer.

During the administration of surfactant, the neonate is placed in one of four positions, head-down, left or right lateral, or head-up, left or right lateral, before each quarter-dose is instilled into the lungs, then hand ventilated for 30 s before the next quarter-dose is given. The apparent reasoning behind this maneuvering is that gravity plays a role in delivering surfactant to the periphery. Espinosa et al. used results from their single-airway model to examine the influence of gravity on transport, finding that gravity could augment spreading in the trachea, but had minimal effect beyond generation 7 (adult airway). In the present neonatal lung model, gravity was examined for the hypothetical case in which all airways were oriented vertically, maximizing the effect of gravity and, in turn, having the largest impact on delivery rate. Transport from the trachea and through generation 8 was significantly
augmented. This is not surprising, considering that surface tension gradients are nonexistent through the intermediate airways, leaving gravity as the sole driving force. These results suggest that maneuvering the infant does indeed help direct delivery through the first several generations, carrying >50% of the exogenous surfactant past generation 6, rather than leaving it in the trachea and main stem bronchi. Gravity also enhances transport in the smaller airways, actually driving the leading edge of the surfactant front through generation 14. In the absence of gravity, the leading edge plateaus, becoming nearly stationary in approximately generation 13 (Fig. 18). Gravity has little effect, however, on the barrier to transport to the periphery imposed by adsorption.

In a separate set of simulations, shear stress from airflow was examined as a possible means of augmenting transport of surfactant to the periphery on the basis that asymmetric flow profiles during inspiration and expiration might lead to a net enhancement. Enhancement was observed, but the effects were not as large as might have been expected. It can be shown that the increase in transport observed is attributable to nonlinearities in the relationship between shear stress and flow rate and that, without these nonlinear effects, no enhancement can be realized. To illustrate, consider a case with rapid inspiration and slow expiration. On inspiration, although the shear stress is high, the duration of inward-directed flow is short. On expiration, the shear stress is lower, but the duration is increased given that the same total volume that enters the lung must exit. The net effect, in the case of a linear flow-shear stress relationship, is no net augmentation. Alternatively, if the flow-shear stress relationship is nonlinear such that shear stress increases more rapidly than flow rate, the forces driving liquid layer flow into the lungs are increased relative to those causing outflow, and a net increase in the rate of transport toward the periphery is observed. Previous studies (4) have shown that these nonlinearities arise as the local Re increases above ~50, consistent with the expressions used in the present simulations (see Eq. A15). Because Re exceeds this critical value only in the first few generations in the neonatal lung, the effects of asymmetric flow are confined to this region (Fig. 19).

One criterion used for quantifying surfactant transport has been to report the transit time of the exogenous surfactant’s leading edge to the periphery. In this study the monolayer propagates from within the conducting airways to the periphery in 4–170 s (Fig. 12), encompassing predictions of Jensen et al. (26) and Espinosa et al. (9). Transport was characterized by rapid advancement up to ~12 s, with a plateau in spreading at ~40 s. These times appear to be in good agreement with the study of Davis et al. (5), in which transit times of 20 s were observed in piglets, although it is uncertain whether this time represents spreading in the airways or all the way to the alveolus. It is important to note that although transit times are rapid, only a minute fraction of exogenous surfactant reaches the alveolar zone, at least for the period of time studied here. This was revealed by tracking the distance different fractions of exogenous surfactant propagated into the lungs. The drastic thinning caused by adsorption of surfactant to the interface essentially traps the surfactant layer in the proximal airways, isolating this volume from the intended region of delivery. Only gravity and ventilation (applied shear stress) helped carry a greater fraction of surfactant distally, although they did not fully mitigate the trapping effect of sorption over the course of these simulations. An alternative means of transporting the surfactant lining not described in this model will be described below.

The modeling assumptions and limitations have been stated earlier, but some deserve further comment. The numerical model considered the exchange of surfactant with the interface to be sorption controlled, appropriate when transport by sorption is slow compared with diffusion, $\tau_{RB}/TA < 1$. Here, the diffusion and sorption time scales are $\tau_{RB} = b_1/D_{RB}$ and $TA = 1/k_1c_{ref}$, where $b_1$ is the diffusion length scale, $D_{RB}$ the bulk diffusivity, $k_1$ the adsorption coefficient, $c_{ref}$ the bulk surfactant concentration, and $\Gamma_{ref}$ the surface surfactant concentration with $b_1$ scaling as $\Gamma_{ref}/c_{ref}$. For conditions examined here, $k_1 = 10^5$ cm$^2$·g$^{-1}$·min$^{-1}$, $c_{ref} = 10$ mg/ml, $\Gamma_{ref} = 3 \times 10^{-6}$ mg/cm$^3$, and $D_{RB} = 10^{-5}$ cm$^2$/s (28), giving $b_1 = 3 \times 10^{-2}$ cm and $\tau_{RB}/TA = 0.015$. Thus the sorption-limited criterion is satisfied here as well as in the clinical setting ($c = 25$ mg/ml (40)). At low bulk concentrations ($c < 0.1$ mg/ml), however, sorption-controlled transfer will not be valid and a full sorption-diffusion model is required (27).

To produce a tractable model, simplifications from the actual situation and a limited set of parameters were employed. One assumption was that the surfactant-deficient air spaces were open from the start or reopened and remained so over the entire period of the recruitment simulation. In reality, airway obstruction and atelectasis are certain to take place in these surfactant-deficient lungs. In addition, thick layers of the surfactant suspension along the airways will likely be unstable and lead to meniscus formation subsequent to phase 1 of delivery. To avoid this in the simulations, liquid layer profiles with volume below that sufficient for meniscus formation given by Kamm and Schröter (31) ($h/R_c < 0.16$) were specified. However, it was shown in the context of initial bolus dispersal (phase 1) that liquid layers with $h/R_c > 0.16$ are readily formed (Fig. 4D). These liquid layers will result in meniscus formation, especially at low lung volumes near end expiration. If this were to occur, the meniscoid form would be drawn into the lungs on the ensuing inspirations, giving rise to a series of reopening and spreading events. This process of repeated formation and displacement of a meniscoid might actually be key in transporting surfactant.

To assess where the present treatment protocol lies, the viscosity of Survanta was measured at 25 and 37°C (6). The viscosity was ~1.0 and 0.75 g·s$^{-1}$·cm$^{-1}$ at these respective temperatures (~100 and 75 times more viscous than water). Using $V = 7$ ml/s with $\mu = 0.8$ g·s$^{-1}$·cm$^{-1}$, Figs. 4 and 5 clearly suggest that 1) the
surfactant suspension lining the airways after the bolus is advanced distally will collapse to form menisci (h/Rc ≥ 0.16) and 2) a significant quantity of surfactant remains in the airways (Vn = 2 ml). The former statement is supported by the “crackles” heard when treatment is administered (personal observation), likely caused by the repeated opening and closing of menisci as they travel distal and proximal on each ventilatory maneuver. The latter statement suggests that for a 1-ml quarter-dose [1-kg neonate, (40)] nearly the entire bolus will reside within the airway tree, with little being delivered to the alveoli on the first inspiration. However, physical factors not incorporated in this model, namely, nonuniform ventilation due to lung heterogeneity and physical lung asymmetry, are likely to result in surfactant reaching some open end units after the inspiration following bolus injection.

A consequence of the simple symmetric lung geometry used here is the assumption that the surfactant bolus travels an equal distance through all generations. This was a useful assumption for understanding the global spreading process over multiple generations; however, to better quantitate how local heterogeneity affects distribution, e.g., airway vs. acini deposition however, to better quantitate how local heterogeneity affects distribution, e.g., airway vs. acini deposition during phase 1 and daughter-to-daughter or parent-to-daughter competition for surfactant during phase 2, an asymmetric model would be useful. Also, the geometry used here only represents the conducting airways. This was sufficient for making rough estimates of the amount of surfactant reaching the periphery but should be extended to explore spreading through the acinus. In doing so, however, it is important to recognize that scaling adult morphology by one-third is only valid for the preacinar airways (22), so neonatal data would need to be used.

Coupling the present results with our previous study on bolus injection (7) provides a useful framework from which to assess new strategies of surfactant administration. Hypotheses such as maximizing the alveolar deposition by controlling the initial inspiration can be tested in animal models and can be interpreted in the context of this model. Our increased understanding of how surfactant reaches the alveoli continues to be important, inasmuch as surfactant therapy is finding an increasing role in treating inflammatory lung diseases (21, 39).

**APPENDIX**

The governing equations that describe spreading of exogenous surfactant through the lungs via surface tension gradients are summarized. A detailed development of these equations has been reported elsewhere (8). The model considers effects of sorption, viscosity, initial thickness and penetration depth of deposited bolus lining, gravity, and shear stress from airflow. First, the conservation equations for liquid, surfactant, and momentum, then the sorption and shear stress models, and finally the model geometry for a neonate are given. These equations are then cast in dimensionless form, and the governing parameters are identified.

Conservation equations for airway liquid, surfactant, and momentum are formulated for one-dimensional transport. These evolution equations for airway liquid layer thickness and surfactant surface and bulk concentrations are (6)

\[
\frac{dW}{dt} + \frac{1}{W} \frac{dx}{dt} (hWt) = 0 \quad (A1a)
\]

\[
\frac{dG_k}{dt} + \frac{1}{W} \frac{dx}{dt} (G_k W_b) = \frac{dG_k}{dt} \quad (A1b)
\]

\[
\frac{dG_c}{dt} + \frac{1}{W} \frac{dx}{dt} (G_c W_b) = - \frac{1}{h} \frac{dG_k}{dt} \quad (A1c)
\]

where h is the liquid layer thickness, \(G\) is the surface concentration, \(c\) is the surfactant bulk concentration, \(dG_k/dt\) is the kinetic sorption rate, \(x\) is the axial coordinate, \(t\) is time, \(\tilde{G}\) is the average velocity, \(u\) is the surface velocity, and \(W\) is the total airway circumference (sum of all parallel airways at position \(x\) in the symmetric model).

For interfacial kinetics, we employ a dynamic surface tension model developed for lung surfactant (36) that describes how a single-component surfactant exchanges with the interface as a function of surface and bulk concentrations

\[
\frac{dG_k}{dt} = \begin{cases} k_1 c (\tilde{G} - \tilde{G}) - k_2 \tilde{G} & 0 \leq \tilde{G} \leq \tilde{G} \\ 0 & \tilde{G} < \tilde{G} < \tilde{G}_{\text{ref}} \end{cases} \quad (A2a)
\]

\[
\frac{dG_k}{dt} = \begin{cases} k_1 c (\tilde{G} - \tilde{G}) - k_2 \tilde{G} & 0 \leq \tilde{G} \leq \tilde{G} \\ 0 & \tilde{G} < \tilde{G} < \tilde{G}_{\text{ref}} \end{cases} \quad (A2b)
\]

where \(k_1\) is the adsorption constant, \(k_2\) is the desorption constant, \(\tilde{G}\) is the maximum equilibrium concentration as \(c\) approaches infinity (with a corresponding minimum surface tension of 22 dyn/cm), and \(\tilde{G}_{\text{ref}}\) is the maximum close-packed concentration at which the surface tension goes to zero. The model allows exchange with the interface for values of \(\tilde{G} \leq \tilde{G}\). If \(\tilde{G}\) were to rise above \(\tilde{G}\), e.g., as the interface is compressed during an exhalation, the surfactant behaves as if it were insoluble and no exchange takes place, \(dG_k/dt = 0\). In the context of our surfactant transport model, Eq. A2 allows exogenous surfactant to adsorb to the interface from the highly concentrated bulk as spreading occurs, keeping the surface concentration near \(\tilde{G}\) and the surface tension low.

The momentum equation provides a force balance on the liquid along the airways and can be described in Cartesian coordinates by

\[
0 = -\frac{\partial}{\partial x} (p - \rho g x) + \frac{\partial^2 u}{\partial y^2} \quad (A3)
\]

where \(p\) is pressure in the liquid layer, \(g\) is gravity aligned along \(x\), \(u\) is the velocity in the \(x\) direction, and \(x\) and \(y\) are the Cartesian coordinates.

Subject to boundary conditions

\[
\left. u \right|_{y=0} = 0 \quad \left. \frac{\partial u}{\partial y} \right|_{y=h} = \frac{\partial y}{\partial x} + \tau_{\text{air}} \quad (A4a)  \\
\left. \mu \frac{\partial u}{\partial y} \right|_{y=h} = \frac{\partial y}{\partial x} + \tau_{\text{air}} \quad (A4b)
\]

Equation A3 can then be integrated to give \(U\) and \(u\) as

\[
U = -\frac{h^2}{3 \mu} \frac{\partial}{\partial x} (p - \rho g x) + \frac{h}{\mu} \frac{\partial y}{\partial x} + \tau_{\text{air}} \quad (A5a)
\]

\[
u = -\frac{h^2}{3 \mu} \frac{\partial}{\partial x} (p - \rho g x) + \frac{h}{\mu} \frac{\partial y}{\partial x} + \tau_{\text{air}} \quad (A5b)
\]

where \(\tau_{\text{air}}\) is air shear stress and \(y\) is the local surface tension. The pressure in the liquid layer is a function of the local surface tension and local curvature of the air-liquid interface and is approximated by a form of Laplace’s law, \(p = -\gamma R\),
where $R$ is the local airway radius. Only the circumferential component of curvature is considered; the longitudinal contribution to curvature has been considered previously (9) but was found to have a small effect on the shape of the interface and a negligible effect on the spreading rate.

To relate the local surface concentration to surface tension, we use a linear equation of state

$$\gamma = \gamma_{\text{max}} - \left(1 - \frac{1}{\Gamma_{\text{ref}}}\right)\gamma_{\text{max}}$$

such that when $\Gamma = \Gamma_{\text{ref}}, \gamma = 0$.

The contribution of shear stress due to ventilation ($\tau_{\text{air}}$) enters through the boundary condition at the interface. The shear stress can be deduced from the results of Collins et al. (4) on the basis of measurements of pressure drop through a branching network. Combining their results in a force balance between shear stress exerted on the airway walls and the pressure gradient, we obtain

$$\tau_{\text{air}} = \frac{4\mu_a V}{\pi R^2 n_1}$$

where $\gamma_{\text{max}}$ and $n_1$ are the viscosity and density of saturated air, $V$ is flow rate at the trachea, and $n$ is the airway generation number. The local shear stress due to Poiseuille flow is given by Eq. A7a and the local Re is

$$R_{\text{Re}} = \frac{\rho_a V}{\pi \mu_a R^{2-1}}$$

Ventilation is prescribed according to

$$V(t) = \begin{cases} -VT\cos\left(\frac{2\pi t}{T_0}\right) & \text{inspiration} \\ VT\cos\left(\frac{2\pi t}{2T_0(1-f)}\right) & \text{expiration} \end{cases}$$

where $V(t)$ is the time-varying volume into the lung, $2VT$ is the tidal volume, $T_0$ is the time for one breath, and $f$ is the fraction of $T_0$ for inspiration. For example, $f = 0.5$ provides a symmetric breathing pattern, whereas $f = 0.25$ gives an asymmetric pattern with a shorter inspiration. The flow rate is now simply given by $V = dV/dt$.

Last, the wetted surface area of the conducting airways along which the exogenous surfactant flows from the trachea to generation 14 is described by a symmetric Weibel model (43). The adult airways were scaled down by one-third for a neonate, valid for the preinaccr airways (22). A continuous functional representation for the total airway circumference ($W$) along the airway tree is generated from knowledge of the generation number ($n$) as a function of the distance into the lung ($x$) and employing a simple curve fit for the airway radius ($R$). By considering the airways as cylindrical tubes and assuming dichotomous branching, $n$, $R$, and $W$ are

$$n(x) = \frac{[2^{0.71-0.2x}(2.81)][14\{x-5.9\}]^{2.81}}{14\{x-5.9\}]^{2.81}}$$

$$R(x) = 0.3 \exp[-0.4n(x) + 0.13n^2(x)]$$

$$W(x) = 2\pi R(x) x^{2n(x)}$$

All dimensions are in centimeters.

To extract the parameters that influence exogenous surfactant transport, these equations were cast in dimensionless form using the following scales, where an asterisk denotes dimensionless quantities: $h^* = h/h_0$, $R^* = R/L_0$, $W^* = W/L_0$, $x^* = x/L_0$, $V^* = V/L_0^3$, $p^* = p/(\gamma_{\text{max}} h_0 L_0)$, $\mu_{\text{air}}^* = \rho_a^*/(\rho_{\text{air}} h_0 L_0)$, $\gamma_{\text{air}}^* = (\gamma - \gamma_{\text{max}})/\gamma_{\text{max}}$, $\Gamma^* = \Gamma/\Gamma_{\text{ref}}$, $c^* = c/\rho_{\text{air}}^2$, $\tau_{\text{air}}^* = \tau_{\text{air}}/(\gamma_{\text{max}} L_0)$, and $v^* = v/\tau_{\text{dyne}}$, where $\tau_{\text{dyne}} = (\mu_{\text{air}} h_0^2) \gamma_{\text{max}}/L_0$ is the viscous time scale, $h_0$ is a characteristic liquid layer thickness, $L_0$ is the total length of the conducting airways ($L_0 = 8.71$ cm), $\gamma_{\text{max}}$ is the maximum surface tension, $\Gamma_{\text{ref}}$ is the maximum concentration where surface tension goes to zero, and $c_{\text{air}}$ is the characteristic bulk concentration. These relationships give the final governing equations that follow.

Evolution equations

$$\frac{\partial h^*}{\partial t^*} + \frac{1}{W^*} \frac{\partial}{\partial x^*} (h^* W^* u_x^*) = 0$$

$$\frac{\partial \Gamma^*}{\partial t^*} + \frac{1}{W^*} \frac{\partial}{\partial x^*} (\Gamma^* W^* u_y^*) = -\beta \frac{\partial c^*}{\partial x^*}$$

where $\beta = \Gamma_{\text{ref}}/c_{\text{air}} h_0$.

Sorption kinetics

$$\frac{dc^*}{dt^*} = \frac{\tau_{\text{dyne}}}{\tau_{\text{dyne}} + \tau_{\text{air}}} c_{\text{air}}^* (\Gamma^* - \Gamma^*) - \Gamma^*$$

$$0 \leq \Gamma^* \leq 1$$

where $\tau_{\text{dyne}} = 1/k_1 C$ and $\tau_{\text{dyne}} = 1/k_2$.

Momentum

$$u_{\text{air}}^* = -\frac{h^*}{3} \frac{\partial}{\partial x^*} \left[\frac{h_0}{L_0} p_{\text{air}}^* - B_0 x^*\right] + \frac{h^*}{2} \frac{\partial^2 h^*}{\partial x^2} + \tau_{\text{air}}^*$$

$$u_{\text{air}}^* = -\frac{2}{3} \frac{\partial}{\partial x^*} \left[\frac{h_0}{L_0} p_{\text{air}}^* - B_0 x^*\right] + \frac{h^*}{2} \frac{\partial^2 h^*}{\partial x^2} + \tau_{\text{air}}^*$$

where $B_0 = \rho g \beta/\gamma_{\text{max}}$ is the $B_0$ ratio of gravity to surface tension effects, and $p^* = -(\gamma^* + 1)/R^*$.

Equation of state

$$\gamma^* = -\Gamma^*$$

Shear stress from airflow

$$\tau_{\text{air}}^* = A_1 \frac{V^*}{R^* x^{3/2} n_1}$$

where $A_1 = 4\mu_a h_0/\pi L_0$ and $A_2 = h_0^2 \gamma_{\text{max}}/\pi \mu_a$. Ventilation

$$V^* = \begin{cases} \frac{V_T}{L_0^3} \cos \left[\frac{2\pi t^*}{2(T/\tau_{\text{dyne}})}\right] & \text{inspiration} \\ \frac{V_T}{L_0^3} \cos \left[\frac{2\pi t^*}{2(1-f)(T/\tau_{\text{dyne}})}\right] & \text{expiration} \end{cases}$$
where $G$ dipalmitoylphosphatidylcholine, giving unaltered for $n$ at $x$ with the bulk is assumed to exist; it is determined by setting the thickness at the trachea, convenient to describe the liquid layer in terms of an initial bolus. This is derived from the first model presented (see rate at the trachea and viscosity and surface tension of the airflow. The thickness is a function of the flow rate and the increased mobility when endogenous surfactant is present. The initial condition for the liquid layer along the airways is set, at the section (see) $G^*$ is the equilibrium surface concentration. This is the endogenous surfactant concentration. This coats the trachea with a uniform concentration, with a transition beginning at the main carina and extending through the lung. The endogenous concentration remains unaltered for $n > n_{bol}$. An equilibrium surface concentration with the bulk is assumed to exist; it is determined by setting $n^* = 0$ to $n_{bol}$ and given the following expression:

$$c^* = \begin{cases} 
1.0 & 0 < n < 1 \\
1.0 - c^*_t \cos^2 \left( \frac{\pi}{2} \left( \frac{n - 1}{n_{bol} - 1} \right) \right) & 1 < n < n_{bol} \\
\frac{n_{bol}}{n} & n_{bol} < n < 14 
\end{cases}$$

where $c^*_t$ is the endogenous surfactant concentration. This coat the trachea with a uniform concentration, with a transition beginning at the main carina and extending through the lung. The endogenous concentration remains unaltered for $n > n_{bol}$. An equilibrium surface concentration with the bulk is assumed to exist; it is determined by setting $n^* = 0$ to $n_{bol}$ and given the following expression:

$$c^* = \frac{c^*(\tau/D_A)}{c^*(\tau/D_A) + 1}$$

where $\Gamma^* = 0.68$.

Boundary conditions of zero slope for $h$, $c^*$, and $\Gamma^*$ at $x^* = 0$ and $\Gamma^* = \Gamma^*_{ref}$ at $x^* = 1.25$ were specified. Because of the increased mobility when endogenous surfactant is present, the numerical domain was extended ($xL_0 > 1.0$) to prevent influence from the downstream end from feeding back into the domain of interest.

Although the 13 parameters (10 from the governing equation and 3 from the initial conditions) appear daunting, only 6 parameters need special attention. Before the parameters examined are described, the minor ones are addressed and values are set for all simulations.

Parameters $A_1$, $A_2$, $V_t/L_0^3$, $\tau/D_A$, $h_0/L_0$, and $\beta$ enter from the shear stress and ventilation components of the model. For $\mu_b = 1.2 \times 10^{-4}$ g/s $^{-1}$ cm$^{-1}$, $\rho_a = 0.001$ g/cm$^3$ for air, $A_1 = 1.7 \times 10^{-7}$, and $A_2 = 18.2$, $\tau/D_A$ was set at 6.6 cm$^2$ and breathing period $T_0 = 2$ s, resulting in $V_t/L_0^3 = 0.005$ and $\tau/D_A = 0.014$. For $c^*_t$, the endogenous concentration was set such that the surface tension was $63$ dyn/cm ($\Gamma^*_{ref} = 0.1$ and $c^* = 0.002$).

$h_0 = 10 \times 10^{-3}$ cm and $L_0 = 8.71$ cm, resulting in $h_0/L_0 = 10^{-4}$. Lastly, $\Gamma^*_{ref} = 3 \times 10^{-10}$ mol/cm$^2$ (28) and $M = 733$ g/mol for dipalmitoylphosphatidylcholine, giving $\beta = 0.03$.

The remaining six parameters varied are $\tau/D_A$, $\tau/D_A$, $h_0$, $n_{bol}$, $B_0$, and $f$, as given in Table 1. $\tau/D_A$ and $\tau/D_A$ describe the effects of sorption and viscosity, $h_0$ and $n_{bol}$ describe the initial thickness and penetration of the exogenous surfactant, $B_0$ provides a measure of gravitational effects when the airways are aligned vertically with gravity, and $f$ represent the effects of shear stress from airflow.

Samples of Survanta for the viscosity measurements (7) were kindly provided by Richard Slavin (Neonatal Respiratory Therapy, Brigham and Women’s Hospital, Boston, MA). The contributions of Drs. Mary Ellen Avery and Jeffrey Fredberg in providing a clear perspective of the clinical setting and of Dr. Ascher Shapiro in offering modeling suggestions are gratefully acknowledged. This work was supported by National Heart, Lung, and Blood Institute Grant HL-33099 and the Freeman Foundation.

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Received 12 January 1998; accepted in final form 17 September 1998.

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