Lewis-Parker Lecture

Core-Annular Film Flows: A Model of Airway Closure

By David Halpern

Introduction

I would like to thank the AACTM for inviting me to give the Lewis-Parker Lecture for 2006. This article, which is based on the lecture, represents a survey of an area of applied mathematics with which I have been intimately involved over the last sixteen years. My goal here is to provide an overview of the research related to the phenomenon of airway closure. I will start with some things of basic physiological significance to this phenomenon. This will be followed by a description of the physical mechanisms that give rise to airway closure. A range of mathematical models, which consist of systems of partial differential equations and which vary in complexity, will be discussed. Additional information on related research topics can be found in several review articles. See, for example, [1, 2, 3].

Background and Significance of Airway Closure

A healthy human breathes approximately 24 quarts of air per minute, or 75 million gallons of air in a lifetime. The air that we breathe through our noses and mouths is conveyed through a network of branching airways to the alveoli, which are the air sacs at the distal parts of the lung (see figure 1). Gas exchange

occurs in the alveoli. The primary mechanism is diffusion: there is a huge surface area over which gas is in close contact with blood vessels. The smaller airways and the alveoli are coated with a thin liquid layer containing surfactant. Surfactant tends to reduce the surface tension at an air-liquid interface. Normally, molecules within a liquid are attracted equally from all sides (see figure 2). However, those near the surface experience unequal attractions. Molecules near a surface experience a net force which tends to pull them back into the liquid. A simple experiment that conveys the effect of surface tension is the blowing of a bubble at the end of a tube. The surface of the bubble contracts as much as it can. The soap bubble takes a spherical shape since it has the smallest possible surface area for a given volume. It can be shown from thermodynamic principles [4], that there is a pressure difference P across the interface, where

$$P = 2\frac{\sigma}{r} \tag{1}$$

depends on the surface tension σ and the radius of the sphere r. This expression for the pressure difference is known as *Laplace's Law of Pressure.* An analogy is the tension on the surface of a balloon which is balanced by the pressure difference across its surface.

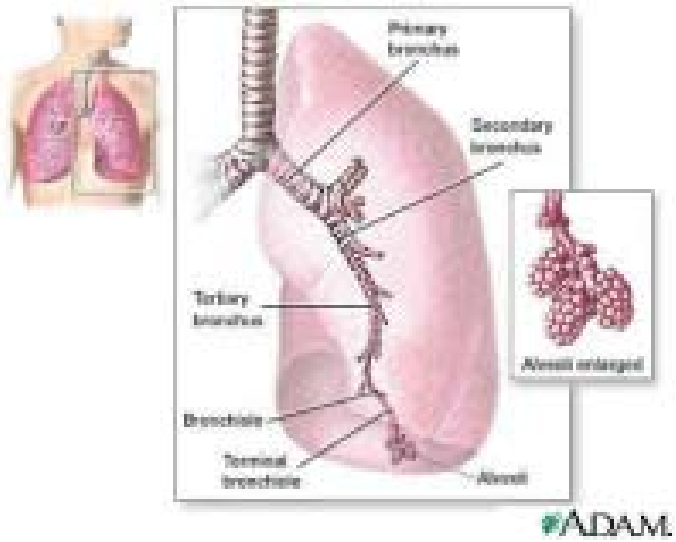

Figure 1: Airway network of the lung. The trachea divides into the primary bronchi, which in turn divide into the secondary bronchi and so on until the terminal bronchioles which are the smallest airways without the alveoli. The terminal bronchioles branch into the respiratory bronchioles (not shown), and these are followed by alveolar ducts and the alveoli.

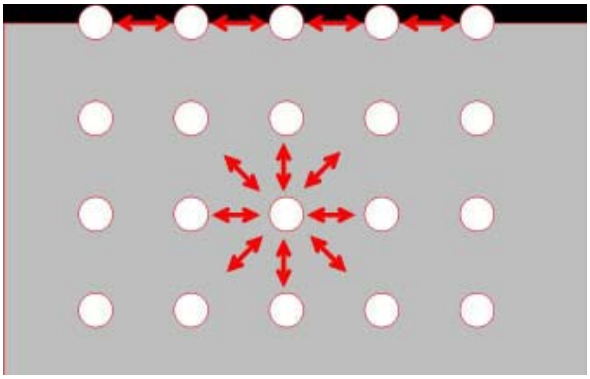

Figure 2: Molecules near the surface experience a net force which tends to pull them back into the liquid. Surface tension is the tendency of liquids to reduce their exposed surface.

A constant surface tension is not desirable in the lung because smaller alveoli will blow up into larger ones as they generate larger pressures. This can also be a problem in the small airways which are also liquid-lined. Consider a rigid cylindrical tube with radius a which is lined with a liquid layer of thickness $b-a$, as shown in figure 3. The difference between the air and liquid pressures, p_{air} and p_a respectively, is

$$p_{air} - p_a = \frac{\sigma}{b}. \tag{2}$$

Suppose the location of the air-liquid interface is perturbed with a disturbance of wavelength λ so that it is now located at $r = b + h(z,t)$ where (r,z) are the usual cylindrical coordinates and $h \sim h_t e^{\frac{i2\pi z}{\lambda}}$. Then the pressure difference is

$$p_{air} - p_a = \sigma\left(\frac{1}{N(b+h)} - \frac{h_{zz}}{N^3}\right) \tag{3}$$

where $N = (1+h_z^2)^{\frac{1}{2}}$ and the subscript z denotes differentiation with respect to z. The first term in equation 3 corresponds to the transverse component of curvature ($\frac{1}{R_1}$ in figure 3) and the second one ($\frac{1}{R_2}$ in figure 3) is the axial component of curvature. The transverse component is destabilizing if the wavelength of the disturbance exceeds the circumference of the core. Thus, flows within the lung's liquid lining can result in the formation of a liquid plug blocking the passage of air. This destabilizing phenomenon due to surface-tension is known as the *Rayleigh instability* [5]. In addition, since the airways are compliant tubes, they can buckle and collapse because a reduction in the film pressure due to the surface-tension instability can lead to a significant pressure drop across the airway wall.

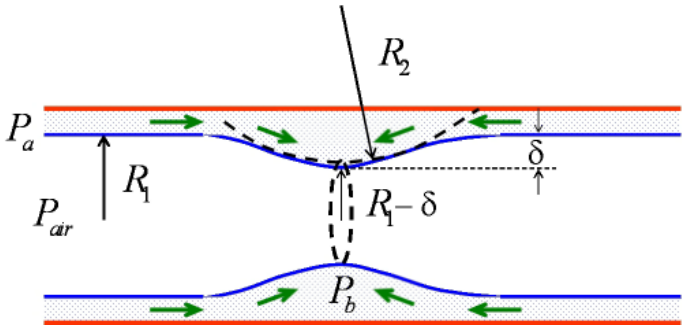

Figure 3: Destabilizing effect of surface-tension at the interface between the air-core and the liquid film coating a cylindrical tube. Here $\frac{1}{R_1}$ and $\frac{1}{R_2}$ are, respectively, the transversal and axial components of curvature.

Normally alveoli do not collapse because of the presence of pulmonary surfactants. These are surface-active molecules produced by type II alveolar cells that like to migrate to air-liquid interfaces. Their proteins and lipids have both a hydrophilic (water-loving) head and a hydrophobic (water-hating) tail. The most energetic configuration is for the heads to be in the water with the tails to stick out in the air. Surfactants reduce the surface tension by interacting with the cohesive force between water molecules at the air-liquid interface. Surfactants can have a stabilizing effect: smaller alveoli no longer have the tendency to empty into larger ones (see figure 4). This is because surfactant molecules are more closely packed, thus reducing the surface tension in smaller alveoli. This stabilizing effect also occurs in the small airways. Consider a thin liquid layer coating a rigid cylindrical tube as shown in figure 5. Based on equation 3, there is a destabilizing pressure difference between peaks and troughs (of the air-liquid interface) that drives flow within the film layer between the peaks and troughs. At the same time, surfactant molecules are swept from the peaks to the troughs by this flow, resulting in a lower surface tension at the troughs compared to the peaks. This surface tension difference induces a surface (Marangoni) flow from troughs to peaks opposing the destabilizing capillary flow.

Airway closure not only occurs in diseases which are due to surfactant deficiency and increase the surface tension, but it can also occur in diseases in which the liquid lining the airways is thicker than normal or the properties of the lining such as its viscosity are not within the normal range. Examples include congestive heart failure, asthma, emphysema and cystic fibrosis. In all these diseases gas exchange is compromised when closure occurs and can be life-threatening.

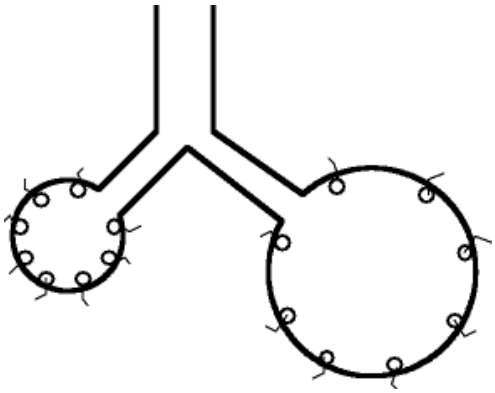

Figure 4: The surfactant molecules on the surface of the smaller bubble are more closely packed. This implies a lower surface tension and therefore the tendency of the smaller bubble to empty is decreased.

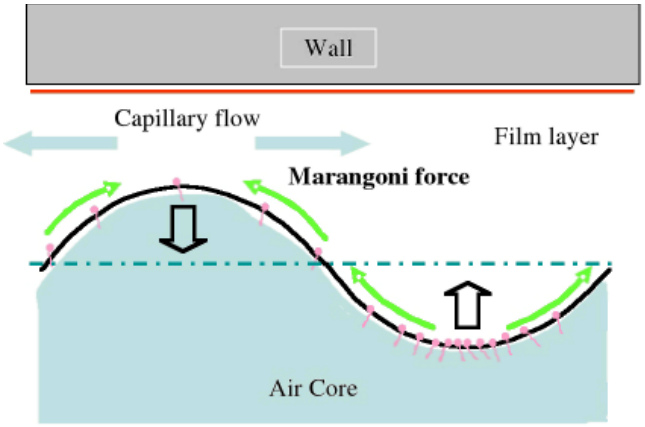

Figure 5: The stability mechanism of surfactant in an airway. Surfactant is swept from peaks to troughs due to the destabilizing surface tension (capillary) flow, producing a surface tension gradient on the air-liquid interface which can then drive a surface flow in the opposite direction to that of the capillary flow.

Previous Theoretical Models of Airway Closure

Airway closure can occur due to the formation of a liquid plug blocking the passage of air as the result of a surface tension instability (the Rayleigh instability). The latter can also provoke the collapse of a compliant airway wall (a capillary-elastic instability). In [6] and [7[it was shown, based on static equilibrium arguments, that if the volume of fluid coating a cylindrical tube exceeds a critical value $V_c = 5.47a^3$, a liquid plug will form. There

have been many theoretical models that have examined the dynamic instability of a liquid-lined tube [8, 9, 10, 11, 12, 13, 14, 15]. Hammond [8] studied the stability of a thin liquid layer coating the inner surface of a cylindrical tube. A partial differential equation that describes the evolution of the deflection of the air-liquid interface was derived using lubrication theory. This is an approximate model which is appropriate for asymptotically thin films. The air-core phase was taken to be passive. In this model, disturbances grew and saturated but closure could not be predicted. Gauglitz and Radke [9] extended the model due to [8] by including a more accurate representation of the interfacial curvature for thicker liquid layers and were able to show that there is a critical value of the thickness parameter $\epsilon \approx 0.12$, the ratio of the film thickness to the tube radius, above which a liquid plug formed. Halpern and Grotberg [11] demonstrated, using an axisymmetric lubrication theory model, that airway wall compliance could magnify the surface tension instability. More recently, Hazel and Heil [16] used a three-dimensional model that allowed for the airway wall to buckle and showed that the critical ϵ could be smaller than that predicted by two-dimensional theory. As explained previously, surfactant can have a stabilizing effect. Using models with varying degrees of complexity, [12, 13, 15] showed that surfactant could delay the onset of closure by approximately a factor of four or five as compared to an interface free of surfactant. However, there are very few models that examine the effects of the air core. Halpern and Grotberg [14] used a lubrication theory model to investigate the effect of an oscillatory core flow and showed that it could prevent closure from occurring by saturating the surface tension instability. Some additional details and results of this model are given in the next section.

A Two-Dimensional Mathematical Model of Airway Closure

We briefly review here some of the previous mathematical models used to describe the phenomenon of airway closure. Consider a thin liquid layer of thickness $a - b$ coating the inner surface of a circular straight tube of radius a. For simplicity we assume the surface tension on the air-liquid interface is constant. The air, which makes up the core phase, oscillates back and forth with a certain frequency and amplitude.

The location of the air-liquid interface is initially perturbed. This initial disturbance drives flows within the liquid layer and the core which will in turn cause the air-liquid interface to deflect so that its radial location at time t^* and axial location z^* is $r^* =$

$R^*(z^*,t^*) = b + h(z^*,t^*)$. By making certain assumptions it is possible to derive a nonlinear evolution equation for $R^*(z^*,t^*)$. The phenomenon of airway closure can then be studied by solving this equation. The fluid motion is governed by the equations for conservation of momentum and mass, also known as the Navier-Stokes and continuity equations. For a Newtonian fluid these are given by

$$\rho\left(\frac{\partial \mathbf{v}^*}{\partial t^*} + \mathbf{v}^* \cdot \nabla^* \mathbf{v}^*\right) = -\nabla^* p^* + \mu \nabla^{*2} \mathbf{v}^*,$$
$$\nabla^* \cdot \mathbf{v}^* = 0$$

where ρ is the density, μ is the viscosity, $\mathbf{v}^* = (w^*, u^*)$ is the velocity vector with axial component w^* and radial component u^*, and p^* is the fluid pressure. In addition, there are boundary and interfacial conditions that are applied at the airway wall and at the air-liquid interface. At the tube wall, $r^* = a$,

$$\mathbf{v}^* = 0, \tag{4}$$

which means no relative motion between the fluid and the tube surface, also known as the no-slip velocity condition, and the wall is impermeable. The interface moves with the fluid and there is no fluid crossing it. Then the total derivative of $r^* - R^*(z^*,t^*)$ is zero, yielding the kinematic boundary condition:

$$\frac{\partial R^*}{\partial t^*} = u^* - w^* \frac{\partial R^*}{\partial z^*}. \tag{5}$$

In addition there is no jump in tangential stress across the interface if the surface tension is constant, and the jump in normal stress is equal to the product of the surface tension and the curvature of the interface (the Laplace law). These two conditions can be expressed as follows:

$$[\mathbf{t}^* \cdot \mathbf{T}^* \mathbf{n}^*] = 0, \quad [\mathbf{n}^* \cdot \mathbf{T}^* \mathbf{n}^*] = \sigma \nabla^* \cdot \mathbf{n}^* \tag{6}$$

where $[A]_f^c = A_c - A_f$ denote the jump in A across the interface, $\mathbf{n}^* = (1 + R_{z^*}^{*2})^{-\frac{1}{2}}(-R_{z^*}^*, 1)$, $\mathbf{t}^* = (1 + R_{z^*}^{*2})^{-\frac{1}{2}}(1, R_{z^*})$ are the unit normal and tangential vectors, and $\mathbf{T}^* = -p^*\mathbf{I} + \mu(\nabla^* \mathbf{v}^* + (\nabla^* \mathbf{v}^*)^T)$ is the stress tensor.

It is convenient to non-dimensionalize the governing equations of motion and boundary conditions and perform a scaling analysis. A small parameter $\epsilon = (a-b)/a << 1$ is introduced which represents the ratio of unperturbed film thickness to the tube radius, and defines a new stretched radial coordinate $y = (a-r)/\epsilon a$.

This, in addition to other simplifications described in [14], allows for analytical expressions for the velocity and pressure fields to be obtained in terms of the deflection $h(z,t)$. These in turn can be substituted into the kinematic boundary condition to yield a nonlinear evolution equation for $h(z,t)$:

(7)
$$\frac{\partial h}{\partial t} = -\frac{1}{3(1-\epsilon+\epsilon h)}\frac{\partial}{\partial z}\left(\left(\frac{\partial \kappa}{\partial z}+\frac{\partial p_c}{\partial z}\right)(1-h)^3+\frac{3}{2}\tau\,(1-h)^2\right)$$

where κ is the interfacial curvature, p_c is the core pressure, τ is the core shear stress and all unstarred variables are dimensionless. Expressions for p_c and τ are given in [14]. This equation can be solved numerically subject to periodic boundary conditions and a small amplitude initial condition. It has no analytical solution. However, at early times, when the deviation from the initial condition is still small, equation 7 can be approximated by the following linear equation:

(8)
$$\frac{\partial h}{\partial t}+\frac{1}{3}\left(\frac{\partial^2 h}{\partial z^2}+\frac{\partial^4 h}{\partial z^4}\right)+A\sin(\Omega t+\phi)\frac{\partial h}{\partial z}=0.$$

The second and third terms represent the transversal and axial components of curvature, and the last term is due to the oscillatory core shear that can be characterized by an amplitude A, a frequency Ω, and a phase shift ϕ. A linear stability analysis is applied in which a small disturbance is expressed in terms of periodic normal modes, and an eigenvalue problem for the growth rate is obtained (see figure 6). This can be done by seeking a solution of the form

(9)
$$h=\hat{h}\ \exp(ikz+st)$$

where k represents a wavenumber. If it is found that the real part of s is positive then the system is unstable, and conversely if the real part of s is negative the system is stable because the disturbance remains small. In this case it can be shown that

(10)
$$s=\frac{1}{3}k^2(1-k^2).$$

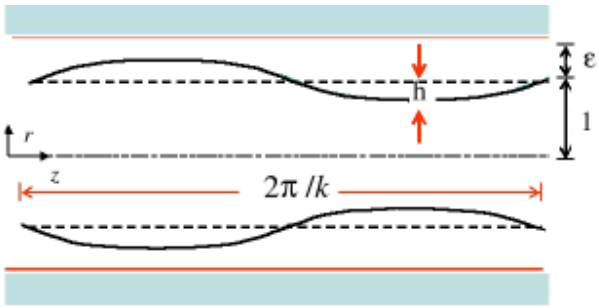

Figure 6: Normal Mode Analysis. Uniform film is perturbed with a sinusoidal disturbance of wavenumber k.

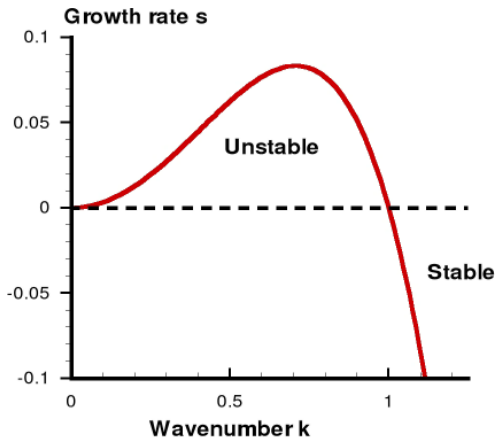

Figure 7: Linear Stability: Growth rate s versus wavenumber k. If $s \geq 0$, system is unstable, and stable if $s < 0$.

Thus the system is unstable for $0 < k < 1$, that is for a disturbance whose wavelength exceeds the circumference of the tube (see figure 7). Note however that the linear stability analysis is only valid while the disturbance remains small. The neglected nonlinear terms which were dropped from the evolution equation (eq. 7) become important once the exponentially growing linear disturbances become sufficiently large. In this case, the nonlinear equation (7) has to be solved numerically. This is accomplished using the method of lines which involves discretizing the spatial derivatives appearing in equation 7 with fourth order finite difference approximations on a uniform grid and then solving the resulting system of ordinary differential equations in time with an implicit backward difference scheme. If there is no core flow, closure of a liquid lined tube can occur if the dimensionless film thickness ϵ exceeds 0.12. Then the minimum core radius R_{min} approaches zero

in finite time. If the frequency of the core flow is sufficiently high, Halpern and Grotberg [14] showed that shear stress supplied by the core to the interface could cause the film to oscillate back and forth in such a way that closure was prevented. Figure 8 shows the shape of the air-liquid interface at different instances of time after this initial exponential growth period. In this figure $r = 1$ defines the tube wall position and $r = 0$ defines the location of the axis of the tube. During the half-cycle shown, the liquid bulge moves from left to right (as indicated by the arrow) with a small wave ahead of it. Behind the advancing bulge, the film thickness (the region between the curve and the wall) decreases monotonically. At this bulge speed, the trailing film is thicker than the precursor film, and so the bulge volume diminishes as shown by an increasing minimum core radius R_{min} for $m = 1$, 2 and 3 (see Figure 9). Then during the turn-around process the magnitude of the shear stress is at its smallest and cannot prevent the growth of the surface-tension driven instability. At this point the bulge grows. However, as the core flow speeds up it again creates a thicker trailing film than precursor film, and the bulge diminishes. With the appropriate tuning of the frequency, the system can thus be stable.

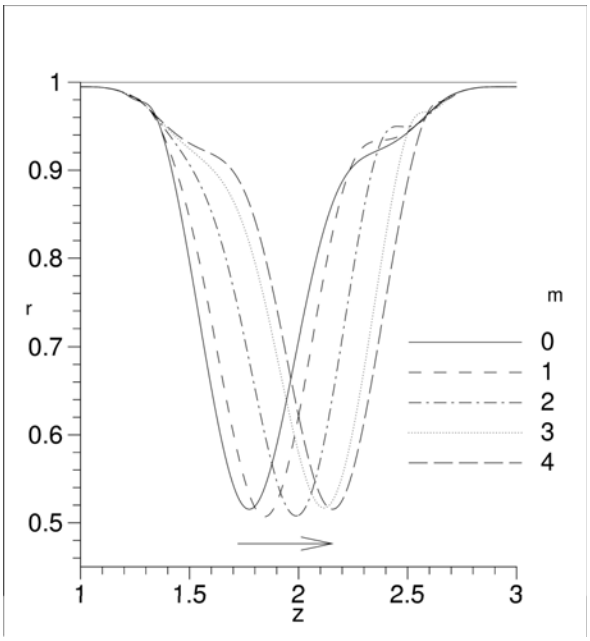

Figure 8: Shape of the air-liquid interface at different times during half a period of oscillation, $t^* = (a/U_{cap})\,(t_0 + m\pi/\,(4\Omega))$ where Ω is a dimensionaless frequency parameter.

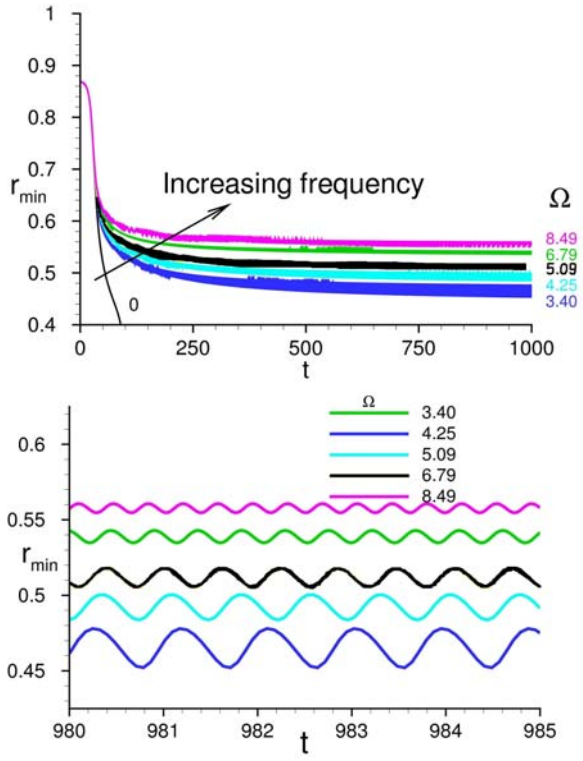

Figure 9: Stabilizing effect of the oscillatory core flow on the minimum core radius, $R_{\min}$ versus time.

Concluding Remarks

The model presented in the previous section has some serious drawbacks. First, the airway was modeled as a rigid cylindrical tube. Including realistic airway wall mechanics is important when considering certain pulmonary diseases. Asthma, for example, is a problem of bronchoconstriction due to active smooth muscle, while emphysema is caused by weakened parenchymal tethering forces. A more realistic mathematical model has to include airway wall compliance and tethering forces. Three-dimensional disturbances need to be considered because airways can buckle if the pressure difference across the airway wall is sufficiently large. Hazel and Heil [16] have a three-dimensional model of airway closure in which an elastic tube may buckle. Their model shows that the critical film thickness required for closure in a buckled tube can be much smaller than a rigid tube with a circular cross-section.

Also, the surface tension was assumed to be constant in the previous section. It is well known that surfactant is present, and can have a stabilizing effect for the case of a passive core [12, 13, 15].

The fluid characteristics of the liquid film lining the airways were also simplified above by assuming that it consisted of a single liquid layer of constant viscosity. In fact, the liquid coating airways consists of a mucus-serous bilayer. The mucus exhibits viscoelastic and non-Newtonian properties, while the serous component is a Newtonian (constant viscosity) fluid. In diseases such as asthma and cystic fibrosis, the mucus has abnormal characteristics. To model airway closure in such settings more realistic rheological models need to be considered.

To conclude, more realistic mathematical models of airway closure need to include more accurate wall compliance characteristics, surfactant effects, more accurate film rheology, as well as the effect of the air-core phase described in the previous section.

1. Acknowledgments

I began working on pulmonary airway closure, the topic of this lecture, as a postdoctoral research fellow in the biofluids laboratory of Professor James Grotberg at Northwestern University in the early 1990s. Dr. Grotberg, who is now at the University of Michigan, has had a profound influence on my research, and we still collaborate on airway closure. I would like to acknowledge many fruitful discussions over the years with many collaborators: Professors D.P. Gaver, O.E. Jensen and A.L. Frenkel, and Drs. H. Fujioka, H.H. Wei, K. Cassidy and B. Hamer.

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