An Investigation
of the Mechanisms Responsible for
Pulmonary Airway Closure

by

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ABSTRACT

Closure of airways in the normal human lung is known to occur near the end of a maximal, unforced expiration. In diseased lungs, airway closure can occur at higher lung volumes, impeding gas transfer between the atmosphere and the bloodstream and therefore endangering health. Historically, the mechanisms responsible for airway closure have not been well understood. It is the objective of the present work to investigate potential closure mechanisms and develop a realistic model of the closure process.

Surface tension-driven instabilities of the thin liquid layer lining the airways may result in the formation of liquid bridges. A numerical model has been developed to examine this closure mechanism. The model accounts for the effects of pulmonary surfactant and the variation of airway dimensions that accompany normal breathing. Predictions of the lung volume corresponding to closure are made for a variety of conditions. Experiments performed to test the validity of several assumptions in the model are also discussed.

An associated model developed to predict the surface tension of the airway liquid lining layer is described. The model accounts for the kinetic mechanisms controlling adsorption and desorption of pulmonary surfactant from the air-liquid interface, and the variation of these mechanisms with lung volume. Moreover, experimental measurements of surface tension vs. interfacial area that validate the model are presented.

A model developed to simulate compliant collapse of the airways is also described. Two approaches to the problem, the first considering parenchymal tethering and the second employing an elastic tube law for pulmonary veins, are considered. Results generated using the first approach are compared with those obtained from the liquid bridging model described above. The combined effect of liquid bridging and compliant collapse is also considered, and it is shown that the dominant closure mechanism is determined by the amount of liquid in the airway.

Finally, an experimental technique employed to assess airway closure and re-opening in excised lungs is presented. Measurements of closing volumes and pressures obtained in a variety of conditions are compared with the predictions from the models described above.

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Dr. Mark Johnson
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"For by wise guidance you can wage your war, and in abundance of counselors there is victory."1

It is doubtful Solomon wrote this with graduate school in mind, but the relevance is clear to me. This project could not have been completed without the assistance of many counselors and helpers that I will now attempt to name.

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Jim Haid first set up the experimental apparatus used in Chapter Five, and Dick Fenner provided a steady stream of good ideas on how to improve it. Kathy Mackenzie helped refine the same apparatus while Hany Michel and Professor C. F. Dewey made their scanner available for some of the associated measurements.

While in Hungary I had the privilege of working with Dr. Zoltan Hantos and Ferenc Peták. They constructed the alveolar capsule oscillation apparatus described in Chapter Six and took the lead in executing the experiments we had designed together.

1Proverbs 24:6
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Finally, I acknowledge that, as Solomon wrote, "A man's mind plans his way, but the Lord directs his steps."² I thank the Lord for His grace and providence which, through the means described above, enabled me to complete this work. This project has allowed me to gain many things, not the least of which is a profound appreciation for the work of the Creator, as revealed in the organ designed by the C. C. D. M. R.³

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²Proverbs 16:9
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Chapter 1

Introduction

Oxygen, the most abundant element on earth (ref. [10]), is essential to human life. To supply the energy needs of the body, oxygen is combined with carbon and hydrogen in each of the 50 trillion cells in the body [Asimov, 1963], forming carbon dioxide and water in the process. The lung conducts the gas exchange necessary to deliver oxygen to, and remove carbon dioxide from, each cell. A schematic view of the oxygen cycle is shown in Figure 1-1. The energetic needs of the body are indirectly provided by the sun, and the individual survives as long as each part of the cycle functions properly.

However, there are several ways in which the oxygen cycle can be disrupted, one of the most common being obstructive lung disease, which ranks second only to heart disease as the cause of Social Security disability benefits in the United States [West, 1987]. As the name suggests, obstructive diseases are characterized by airway obstruction. The airways, shown in Fig. 1-2, are remarkably designed to allow a free flow of gas between the windpipe (trachea) and the airspaces, where gas transfer to and from the blood takes place. Clearly, any obstruction in or collapse of the airways can threaten health and life.

It is known that some airways in healthy individuals will close if lung volume is reduced to sufficiently low values, and that the airways in the base of the lung close first [Engel et al., 1975]. Airway closure has at least two beneficial effects [Greaves et al., 1986], viz. (i) gas exchange between alveolar gas and capillary blood can continue in trapped regions, whereas complete collapse of the airspaces would prohibit this, and (ii) it is much easier to re-inflate a lung with closed airways than one with collapsed airspaces. However, airway closure at higher-than-normal lung volumes, as occurs in chronic obstructive lung disease and emphysema [West, 1987], disrupts gas transfer and can endanger human health.
Fig. 1-1. The oxygen cycle. From Weibel [1984].

Fig. 1-2. The bronchial tree. T=trachea; B=bronchial tree; A=pulmonary artery; V=pulmonary veins. From Weibel [1984].
SCOPE

The mechanisms responsible for airway closure are not well understood, and it is the objective of this thesis to investigate such mechanisms and develop a realistic model of the closure process. Relevant model experiments and animal experiments will be described. Computational models, developed to analyze liquid bridging and compliant collapse mechanisms and the dynamic surface tension behavior of pulmonary surfactant, will also be discussed. The effect of pulmonary surfactant will receive special attention, as it is known to be critical to proper lung function and is likely to influence airway closure.

OVERVIEW

Chapters Two through Six have been written in an article format. As such, each begins with an abstract summarizing its content and concludes with its own list of references. The motivation of each chapter and its relation to the rest of the work will now be described.

Chapter Two focuses on the liquid bridging mechanism that has been shown to close airways in excised cat lungs [Macklem et al., 1969]. The effect of pulmonary surfactant is included, as is the variation of airway dimensions that accompanies normal breathing. Airway closure by liquid bridging during both inspiration and expiration are simulated. This Chapter is an expanded version of reference [8] with an expanded Appendix 2A and additional Appendices 2B and 2C. Appendix 2B explores the possibility of airway closure by liquid bridging during inspiration and was presented at Experimental Biology 93 [7].

Analysis of airway liquid layer dynamics during breathing clearly requires a knowledge of the liquid layer surface tension. It is known that surface tension of this layer varies with lung volume and that for a given lung volume is greater on inspiration than expiration [Weibel, 1984]. No existing model known to us adequately describes the
dynamic surface tension behavior of pulmonary surfactant. This is the motivation for Chapter Three, in which we describe a theoretical model developed to predict the kinetic mechanisms responsible for pulmonary surfactant adsorption and desorption. The model successfully predicts the behavior of surface tension-area loops for TA surfactant, a modified natural surfactant used clinically to treat Respiratory Distress Syndrome; the TA surfactant data was generously provided to us by Dr. E. P. Ingenito of the Brigham and Women's Hospital in Boston. A paper based on this chapter has been submitted to the *Journal of Applied Physiology* [6].

In Chapter Four we consider how an airway might close by compliant collapse. Two approaches to the problem, the first considering parenchymal tethering and the second employing an elastic tube law for pulmonary veins, are presented. The first approach, judged to be the better of the two, is compared with the liquid bridging mechanism. The combined effect of compliant collapse and liquid bridging is considered and it is shown that the dominant closure mechanism is determined by the amount of liquid in the airway.

The validity of some of the assumptions underlying the liquid bridging model described in Chapter Two are tested in Chapter Five. *In vitro* experiments designed to compare the time-scale for liquid bridging in an actual branching network with those calculated from the model are summarized. It is shown that the computed and measured results are in reasonably close agreement although the latter stages of closure proceed more slowly than predicted. This work was presented at the 1993 ASME Winter Annual Meeting [5].

Chapter Six describes experiments performed using the alveolar capsule oscillation apparatus in the laboratory of Professor Zoltan Hantos in Szeged, Hungary. This apparatus can be used to measure the acoustic impedance of the terminal airways and allows one to determine at what lung volume and pressure airway closure and re-opening take place. While the previous chapters consider computational and physical models designed to elucidate the mechanisms responsible for airway closure, the experiments
described in this chapter provide real data on the closure process and shed light on the models. Part of this work has been summarized in Peták et al. [1993].

Finally, Chapter Seven lists the conclusions of this study, considering together the results from each of the chapters. Topics for further investigations are proposed.

REFERENCES


Chapter 2

Airway Closure by Liquid Bridging: a Computational Model

ABSTRACT

A numerical model that simulates airway closure by liquid bridging during expiration has been developed. The effects of both surfactant and time-varying geometry have been included; the model determines the liquid layer flow resulting from a surface tension-driven (Rayleigh) instability, and the computation traces the film's development all the way to closure, yielding pressure, velocity, surface shape and surfactant concentration distributions. It is found that surfactant is effective in retarding or eliminating liquid bridging through the reduction of the mean surface tension and the action of surface tension gradients. The former effect is also critical in minimizing the magnitude of the negative pressure in the liquid layer and thus presumably in reducing the tendency for airway compliant collapse.
INTRODUCTION

Airways in the lower regions of the lung are known to close upon expiration to low lung volumes [Engel et al., 1975]. The mechanisms responsible for airway closure, however, remain to be fully elucidated. In this chapter we consider one possible closure mechanism, that of liquid bridging (Fig. 2-1) and simulate, by means of a theoretical model, the effect of pulmonary surfactant on closure during expiration. Lung volumes at closure are determined in a variety of circumstances.

Liquid bridging is caused by a surface-tension driven instability of the thin liquid layer that lines the pulmonary airways. This layer prevents dehydration of the pulmonary epithelium and provides a pathway for the clearance of particles from the lung. The associated gas-liquid interface exhibits a surface tension that is altered by the presence of a surfactant secreted primarily by type II epithelial cells in the alveolar region [Weibel, 1984]. This surfactant is composed largely of phospholipids such as dipalmitoylphosphatidylcholine (DPPC) but also contains small amounts of protein [Hawgood, 1991, & Schürch et al., 1989]. An increase in surfactant concentration causes the surface tension to fall; in particular, a marked drop occurs during expiration, since the corresponding fall in the surface area of the liquid layer is accompanied by a rise in surfactant concentration. The surface tension approaches zero when the lung is deflated below approximately 60 % Total Lung Capacity (TLC) [Weibel, 1984]. Although the amount of surfactant in the small airways is unknown, the existence of a continuous liquid layer would assure its presence at some level of concentration; indeed, Macklem et al. [1969] report that the surface tension of the liquid lining the peripheral airways is similar to that in the airspaces.

Consider first what would be expected to happen during expiration if there were no surfactant present so that the surface tension is uniform. As lung volume falls, the radii of
the airways are reduced, increasing the curvature of the air-liquid interface. This rise in curvature makes the negative pressure in the liquid increase in magnitude. At the same time, tethering forces on the external surface of the airways fall due to the gradual relaxation of tension in the lung parenchyma. This combination of reduced inner wall pressure and relaxation of tethering forces decreases the effective transmural pressure of the

Fig. 2-1. Schematic of a sectioned airway showing airway liquid in (a) unduloid and (b) liquid bridge configurations. \( a \) = radius to free surface, \( s \) = radius to airway wall, \( h = s - a \) = film thickness, \( 2L \) = airway length.
airway and promotes the tendency of the airway to buckle, producing what is referred to as "compliant collapse". This closure mechanism will be addressed in Chapter Four.

A second mode of airway closure can also occur, particularly in diseased conditions that lead to accumulation of excess airway liquid. It has been observed [Kamm and Schroter, 1989] that a thin liquid layer on the inner wall of a small tube can undergo a fluid dynamic instability leading to total obstruction of the tube by a liquid plug or "bridge", provided there is sufficient liquid present. This phenomenon is similar to the well-known Rayleigh instability [Rayleigh, 1879] that causes a cylinder of liquid to break up into a sequence of droplets with lower aggregate surface area if the cylinder length exceeds its circumference. On the inner wall of a tube, the instability leads to the formation of a liquid bridge or an unduloid (Fig. 2-1), depending on how much liquid is present. Unduloidal surfaces [Everett and Haynes, 1972] are axisymmetric and possess constant mean curvature and lower surface area than the original cylinder; they will form if there is insufficient liquid to form a bridge. For tubes with length-to-diameter ratios in the range found in pulmonary airways, a bridge is formed if the amount of liquid in the tube, $V_{liq}$, is greater than $5.6s^3$, where $s$ is the tube radius [Kamm and Schroter, 1989]. If this condition is not met in a particular airway at TLC, it may be met after expiration to a lower lung volume with reduced airway radius. Recent in vitro experiments suggest that, given a liquid layer thickness of about 10 μm at TLC, and a liquid layer instability that proceeds very rapidly, airway closure can take place at a lung volume of about 25% TLC, approximately equal to residual volume [Kamm and Schroter, 1989]. Numerical simulations have also been performed, analyzing the process of liquid bridge formation [Johnson et al., 1991, Kamm and Johnson, 1990] and suggesting that the time-scale for this fluid dynamic instability is inversely proportional to the surface tension and small compared to the breathing period provided that no surfactant is present.

In reality, both compliant collapse and liquid bridge formation will tend to occur simultaneously although their relative importance will depend on local factors such as
airway stiffness and liquid volume. Halpern and Grotberg [1992] considered the additional role of airway compliance in liquid bridge formation and demonstrated that compliance can both augment the rate of closure by liquid bridging and cause it to take place at a higher lung volume. Both processes are more likely to occur in diseased lungs that have a surplus of airway liquid and/or species in the airway liquid that interfere with normal surfactant function [Hall et al., 1990, Hawgood, 1991].

Otis et al. [1990] analyzed the effect of surfactant on liquid bridge formation in airways of fixed dimension while Halpern and Grotberg [1993] treated a similar problem in a compliant airway. In this paper we extend the theoretical model of bridge formation, developed for constant surface tension by Johnson et al. [1991], to include surfactant effects in tubes whose dimensions fall with time as occurs in airways during expiration. Predictions are thereby made of the time to airway closure and of absolute lung volume at closure for various expiration rates.

It will be shown that surfactant has two effects on the closure process. First, surfactant causes an overall reduction in surface tension as lung volume decreases. This reduction in tension does not affect the critical value of $V_{liq}/s^3$ necessary for bridge formation, but does produce a substantial increase in the time-scale for bridge formation. Thus lung volume will fall further before a bridge forms. Second, axial variations in concentration cause surface tension gradients that impede the movement of the liquid layer, reducing the lung volume at closure still further.

METHODS

A single airway is modeled as a circular cylinder (Fig. 2-1), whose radius $s$ and length $2L$ are taken to decrease in proportion to the $1/3$ power of lung volume [Hughes et al., 1972], but remain proportional so that airway shape is preserved:
\[ s = s_0 \left( \frac{V_L}{TLC} \right)^{1/3} \]  
(2.1)

\[ L = L_0 \left( \frac{V_L}{TLC} \right)^{1/3} \]  
(2.2)

The airway dimensions are chosen to be typical of a terminal or respiratory bronchiole with initial radius \( s_0 = 0.025 \) cm, initial length \( 2L_0 = 0.150 \) cm, and initial air-liquid interface radius \( a_0 = 0.024 \) cm, so that the initial film thickness = \( s_0 - a_0 = 10 \) \( \mu \)m.

In the expiration simulations we let lung volume, \( V_L \), decrease from Total Lung Capacity linearly in time (Fig. 2-2):

\[ \frac{V_L}{TLC} = 1 - \frac{t}{T_{exp}} \]  
(2.3)

(In Appendix 2B of this chapter we consider airway closure during both expiration and inspiration, and so allow the lung volume to vary sinusoidally in time.) \( T_{exp} \) is the hypothetical time it would take to empty the airway (and entire lung) of all air if no liquid layer were present; we performed simulations for values between 0.05 s (for a very fast expiration) to 5 s. Calculations terminate when closure takes place at \( t = t_E < T_{exp} \), typically at lung volumes between 10 and 30\% TLC; we will call the absolute lung volume at which closure occurs \( V_{LE} \) in reference to point \( E \) labeled in Fig. 2-2.

The amount of liquid in the airway is taken to be constant over the time-scale \( T_{exp} \) and has been set by the specification of \( a_0 \), \( L_0 \), and \( s_0 \). For closure to occur, two conditions must be satisfied: the first, the Rayleigh condition, will be met when \( L > \pi a \) which for our parameters corresponds to

\[ \frac{V_L}{TLC} < \left( 1 - \frac{a_0}{s_0} \right)^2 / \left( 1 - \frac{L_0}{\pi s_0} \right)^2 \]  
(2.4)
The second condition is that sufficient liquid be available to form a bridge; it is met when the airway radius $s$ decreases to the point where $V_{liq} / s^3 > 5.6$ so that

$$\frac{V_L}{TLC} < \frac{V_{liq}}{5.6s_0^3} = 6\pi(1 - \frac{a_0^2}{s_0^2}) / 5.6$$

(2.5)

Fig. 2-2. Expiration modeled as linear decrease in lung volume ($V_L$) with time, starting from Total Lung Capacity (at time = 0, from A). Rayleigh condition first satisfied at B; minimum surface tension $\gamma_{min}$ first reached at C; sufficient liquid for closure condition first met at D; airway closes at E. The dotted curved shows schematically how lung volume at closure, $V_{LE}$, varies with $T_{exp}$; such a curve is an output of the model. A schematic of a sectioned airway is shown at three times during the expiration. $a_0 = 0.024$ cm, $s_0 = 0.025$ cm, $L_0 = 0.075$ cm, $\Gamma_0 = \Gamma_A = 1.0$. 
For the parameter values we have chosen, the Rayleigh condition is satisfied for lung volumes below 89% TLC; that of sufficient liquid for closure is met for volumes below 26% TLC.

Once these conditions are met, a bridge can form but takes a finite time to do so. If the expiration rate is relatively high, the lung will contract to a volume significantly less than 26% TLC before airway closure occurs. Alternatively, if the rate of bridge formation is high (due to high surface tension and/or low liquid viscosity) relative to the expiration rate, the bridge may form as soon as the conditions are met, i.e., at 26% TLC.

Figure 2-2 shows points B and D at which the Rayleigh and sufficient liquid for closure criteria are satisfied, respectively. Closure takes place at E, and the dotted curve is the locus of E as $T_{exp}$ is varied; such a curve is an output of the model and will depend on the surface tension behavior of the lining layer.

The liquid is taken to have density $\rho = 1$ g/cm$^3$ and viscosity $\mu = 0.01$ dyne-sec/cm$^2$, values close to those of water. These are reasonable values for the most peripheral airways because of the relative absence of mucus-secreting cells beyond the fifteenth generation [Clarke & Pavia, 1991]. In simulations with variable surface tension, the surface tension at TLC is taken to be 30 dynes/cm, as in rat lungs at such a volume [Schürch, 1982].

It is assumed that the surfactant is concentrated in an insoluble monolayer at the air-liquid interface so that the total amount of surfactant in the interface remains constant. In the simulations we solve for the local dimensionless surfactant surface concentration $\Gamma$ and then assign a corresponding surface tension to this location through the relation shown in Fig. 2-3, based on data for DPPC [Schürch et al., 1989]; the data have been fit to a curve with the minimum surface tension set equal to 1 dyne/cm ($\gamma = \gamma_{min} = 1$ dyne/cm for $\Gamma > \Gamma_C$). Note that this minimum value, while not unrealistic, is arbitrarily chosen and could range between zero and 5 dyne/cm.
Fig. 2-3. Surfactant equation of state which yields surface tension $\gamma$ for a given dimensionless surfactant surface concentration $\Gamma$. A curve is fit through data for DPPC, marked with circles, and is used as a model input. Minimum surface tension $\gamma_{\text{min}}$ is taken to be 1 dyne/cm; the surfactant concentration has been normalized with the dimensional concentration corresponding to 30 dynes/cm, $\Gamma^* = 2.3 \times 10^{18}$ molecules/m². A, B, C, and D mark the same events as in Fig. 2-2. DPPC data from [Schürch et al., 1989]. As $\Gamma \to 0$, $\gamma \to \gamma_{H_2O} = 72$ dynes/cm.

The letters A, B, C, D, and E in Figs. 2-2 and 2-3 represent the following: A, the start of the simulation at TLC; B, the Rayleigh condition first satisfied; C, the minimum surface tension value $\gamma_{\text{min}}$ first reached; D, the sufficient liquid for closure condition first satisfied; and E, airway closure. The positions of these events on the curves are fixed by selection of the initial surface tension $\gamma_A$ and the initial dimensions of the airway and liquid layer; in addition, the lung volume at point E will vary with $T_{\text{exp}}$, but that at B, C, and D will not. Each of the events identified by the letters A-E corresponds to a point on the line in Fig. 2-2. However, spatial nonuniformities in surfactant concentration cause each of the letters B-E to be associated with a segment of the curve in Fig. 2-3; the arrows for B and C in this figure point to the mean surfactant concentration at times $t_B$ and $t_C$, respectively.
A is associated with a point in this figure because the surfactant concentration is initially uniform.

The dynamic equations governing the evolution of the liquid layer are set out in full in Appendix 2A. They represent conservation of liquid mass, conservation of surfactant and conservation of liquid momentum (balancing fluid inertia, the pressure gradient driving the flow, the surfactant-induced shear stress, and the viscous resistance). Forces on the liquid layer caused by gravity are taken to be negligible in comparison to those caused by surface tension. The pressure in the liquid layer is a function of the interfacial curvature and tension and is calculated using a form of Laplace's Law.

**Calculation Procedure**

The basic equations were first manipulated to put them in the form most suitable for numerical computation; this process is described in Appendix 2A. Then the equations were integrated numerically by the same technique as employed by Johnson et al. [1991].

The initial condition for each simulation was the same. The tube radius, \( s_0 \), was taken to have the value corresponding to \( TLC \). However, the interface radius, \( a \), was taken to be slightly non-uniform, equal to the appropriate initial undisturbed radius, \( a_0 \), plus a small sinusoidal perturbation of amplitude \( 0.001a_0 \) and wavelength equal to the tube length \( 2L_0 \) since non-uniformity of radius is necessary to trigger the growth of the instability. In nature or in a laboratory experiment, small fluctuations are ubiquitous and a perfectly cylindrical interface is never achieved; if an instability is possible it will occur. A small initial perturbation must be specified, however, for computer simulations in which the expiration rate is zero, i.e., \( T_{exp} \to \infty \). In such simulations, the time to closure decreases logarithmically with the perturbation amplitude. For simulations with finite expiration rates, a perturbation occurs naturally due to the wall movement so that no initial perturbation need be specified. For the sake of uniformity, however, the same initial
perturbation was used in all the simulations, regardless of expiration rate. The choice of a sinusoidal perturbation of wavelength equal to the length of the tube is most appropriate because, as the mean radius is reduced, an instability first becomes possible when the circumference $2\pi a$ falls below the length $2L$, and the wavelength of the disturbance that can then grow is indeed $2L$.

**RESULTS**

We first examine a relatively slow expiration, with $T_{exp} = 5 \text{ s}$, starting at point A in Fig. 2-2. The initial perturbation has set the radius $a$ at the tube center ($\xi = 0$) to be less than that at the ends ($\xi = \pm l$). For $t > t_B$ the Rayleigh condition is satisfied and so the minimum pressure is also at $\xi = 0$. This pressure distribution tends to drive liquid towards $\xi = 0$, causing the difference in film thickness between the tube ends and center to be magnified. However, these liquid velocities are initially very small relative to the airway contraction rate, so the interface remains nearly cylindrical and $a$ decreases almost uniformly as the airway contracts, as shown in Fig. 2-4(a) for $t \leq 3 \text{ s}$. Once $t > t_D = 3.68 \text{ s}$ (or $V_L / TLC < 0.264$) the condition of sufficient liquid for closure has been met and a bridge can form; the finite rate of growth of the instability, however, causes bridge formation to lag behind this event, and is completed at $\xi = 0$ after the lung has further contracted to $V_L = V_{LE} = 0.186TL$ (at $t = t_E = 4.07 \text{ s}$).

As the airway contracts, the dimensionless surfactant concentration $\Gamma$ rises as shown in Fig. 2-4(b); the flow towards $\xi = 0$ carries surfactant to that position, eventually making the maximum concentration there very evident. A rise in $\Gamma$ causes the surface tension $\gamma$ to fall through the relationship shown in Fig. 2-3. This figure reveals that for $\Gamma > \Gamma_C = 1.3$ the surface tension is constant at $\gamma_{min} = 1 \text{ dyne/cm}$; hence the large gradient in $\Gamma$ at $t = 4 \text{ s}$
Fig. 2-4. Results for expiration with surfactant (variable surface tension). (a) radius to air-liquid interface, (b) dimensionless surfactant surface concentration, (c) surface tension, and (d) liquid layer pressure (980 dynes/cm² = 1 cm H₂O) vs. normalized axial position at t = 0.00 s, 0.55 s, 1.50 s, 3.00 s and 4.00 s. T_{exp} = 5.00 s, Γ₀ = 1; t_{B} = 0.55 s, t_{C} = 1.54 s, t_{D} = 3.68 s, t_{E} = closure time = 4.07 s, V_{LE}/TLC = 0.186.
Fig. 2-4 (continued). For caption, see previous page.

(Fig. 2-4(b)) does not result in a surface tension gradient; instead, \( \gamma \) is uniform and equal to \( \gamma_{\text{min}} \). The surface tension distribution for this and previous times is shown in Fig. 2-4(c), revealing a thirty-fold decrease in \( \gamma \) as \( \Gamma \) rises to \( \Gamma_C \) and higher values.
This large drop in $\gamma$ makes the magnitude of the film pressure $p$ drop because $\gamma$ and $p$ are proportional. Moreover, this reduction in the absolute value of $p$ reduces the axial pressure gradient driving the flow, so the closure process is retarded. Figure 2.4(d) illustrates that the pressure is initially negative, of relatively large magnitude, and nearly constant at $p = -1250$ dynes/cm$^2$. The magnitude of the pressure drops rapidly as the airway contracts, and once $\gamma_{\text{min}}$ is reached at $t = t_C$, it increases a small amount with further contraction because the surface curvature continues to increase while $\gamma$ remains constant. The pressure profiles appear to be flat, but an axial pressure gradient exists and grows through the whole expiration; for $t > t_C$ the gradient drives liquid towards the low pressure at $\xi = 0$, causing velocity profiles like those shown in Fig. 2.5. These profiles show all the liquid in the airway flowing towards $\xi = 0$, and the velocity of the air-liquid interface approximately $3/2$ the mean, the expected value for the flow of a viscous layer of liquid with no stress applied at the interface $r = a$.

Although the concentration profiles in Fig. 2.4(b) also appear flat until $t = 3$ s, axial variations in concentration exist through the whole expiration, with the largest concentration at $\xi = 0$ due to surface contraction and convection. For $t < t_C$ this variation gives rise to minute surface tension differences between $\xi = 0$ and $\xi = \pm l$, on the order of $10^{-6}$ times the mean surface tension. Even a gradient of this magnitude, however, exerts a significant tangential force on the interface that can pull surface fluid from regions of low tension ($\xi = 0$) towards those of high tension ($\xi = \pm l$). Hence the surface tension gradient opposes the pressure gradient by impeding surface motion towards or causing flow away from the minimum pressure at $\xi = 0$. Once the surface tension reaches its minimum value at $t = t_C$, the gradient in surface tension disappears and the liquid velocities become as shown in Fig. 2.5. While it is present, the surface tension gradient tends to hinder flow towards $\xi = 0$ and so retard the closure process.
Fig. 2-5. Mean ($\overline{V}$) and surface ($V_a$) axial velocity vs. normalized axial position at $t = 1.55 \text{ s} > t_C$. In the absence of the surface tension gradient, the surface velocity is $3/2$ the mean and is directed towards the point of lowest pressure ($\xi = 0$) as shown. For $t_B < t < t_C$ surface tension gradients exert tangential stresses on the surface that are directed away from the point of minimum pressure, tending to drag liquid away from this point and so retard the closure process.

The surface tension gradient returns at the very end of the simulation, as can be seen by the decreasing concentrations at $\xi = \pm l$ between $t = 3$ and $4 \text{ s}$ (Fig. 2-4(b)): convection towards $\xi = 0$ causes the surfactant concentration at the airway ends to eventually fall below $\Gamma_C$, making variations in surface tension reappear. However, because the liquid velocities near closure are very large, this late-appearing gradient acts for only a small fraction of the closure time and therefore has a minimal effect on the lung volume at closure.
Fig. 2-6. Results for expiration with $\gamma=$ constant=30 dynes/cm. (a) radius to air-liquid interface, (b) liquid layer pressure vs. normalized axial position in airway at $t = 0.00$ s, $1.50$ s, $3.00$ s, and $3.65$ s. The rate of growth of the instability is higher than in the surfactant case (Fig. 2-4) because of the higher surface tension, and the bridge is formed at nearly the highest lung volume allowed by the sufficient liquid condition. As lung volume falls, the increasing interfacial curvature causes the negative pressure in the liquid layer to increase in magnitude. Axial variations in $a$ and $p$ become apparent as the instability grows. $T_{exp} = 5.00$ s, $t_B = 0.55$ s, $t_C = 1.54$ s, $t_D = 3.681$ s, $t_E =$ closure time $= 3.683$ s, $V_{LE}/TLC = 0.263$. 
If the surface tension is held constant at $\gamma = 1$ dyne/cm for the entire expiration, the interfacial shape profiles are quite similar to those obtained in the surfactant simulation (Fig. 2-4(a)) and $V_{LE} = 19.1\%$ TLC, slightly greater than the $V_{LE}$ of 18.6\% TLC obtained with surfactant. Figure 2-6(a) illustrates how a bridge develops if the surface tension remains constant at $\gamma = 30$ dynes/cm for the entire expiration. This relatively high tension accelerates the instability, causing closure at 26.3\% TLC, immediately after the sufficient liquid for closure condition is met at $V_L = (V_L)_D = 26.4\%$ TLC. This lung volume at closure is approximately 8\% TLC greater than would have obtained if surfactant were present. The negative pressure in the liquid layer, shown in Fig. 2-6(b), is not moderated by a decreasing surface tension and so rises to large magnitudes as lung volume decreases.

Simulations of faster expirations for the same three surface tension conditions yield the results in Fig. 2-7, revealing that $V_{LE}$ increases with increasing $T_{exp}$ and surface tension. The $V_{LE}$ values obtained with the variable surface tension nearly coincide with those obtained for $\gamma = constant = \gamma_{min} = 1$ dyne/cm, with a small difference that becomes apparent as $T_{exp} \rightarrow 5$ s. It is surprising that the variable surface tension condition yields a $V_{LE}$ that is as low or lower than that obtained with $\gamma = \gamma_{min}$. This can be explained, however, in that in the former case, a surface tension gradient is operative for $t < t_C$ and counteracts the pressure gradient, which is small because large variations in curvature have not yet developed. Hence for $t < t_C$ more flow in the direction of bridge formation has occurred in the $\gamma = \gamma_{min}$ case than in the variable surface tension case. For $t > t_C$ the surface tension conditions for the two cases are essentially identical, and because bridge formation in the $\gamma = \gamma_{min}$ case has received a head start, it will have a slightly higher lung volume at closure.

As mentioned previously, all simulations were started with a radial perturbation of 0.001$a_0$. If a larger value were used, the lung volume at closure would increase. However, for perturbation amplitudes ranging from 0 to 0.01$a_0$, $V_{LE}$ varies by no more than $\pm 2.5\%$ TLC about its mean value.
Fig. 2-7. Lung volume at closure as % TLC vs. $T_{exp}$ for $h_0 = s_0 - a_0 = 10 \mu m$. Results for constant surface tension ($\gamma = 1$ and 30 dynes/cm) and variable surface tension ($\gamma = \gamma(\Gamma)$ in Fig. 2-3) show that for $T_{exp} > 2$ s, a surface tension of 30 dynes/cm or more will cause airway closure as soon as the sufficient liquid for closure condition has been satisfied. Lower values of the surface tension, made possible by surfactant, reduce $V_{LE}$ significantly. The two horizontal lines mark the limits of $V_{LE}$ for the given airway and liquid layer dimensions.

**DISCUSSION**

In this chapter, we have examined airway closure via a theoretical model of a liquid-lined tube whose dimensions change in a manner similar to that for a single pulmonary airway during expiration. The consequent reduction in airway volume causes the airway film to thicken, producing a situation in which small perturbations in film thickness can grow via the Rayleigh instability, eventually forming a meniscus that bridges the tube, producing airway closure.
The effects of pulmonary surfactant

The studies reported here were undertaken to determine whether the presence of pulmonary surfactant in the small airways might play an important role in stabilizing the liquid layer and preventing airway closure in a model of a contracting airway. The results of these numerical simulations show that surfactant, at a concentration similar to that in the respiratory zone, can indeed influence the lung volume at which closure occurs by liquid bridging.

The curves in Fig. 2-7 reveal the effect of surface tension and expiration rate on $V_{LE}$. As $T_{exp} \to 0$, the rate of expiration is so great that the liquid layer instability has no time to act, and $V_{LE}$ is independent of the surface tension, closure taking place when the airway is virtually full of liquid. As $T_{exp} \to \infty$, the expiration rate is so small that any liquid layer with a finite surface tension will form a liquid bridge as soon as the sufficient liquid for closure condition has been met. In between these two limits, the surface tension condition of the air-liquid interface will determine the lung volume at closure.

The same figure makes apparent the difference between $V_{LE}$ calculated with a constant surface tension of 30 dynes/cm and that with a variable surface tension representative of pulmonary surfactant. For humans, physiologically realistic values of $T_{exp}$ range from 2 s upwards. For $2 \text{ s} < T_{exp} < 5 \text{ s}$, $V_{LE}$ for $\gamma = 30$ dyne/cm is virtually flat near 26% TLC, while that for variable surface tension is about 10% TLC lower, ranging from 16 to 18% TLC. Hence surfactant, which makes variable surface tension possible, might eliminate liquid bridge formation if it reduced the lung volume at closure to a value less than that encountered in normal breathing. The expiration rate does not have a strong effect on $V_{LE}$ for $T_{exp} \geq 2 \text{ s}$, but if $T_{exp}$ is increased sufficiently, $V_{LE}$ for the variable surface tension and $\gamma = 30$ dyne/cm conditions will converge.

There are two mechanisms by which surfactant reduces the lung volume at closure. The principal means by which surfactant slows bridge formation is that of greatly reducing
the mean surface tension as lung volume decreases. The large reduction in $\gamma$ occurs because the surfactant is confined to the air-liquid interface and therefore concentrated as the interface contracts during expiration. Figure 2-3 reveals that a concentration increase of 30% above the initial value causes the surface tension to fall from 30 dynes/cm to its minimum value, here taken to be 1 dyne/cm. Because the pressure is proportional to the surface tension, the thirty-fold drop in tension causes a thirty-fold reduction in the pressure gradient that drives the flow.

Surface tension gradients can also impede the growth of the instability. Perhaps their effect can best be appreciated by considering two extreme cases in a non-contracting tube in which the Rayleigh condition is satisfied and the amount of liquid is sufficient to form a bridge. (We consider a non-contracting tube to separate the surface tension gradient effect from that of the decreasing mean surface tension. The air-liquid interfacial area in a non-contracting tube does decrease during the closure process, but the mean surface tension stays very nearly constant.)

Consider first the case of no surfactant present. Once the interface is perturbed from its initial cylindrical geometry, the Rayleigh instability causes the perturbation to grow. Because no surface tension gradients are present, no tangential stress is exerted on the air-liquid interface, and the axial velocity of the surface is directed towards the minimum pressure, with magnitude equal to $3/2$ the mean value. This flow leads to the formation of a bridge in time $t_1$.

Alternatively, if the air-liquid interface is coated with a surfactant for which the surface tension is sensitive to changes in surface concentration, and the mean surface tension is equal to the surface tension in the previous no-surfactant case, the flow leading to closure will create surface concentration gradients by both (i) surface convection and (ii) increasing deformation of the initially cylindrical interface. These gradients are characterized by the maximum concentration (and hence minimum surface tension) being at the axial position where the bridge will form. The resultant surface tension gradient exerts
a tangential stress in the direction of greater surface tension (cf. eq. (2.22) in Appendix 2A), so that the flow leading to closure will be retarded. Therefore the closure time with surfactant, \( t_2 \), will be greater than \( t_1 \).

If the surface is stopped or "frozen" by gradients in the surfactant case, creating a zero-velocity condition at the air-liquid interface, \( t_2 / t_1 = 4 \) because, for a given pressure gradient, the flow rate of a viscous fluid through a channel with two zero-velocity surfaces is one-quarter that with only one zero-velocity surface. If the slope of the surface tension vs. concentration relation is sufficiently steep (cf. Fig. 2-3 between A and C), the gradients can go beyond simply stopping the surface from moving, and can in fact drive it in the direction opposite the mean flow. In this case, the time to closure can exceed \( 4t_1 \). A parameter that characterizes the slope of the surface tension vs. surfactant concentration in the neighborhood of its mean concentration is the Gibbs Elasticity \( E \) [Edwards et al., 1991], defined in dimensionless form as:

\[
E = -\Gamma_m^* \left[ \frac{\partial \gamma}{\partial \Gamma^*} \right]_{\Gamma_m^*}
\]

(2.6)

where \( \Gamma_m^* \) and \( \gamma_m \) are the mean dimensional surfactant concentration and mean surface tension, respectively. For DPPC, we used values of \( \Gamma_m^* = 2.3 \times 10^{18} \) molecules/m\(^2\) [Schurch et al., 1989] and \( \gamma_m = 30 \) dynes/cm, giving \( E = 7 \). Figure 2-8 shows how the time to closure \( t_2 \) varies with \( E \). For \( E \geq 1 \), there is the maximal surfactant effect, with the closure time more than four times greater than that for \( E \leq 10^{-6} \), representative of no surfactant.
Fig. 2-8. Closure time $t_2$ vs. Gibbs Elasticity $E$. $t_1$ = closure time when no surfactant is present. Results for non-contracting airway with $a_0 = 0.020$ cm, $s_0 = 0.025$ cm, $L_0 = 0.075$ cm, and $\gamma_m = 20$ dynes/cm.

Figure 2-7 provides a comparison between the reduced mean surface tension and surface tension gradient effects. For $T_{exp} = 5$ s, the lung volume at closure with $\gamma = 30$ dynes/cm is 26.3% TLC; for $\gamma = \gamma_{min} = 1$ dyne/cm, it is 19.1% TLC, and with variable surface tension with $\gamma_A = 30$ dynes/cm (Fig. 2-3), it is 18.6% TLC. The difference between the first two $V_{LE}$ values is due solely to differences in mean surface tension. The much smaller difference between the last two is caused chiefly by surface tension gradients. As mentioned previously, $V_{LE}$ in the variable surface tension case is slightly less than that obtained with $\gamma = \gamma_{min}$ because surface tension gradients existing early in the expiration ($t < t_C$) effectively counter the pressure gradient at that stage, and no such mechanism impedes the flow when the surface tension is constant.

It was mentioned in the Results section that the surface tension gradient can re-emerge as closure approaches ($t \to t_E$). This is especially true if the surfactant experiences a maximum surface concentration $\Gamma_{max}$ or "closest packing state" [Djabbarah and Wasan, 1982] which cannot be exceeded. We have performed simulations in which
\[ \Gamma_{\text{max}} = \Gamma_{\text{C}} = 1.30 \] (Fig. 2-3); the resultant lung volumes at closure are less than those shown in Fig. 2-7 for the variable surface tension condition (e.g. at \( T_{\text{exp}} = 5 \text{ s}, V_{\text{LE}} = 17.1\% \text{ TLC} \) compared with 18.6\% TLC) because the surface tension gradient is active for a larger fraction of the closure time near \( t = t_E \). The effect is small, and emphasizes the secondary importance of the surface tension gradient in slowing bridge formation.

If closure does not occur at end-expiration when the surface tension is at its minimum value, it is possible that it may occur early in inspiration, when the surface tension rises sharply. We consider this possibility in Appendix 2B. It is well known that, for a given interfacial area, the surface tension of pulmonary surfactant is greater during surface expansion than contraction [Weibel, 1984]. This causes the surface tension at a particular lung volume to be higher during inspiration than expiration [Frazer and Weber, 1980]. Indeed, Frazer and Weber [1976] demonstrated that the most important factor in determining how much gas is trapped in an excised rat lung is the rate of inflation, not that of deflation. If liquid bridging is the mechanism responsible for closure, and if no bridge has formed by end-expiration, it is conceivable that closure could take place during inspiration if the increased surface tension accelerated the instability enough to form a bridge. This would depend on the inspiration rate: if low, a bridge could form before lung volume was so great that the sufficient liquid for closure condition was no longer satisfied. This sensitivity to inspiration rate might explain Frazer and Weber's result.

**Airway closure in disease**

The loss of normal surfactant function in the small airways due to (i) impairment of surfactant production, (ii) interference with its surface tension reducing capability (as would occur if plasma proteins invaded the airway film [Hawgood, 1991]), or (iii) restriction of surfactant movement from the respiratory zone to the small airways, will
result in increased surface tension in these same airways. This raised tension promotes
airway closure at higher-than-normal lung volumes for a number of reasons.

First, Fig. 2-7 makes clear that for a given expiration rate, an increased surface
tension results in a higher lung volume at closure. This is because the increased tension
accelerates liquid bridge formation. Second, comparison of Figs. 2-4(d) and 2-6(b) makes
clear that at low lung volume (e.g. $t = 3.65$ s), the magnitude of the negative pressure
tending to collapse the airway with constant surface tension $\gamma > \gamma_{\text{min}}$ is much greater than
when surfactant function is normal (i.e. $\gamma = \gamma_{\text{min}}$). Although we have not included the
effect of airway compliance in our model, this reduced transmural pressure would promote
compliant collapse of the airway or a decrease in the lumen area, facilitating liquid bridge
formation.

Third, the accentuated negative pressure in the liquid layer may draw additional liquid
from surrounding interstitial and capillary regions (or impede liquid transfer from the
airways into those regions), causing the liquid layer thickness to grow. As was stated in
the Introduction, the greater the volume of liquid in the airway, the higher the lung volume
at which closure can occur. In diseased conditions the amount of airway liquid can
increase markedly; for example, exposure to smoke has been found to increase the
thickness of the mucous layer in the trachea by up to ten times the normal value of 10 $\mu$m
[Hulbert et al., 1982]. While the thickness and composition of the liquid layer in the
peripheral airways of normal lungs is not known with certainty, it is believed that in all but
the smallest airways the epithelium is lined with two layers of liquid: the first a periciliary
fluid with depth equal to the length of the ciliary shafts (approximately 6 $\mu$m) that lies
beneath the second, composed of mucus. The mucus layer is believed to be contiguous in
the large airways, with a depth of approximately 5 $\mu$m; the layer coverage is less uniform in
the smaller airways, and disappears completely by the respiratory bronchioles [Wanner,
1985]. We have used a liquid layer thickness of 10 $\mu$m for airways in the terminal
bronchial region at TLC and assumed it to be composed of the low-viscosity periciliary
fluid due to the relative absence of mucus-secreting glands in the smallest airways. If a larger thickness were employed, the calculated $V_{LE}$ values would rise accordingly.

**Interpretation of $V_{LE}$**

If liquid bridging plays a significant role in airway closure, we would expect that the calculated values of $V_{LE}$ would correspond approximately to clinical values obtained for lung volume at closure and that factors that promote closure in the clinical setting would have a similar effect in the model. However, the clinical means used to ascertain whether closure has occurred are a subject of some debate. In addition, due to inhomogeneities in the lung, closure of individual airways likely occurs over a range of volumes, the mean value of which varies with age, height, sex and possibly other factors [West, 1987].

It might seem most natural to compare $V_{LE}$ with the closing capacity (CC), commonly believed to be the lung volume at which closure first occurs during a slow expiration from TLC to RV [West, 1987], hence the name. Closing capacity is measured by noting the lung volume at which phase IV begins in a nitrogen washout test (see [West, 1987]). However, Hyatt et al. [1973] and Rodarte et al. [1975] have demonstrated that closing capacity increases with increasing expiration rate and may well be determined by regional flow limitation, not airway closure. Figure 2-7 reveals that $V_{LE}$ decreases with increasing expiration rate, the opposite of the observed trend for closing capacity. Moreover, closing capacities are significantly larger than the calculated $V_{LE}$ values despite our choice of an initial liquid layer thickness (10μm) on the high end of the anticipated range in normal lungs. For example, the average CC for a 20 year-old, 1.8m male is 32% TLC; for a 50-year old man of the same height, the mean CC is 46% TLC [West, 1987], compared with the largest $V_{LE}$, 26% TLC. For these reasons, the mechanism we have modeled does not seem to be that responsible for the onset of phase IV; therefore we conclude, as did Rodarte et al., that $V_{LE}$ and CC result from different physical events.
On the other hand, there is reason to believe that the mechanism we have modeled may determine residual volume. The residual volume of an average 20 year-old, 1.8m tall male is 26% TLC, comparable to the maximum V_LE we calculated. For a 50 year-old male of the same stature, RV = 34% TLC [West, 1987]. Our calculated V_LE's fall below these values, but would tend to them as additional factors that reduce the lumen area, such as airway compliance and excess airway liquid, were taken into account. Also, the model formulation of constant expiration rate for the entire expiration ignores the fact that at low lung volume, the flow rate will be limited by maximal flow-volume envelope [West, 1987]. The expiration rate at these low lung volumes is reduced, tending to shift the computed V_LE values upward, closer to typical RV values; the effect becomes more pronounced at higher expiration rates. Factors that are known to increase RV, such as excess airway secretions (as in chronic obstructive pulmonary disease) and increased airway compliance (as in emphysema) would also tend to increase V_LE (through increased liquid layer thickness and decreased airway radius, respectively).

It was pointed out above that the results presented in Fig. 2-7 are physiologically relevant in humans for T_exp greater than approximately 2 s; in this range the lung volume at closure is not highly sensitive to expiration rate, but is sensitive to the magnitude of the surface tension. This is consistent with the finding that additional air trapping in excised lungs (and hence, presumably, RV) is reduced by the presence of surfactant [Enhorning, 1977]. While recognizing that other factors may contribute to airway closure, we conclude that the liquid bridging mechanism becomes more important as the airway lumen is increasingly obstructed and surfactant function is impaired and may contribute to the observed increase in RV in such cases [West, 1987].
Modeling considerations

Although every attempt was made to produce a model for airway closure that was realistic, as in any model, it was necessary to introduce various assumptions and approximations. Some of the more critical assumptions are discussed in this section.

One surfactant property not included in our model, that of surface shear viscosity, would tend to further stabilize the interface and delay or prevent bridge formation. Meban [1978] has determined that compression of pulmonary surfactant, as occurs during expiration, produces a sharp rise in surface shear viscosity, tending to retard surface movement. In the limit, this viscosity would immobilize the interface by making it solid-like [Goerke and Clements, 1986], and so decrease the \( V_{LE} \) values in Fig. 2-7. The magnitude of this effect would be comparable to that caused by a surface tension gradient that hinders axial movement of the interface just before closure occurs. Calculations have shown that this effect can reduce \( V_{LE} \) by a few percent of TLC.

The lung volume at closure would be decreased still further if the minimum surface tension employed in the simulations was less than the 1 dyne/cm we used. Pattle [1955] argued that the minimum surface tension is zero, in which case the lung volumes at closure we calculated would be overestimates, and the actual values would be closer to that dictated by geometry alone (the limit for very low \( T_{exp} \) values in Fig. 2-7), provided compliant collapse does not occur. A lower minimum surface tension would also reduce the magnitude of the negative pressure in the liquid layer and therefore increase the effective transmural pressure of the airway, making compliant collapse less likely.

We have assumed that the surfactant is confined to an insoluble monolayer so that its surface concentration increases without bound to many times its initial value as expiration proceeds, as in Fig. 2-4(b). Many surfactant films experience a limiting or maximum concentration during film compression, however, reaching a "solid" state [Adamson, 1990] in which further compression may result in complex behavior such as folding of the
monolayer or desorption of surfactant. Although our insoluble monolayer approach would not be valid in these cases, such phenomena would not significantly alter the surface tension experienced at low lung volume during expiration; therefore, we would not expect this aspect of surfactant function to have a large effect on the lung volume at closure.

We have taken the liquid layer viscosity to be equal to that of water, based on a relative absence of mucus-secreting cells past the fifteenth generation of airways [Clarke and Pavia, 1991]. There may be circumstances, however, that cause the viscosity of the liquid layer in the peripheral airways to increase which would have the effect of prolonging liquid bridge formation and thus delaying or preventing closure. This assumes, however, that the conditions that lead to an increase in viscosity do not simultaneously produce a thicker liquid layer.

Stresses exerted on the air-liquid interface by gas in the peripheral airways were neglected because, during normal breathing, they are negligible when compared to the maximum stresses caused by surface tension gradients. However, in the late stages of closure, when the airway is very narrow, and after closure, when it is blocked, shear and pressure forces exerted on the liquid by the airway gas would have to be taken into account to properly model bridge formation and movement. Also, gravity forces clearly become important relative to surface tension forces as the surface tension tends towards zero. Significant gravitational effects might (i) cause more liquid to collect in the dependent regions of the lung, where closure is first observed and where the fraction of closed airways is highest [Engel et al., 1975] and (ii) lead to liquid pooling on the lower walls of the airways and thus alter the lung volume at closure.

The quantity of liquid lining an airway, $V_{liq}$, was taken to be constant during the expiration. The radial transfer of liquid through the airway wall can be estimated using measurements of pulmonary epithelial and endothelial hydraulic permeability [Taylor and Gaar, 1970], and indicate that the time-scale for transepithelial flow of a quantity of liquid comparable to $V_{liq}$ is much greater than $T_{exp}$. The axial, intergenerational transfer of
airway liquid is also considered to be negligible over $T_{\text{exp}}$. Support for this hypothesis has been provided by experiments in a branching network airway closure model described in Chapter 5, revealing no significant exchange of liquid between adjoining generations over the time-scale required for a bridge to form.

An airway length-to-diameter ratio $(2L/2s)$ of 3.0 was employed in all the simulations. While a range of such ratios have been reported for the peripheral airways, the value we used falls near the upper bound of reported values. Ratios closer to 2.0 for the airways in the vicinity of the terminal bronchioles are more common [Horsfield, 1986]; in these shorter tubes, the Rayleigh condition is met at a lung volume lower than that at which the condition of sufficient liquid for closure is met (so that $t_B > t_D$, the opposite of airways we have modeled, for which $L/s = 3.0$ and $t_B < t_D$), and the film thickness required to meet both conditions is greater than that in longer tubes; hence closure by bridging in shorter airways requires a thicker liquid layer.

It has been assumed in all the calculations that the airway retains a circular-cylindrical geometry during expiration, as shown in Fig. 2-1. In one extreme, that of a highly constricted airway, Yager et al. [1989] have reported that the peripheral airways have a rosette-shaped cross section, not a circular one. Yager [personal communication] has found that the degree of this axial "folding" of the airway wall is much less in normal guinea pigs than in those with bronchoconstriction. However, this airway characteristic would need to be factored into the model in situations where the amplitude of the folds was comparable to or greater than the liquid layer thickness. In such a case, surface tension will cause the liquid to redistribute so that a more uniform curvature of the gas-liquid interface is attained. If the time-scale for this redistribution (considered in Appendix 2C) is small compared to $T_{\text{exp}}$, and if there is sufficient liquid in the airway to cover the epithelial folds and thus form a continuous liquid layer cuff, the thin film dynamics leading to airway closure will be qualitatively similar to that in the simulations we have described.
In addition, Yager [personal communication] has found that the average thickness of the airway lining layer in normal guinea pigs (which were frozen and then sectioned for measurement) actually decreases as lung volume is decreased from TLC to FRC. This runs contrary to our model assumption that the amount of liquid in the airway stays constant over $T_{exp}$, causing the liquid layer thickness to increase during expiration. Clearly, this emphasizes the need for a better understanding how the liquid layer thickness varies during the breathing cycle and again suggests that the liquid bridging mechanism we have modeled may only occur in diseased lungs with significant excess airway liquid.
APPENDIX 2A: MODEL DERIVATION

The governing equations for conservation of mass, momentum, and species together with the boundary conditions for pressures and velocities are derived in the following sections. Where necessary, a transformation of coordinates is performed to facilitate calculations for the contracting airway. The nomenclature is found at the end of the appendices.

Conservation of mass

For the axisymmetric, incompressible liquid annulus under consideration (Fig. 2-1(a)), the continuity equation is

\[
\frac{\partial}{\partial r} (ur) + \frac{\partial}{\partial z} (rw) = 0
\]

(2.7)

The integral form, neglecting liquid flux through the wall, is

\[
\frac{\partial}{\partial t} (A) = -\frac{\partial}{\partial z} (Aw)
\]

(2.8)

where the subscript identifies which spatial coordinate is held constant in the partial differentiation with respect to time (for all spatial partial derivatives, time \( t \) is held constant and the subscript is omitted). \( \bar{w} \) is the mean axial velocity in the annulus, in a fixed frame of reference,
\[
\bar{w} = \frac{\int_a^b wr \, dr}{\int_a^b r \, dr}
\]  \hspace{1cm} (2.9)

and

\[
A = (s^2 - a^2) / 2
\]  \hspace{1cm} (2.10)

which is proportional to the cross-sectional area of the liquid film. For simulations with contracting airways, we define a new spatial coordinate

\[
\xi = z / L(t)
\]  \hspace{1cm} (2.11)

which varies between \(-1\) and \(1\) in the airway (see Fig. 2-1). A constant value of \(\xi\) corresponds to a fixed material point on the airway wall as the airway shrinks. In general,

\[
(\partial / \partial t)_z = (\partial / \partial t)_\xi - \frac{\xi \dot{L}}{L} (\partial / \partial \xi)
\]  \hspace{1cm} (2.12)

and

\[
(\partial / \partial z) = \frac{L}{L} (\partial / \partial \xi)
\]  \hspace{1cm} (2.13)

where \(\dot{L} = dL / dt\). We also introduce \(\bar{V}(\xi, t)\), the mean fluid velocity relative to the moving wall at a given \(\xi\):

\[
\bar{V} = \bar{w} - \xi \dot{L}
\]  \hspace{1cm} (2.14)
so that (2.8) can be re-written as

\[
\frac{\partial}{\partial t} (A)_{\xi} = -\frac{1}{L} \frac{\partial}{\partial \xi} (A \bar{V}) - \frac{A \dot{L}}{L}
\]  

(2.15)

**Conservation of surfactant**

Assuming negligible transfer of surfactant between the surface and the adjacent liquid (as in an insoluble monolayer), negligible degradation of surfactant in the interface, and circumferential symmetry, the conservation of surfactant in the surface at \( r = a \) may be expressed as

\[
\frac{\partial}{\partial t} (a \Gamma / \psi)_{z} = -\frac{\partial}{\partial z} (a \Gamma w_{a} / \psi) + \frac{\partial}{\partial z} (a D_{s} \psi \frac{\partial \Gamma}{\partial z})
\]  

(2.16)

where \( w_{a} \) is the axial velocity of the liquid layer at \( r = a \), \( D_{s} \) is the surfactant surface diffusivity, and \( \psi = (1 + (\partial a / \partial z)^{2})^{-1/2} \). Using the transformation in (2.11)-(2.13), we obtain

\[
\frac{\partial}{\partial t} (a \Gamma / \psi)_{\xi} = -\frac{1}{L} \frac{\partial}{\partial \xi} (a \Gamma V_{a} / \psi) - \frac{a \Gamma \dot{L}}{L \psi} + \frac{1}{L^{2}} \frac{\partial}{\partial \xi} (a D_{s} \psi \frac{\partial \Gamma}{\partial \xi})
\]  

(2.17)

where \( V_{a} = w_{a} - \xi \dot{L} \). This equation is "exact" in that it holds equally well for small and large departures from the initial annular geometry.

Calculations have been performed with diffusion present, but even with an excessively large value of the surface diffusivity of \( 10^{-5} \) cm\(^2\)/sec, compared with
2.4 \times 10^{-5} \text{ cm}^2/\text{sec} \text{ for oxygen in water [Incropera, 1981] and } 10^{-7} \text{ cm}^2/\text{sec} \text{ for a myristic acid monolayer [Adamson, 1990], diffusion had a negligible effect on the results.}

**Conservation of axial momentum**

For axisymmetric flow with negligible body forces, the axial momentum equation is

\[
\frac{\partial w}{\partial t} + u \frac{\partial w}{\partial r} + w \frac{\partial w}{\partial z} = \frac{1}{\rho} \frac{\partial p}{\partial z} + \frac{\mu}{\rho r} \frac{\partial}{\partial r} \left( r \frac{\partial w}{\partial r} \right) + \frac{\mu}{\rho} \frac{\partial^2 w}{\partial z^2}
\]  

(2.18)

The airway liquid is taken to be Newtonian with constant viscosity. In the radial momentum equation, we make the thin-film approximation [Johnson, 1991] and deduce that \( p \) does not vary significantly in the radial direction. Because the perturbation wavelength is long in comparison to the film thickness, the second viscous term is negligible in comparison to the first.

The radial velocity boundary conditions are

\[
u_{s} = \frac{\partial s}{\partial t} + w_{s} \frac{\partial s}{\partial z}
\]  

(2.19)

at the airway wall and

\[
u_{a} = \frac{\partial a}{\partial t} + w_{a} \frac{\partial a}{\partial z}
\]  

(2.20)

at the gas-liquid interface; the subscripts \( a \) and \( s \) refer to radial position. The no-slip condition at the airway wall gives

\[
w_{s} = \xi \dot{\ell}
\]  

(2.21)
and the condition matching the surface tension gradient in the air-liquid interface to the viscous shear stress in the liquid layer is

\[ \mu(\partial w / \partial r)_a = -\frac{\partial \gamma}{\partial z} \]  

(2.22)

This neglects the effects of surface viscosity and surface shear imposed by airway gas and assumes the perturbation is of very long wavelength (i.e. \( \psi = 1 \)). The boundary conditions at the airway center \( (z = 0) \) and ends \( (z = \pm L) \) are

\[ (w)_{z=0} = 0 \]  

(2.23)

\[ (w)_{z=\pm L} = \dot{L} \]  

(2.24)

The first condition is due to symmetry; the latter implies that there is no significant liquid flow through the bifurcations during a single expiration. To calculate \( p(z,t) \), the pressure in the liquid film, we use Laplace's law as the normal stress boundary condition:

\[ p(z,t) - p_{gas} = \gamma \left( \frac{-\psi}{a} + \frac{\partial}{\partial z} \left( \psi \frac{\partial a}{\partial z} \right) \right) \]  

(2.25)

This law equates the pressure jump across the air-liquid interface to the product of the surface tension and the interfacial curvature. Surface viscosity has been omitted and the gas core is assumed to be at constant pressure \( p_{gas} \).

Multiplying (2.18) by \( r \), combining the second and third terms using (2.7) and dropping the last viscous term, we obtain
\[
\left( r \frac{\partial w}{\partial t} + \frac{\partial (ruw)}{\partial r} + r \frac{\partial (w^2)}{\partial z} \right) = -\frac{r \partial p}{\rho \partial z} + \frac{\mu}{\rho} \frac{\partial}{\partial r} (r \frac{\partial w}{\partial r})
\]  

(2.26)

Integrating across the film, employing Leibniz's rule and (2.21), the first term becomes

\[
\int_{a(z,t)}^{s(z,t)} r \frac{\partial w}{\partial t} \text{dr} = \frac{\partial}{\partial t} \int_{a(z,t)}^{s(z,t)} r \text{dr} - s \xi \frac{\partial s}{\partial t} + aw \frac{\partial a}{\partial t}
\]  

(2.27)

The second term in (2.26) becomes

\[
\int_{a}^{s} \frac{\partial (ruw)}{\partial r} \text{dr} = s \frac{\partial s}{\partial t} + \xi \frac{\partial s}{\partial z} \xi \frac{\partial s}{\partial z} - aw \frac{\partial a}{\partial z}
\]  

(2.28)

where (2.19) and (2.21) have been incorporated. Again using Leibniz's rule and (2.21), the third term in (2.26) becomes

\[
\int_{a}^{s} r \frac{\partial (w^2)}{\partial z} \text{dr} = \frac{\partial}{\partial z} \int_{a}^{s} r \text{dr} - s \left( \xi \frac{\partial s}{\partial z} \right)^2 + aw^2 \frac{\partial a}{\partial z}
\]  

(2.29)

Assuming that the pressure gradient does not vary with \( r \), integration of the fourth term in (2.26) yields

\[
-\frac{1}{\rho} \int_{a}^{s} r \frac{\partial p}{\partial z} \text{dr} = -\frac{A}{\rho} \frac{\partial p}{\partial z}
\]  

(2.30)

Finally, integrating the viscous term,
\[
\frac{\mu}{\rho} \int_0^s \left( r \frac{\partial w}{\partial r} \right) dr = \frac{\mu}{\rho} \left[ s(\frac{\partial w}{\partial r})_{r=s} - a(\frac{\partial w}{\partial r})_{r=a} \right] \quad (2.31)
\]

Combining (2.26)-(2.31) and simplifying, (2.26) becomes

\[
\frac{\partial}{\partial t} \int_a^s r w dr + \frac{\partial}{\partial z} \int_a^s r w^2 dr = -\frac{A}{\rho} \frac{\partial p}{\partial z} + \frac{\mu}{\rho} \left[ s(\frac{\partial w}{\partial r})_{r=s} - a(\frac{\partial w}{\partial r})_{r=a} \right] \quad (2.32)
\]

We will now calculate the viscous terms assuming that they are balanced by the pressure gradient and the inertial terms are negligible. For viscous flow of an axisymmetric annulus of fluid with the boundary conditions (2.21)-(2.22), we have:

\[
w(r) = \frac{L}{4\mu} \left( \frac{\partial p}{\partial z} \right)^{\nu} (r^2 - s^2) + \frac{a}{\mu} \ln \frac{s}{r} \left( \frac{\partial \gamma}{\partial z} + \frac{a}{2} \left( \frac{\partial p}{\partial z} \right)^{\nu} \right) + \xi \mathcal{L} \quad (2.33)
\]

where the superscript \( \nu \) on \( \frac{\partial p}{\partial z} \) indicates that we are considering the viscous contribution to the pressure gradient. We will consider the viscous and inertial contributions separately, then add them back together. This ad hoc approach will be correct in the high and low Reynolds number limits but may be inaccurate when inertial and viscous forces are comparable. Johnson et al. [1991] discuss the error introduced by these assumptions. We can now calculate \( \bar{w} \), defined by (2.9):

\[
\bar{w} = \frac{-L}{4\mu} \left( \frac{\partial p}{\partial z} \right)^{\nu} (A - a^2 (1 - \frac{a^2}{A} \ln \frac{s}{a})) + \frac{a}{2\mu} \frac{\partial \gamma}{\partial z} \left( A - a^2 \ln \frac{s}{a} \right) + \xi \mathcal{L} \quad (2.34)
\]
From (2.33), we simplify the viscous terms (2.31) to give

\[
\frac{\mu}{\rho} \left[ s \left( \frac{\partial w}{\partial r} \right)_{r=s} - a \left( \frac{\partial w}{\partial r} \right)_{r=a} \right] = \frac{A}{\rho} \left( \frac{\partial p}{\partial z} \right)^\nu
\]  

(2.35)

Using (2.34) we can put \(\frac{\partial p}{\partial z}\) in terms of \(\bar{w}\), transforming (2.35) to

\[
\frac{A}{\rho L} \left( \frac{\partial p}{\partial \xi} \right)^\nu = \frac{\mu}{\rho} \left( s \left( \frac{\partial w}{\partial r} \right)_{r=s} - a \left( \frac{\partial w}{\partial r} \right)_{r=a} \right) = - \frac{4 \mu A (\bar{V} + \frac{a}{2 \mu L} \frac{\partial \gamma}{\partial \xi} \left( \frac{a^2 \ln(s/a)}{A} - 1 \right))}{\rho (A - a^2 (1 - \frac{a^2}{A} \ln(s/a)))}
\]  

(2.36)

where we have employed the coordinate transformation described in (2.11)-(2.14). Now, taking \(w(r) = \bar{w}\) in the inertial terms in (2.32), we obtain

\[
\frac{\partial}{\partial t} (\bar{w} A) + \frac{\partial}{\partial z} (\bar{w}^2 A) = - \frac{A}{\rho} \left( \frac{\partial p}{\partial z} \right)^\nu
\]  

(2.37)

where the superscript \(\nu\) indicates that we are considering the inertial contribution to the pressure gradient. Expanding out the inertial terms and using continuity to simplify,

\[
\frac{\partial}{\partial t} (\bar{w} A) + \frac{\partial}{\partial z} (\bar{w}^2 A) = \bar{w} \frac{\partial A}{\partial t} + A \frac{\partial \bar{w}}{\partial t} + \bar{w} \frac{\partial (\bar{w} A)}{\partial z} + \bar{w} A \frac{\partial \bar{w}}{\partial z} = A \left( \frac{\partial \bar{w}}{\partial t} + \bar{w} \frac{\partial \bar{w}}{\partial z} \right)
\]  

(2.38)

so that, employing the transformation in (2.11)-(2.14), we obtain
\[
A\left(\frac{\partial w}{\partial t} + w \frac{\partial w}{\partial z}\right) = A\left(\frac{\partial}{\partial t}(\bar{V}_\xi) + \xi \ddot{\xi} + \frac{\bar{V}}{L} \frac{\partial}{\partial \xi}(\bar{V}_\eta) + \frac{\bar{V}L}{L} \frac{\partial^2}{\partial \xi^2} (\bar{V}_\eta) \right) = -\frac{A}{\rho L} \frac{\partial p}{\partial \xi}
\]  
(2.39)

Recalling that

\[
\left(\frac{\partial p}{\partial \xi}\right)' + \left(\frac{\partial p}{\partial \xi}\right)'' = \frac{\partial p}{\partial \xi}
\]
(2.40)

we combine (2.36) and (2.39) to obtain

\[
\frac{\partial}{\partial t}(\bar{V}_\xi) + \frac{\bar{V}}{L} \frac{\partial \bar{V}}{\partial \xi} + \xi \ddot{\xi} + \frac{\bar{V}L}{L} = -\frac{1}{\rho L} \frac{\partial p}{\partial \xi} + \frac{4\mu(\bar{V} + \frac{a}{2\mu L} \frac{\partial \gamma}{\partial \xi} \left(\frac{a^2 \ln(s/a)}{A} - 1\right))}{\rho(A - a^2 \ln(s/a))}
\]
(2.41)

while the boundary conditions at the airway ends become

\[
(\bar{V})_{\xi=0} = (\bar{V})_{\xi=\pm l} = 0
\]
(2.42)

Finally, the velocity at the air-liquid interface, required in the surfactant conservation equation, (2.17), can be shown from (2.33) and (2.36) to be

\[
V_a = w(a) - \xi \ddot{\xi} = \left(-2\bar{V} + \frac{a}{\mu L} \frac{\partial \gamma}{\partial \xi} \left(1 - \frac{a^2 \ln(s/a)}{A}\right)\right) \left[a^2 \ln\left(\frac{s}{a}\right) - A\right] + \frac{a}{\mu L} \frac{\partial \gamma}{\partial \xi} \ln\left(\frac{s}{a}\right)
\]
(2.43)
Calculation technique

The approach of Johnson et al. [1991] was employed to solve the coupled set of equations (2.15), (2.17), and (2.41), together with the specified boundary conditions and the surfactant equation of state in a simultaneous manner. A third-order Adams-Bashforth technique was used for the temporal derivatives, which were calculated explicitly, except for the viscous term, which was treated implicitly. Spatial derivatives were calculated using a central-differencing method, and the computational domain was the half-airway 

\( 0 \leq \xi \leq 1 \), with spatial discretization \( \frac{\Delta z}{L} = \Delta \xi = \frac{1}{40} \); no-flow conditions were imposed at \( \xi = 0 \) and \( \xi = 1 \). See Johnson et al. [1991] for complete details.
APPENDIX 2B: AIRWAY CLOSURE BY LIQUID BRIDGING DURING INSPIRATION

As was stated in the Discussion, it has been shown that the amount of gas trapped in an excised lung is more sensitive to the inspiration rate than the expiration rate [Frazer et al., 1976]. In this appendix we investigate the possibility of bridge formation early in inspiration, employing the model described previously, but allowing lung volume to vary sinusoidally in time instead of decreasing linearly. Hence we replace (2.3) with

\[ \frac{V_L}{TLC} = \frac{EEV}{TLC} + \left( \frac{TLC - EEV}{2TLC} \right) \left( l + \sin(2\pi ft + \pi / 2) \right) \tag{2.44} \]

where \( f \) is the breathing frequency. If lung volume is varied in this way, and the end expiratory volume (EEV) is sufficiently large, closure by liquid bridging cannot occur because the sufficient liquid condition will not be satisfied; as EEV is decreased to meet this condition, however, liquid bridging may occur on either inspiration or expiration.

Figure 2B-1 displays the result of a simulation in which closure by liquid bridging occurred on inspiration. The simulation was begun at \( t = 0 \), with \( \frac{V_L}{TLC} = 1.0 \), and the same geometrical parameters employed in Fig. 2-2. As the lung contracts, the airway length and diameter fall, causing the liquid layer to thicken. The concentration of surfactant lining the air-liquid interface grows as the interface contracts, causing the surface tension to fall through the relation shown in Fig. 2-3. As in Fig. 2-2, in this simulation the Rayleigh condition is met at 89% TLC, the minimum surface tension is reached at 69% TLC, and the sufficient liquid condition is met at 26% TLC. For \( V_L < 26\% TLC \), closure can occur if enough time is allowed prior to inspiration to larger lung volumes at which the sufficient liquid condition is not met. This time required for bridge formation is proportional to
Fig. 2B-1. Sinusoidal variation of lung volume $V_L$ in time, ending with closure during inspiration at $V_L/TLC=0.221$. Five successive snapshots of the airway liquid layer are shown. $f=0.25$ breath/s, EEV/TLC=0.19. Surface tension varies per Fig. 2-3. Initial liquid layer and airway parameters are the same as in Fig. 2-2.
\( \mu / \gamma h^3 \) [Johnson et al., 1991]. At low lung volume during expiration, the film thickness \( h \) is large, favoring rapid bridge formation. Offsetting this, however, the surface tension \( \gamma \) is very low, at near-zero value (cf. Fig. 2-3), owing to the presence of surfactant. As surface tension tends to zero, the driving force for closure by bridge formation vanishes. Because we have chosen a finite value for the minimum surface tension, \( \gamma_{\text{min}}=1 \text{ dyne/cm} \), the instability grows all through the expiration, but at rate insufficient to accomplish closure by the end of expiration. This is shown schematically in Fig. 2B-1, which also shows rapid growth of the instability once inspiration begins, resulting in bridge formation soon after.

Clearly, the behavior of the liquid layer on inspiration will depend on how the surface tension varies in that breathing phase. It is well-known that surface tension of the lining layer rises sharply on inspiration [Weibel, 1984], and this provides a strong driving force for bridge formation in that breathing phase if the bridge has not had time to form during expiration.

The reasons why surface tension rises abruptly at the start of inspiration will be discussed in the next chapter. The simulations performed in this chapter were performed using the equation of state shown in Fig 2-3, but assuming that the maximum concentration \( \Gamma \) was equal to \( \Gamma_C \) (see Fig. 2-3), so that once the surface began to expand from its compressed state, the surface tension rose immediately.

Computer simulations have been performed in which EEV and the breathing rate have been systematically varied to determine lung volume and breathing phase at closure. Simulations for constant (\( \gamma = 1 \text{ dyne/cm} \)) and variable (Fig. 2-3) surface tensions have been performed and the results are shown in Figs. 2B-2 for \( h_0 = 10 \mu \text{m} \) and the airway geometry employed in the simulations shown in Fig. 2-4.

The model predicts that for sufficiently high EEV, closure will not occur. As EEV is reduced, closure first occurs on inspiration, and if EEV is reduced further, closure is found to occur on expiration. This is true for both the constant and variable surface tension cases.
The $V_{LE}$ values for these cases are identical when $f$ is large and EEV is small. For lower frequencies, however, $V_{LE}$ values in the closure on expiration zone with surfactant are less than those obtained with $\gamma = l$ due to the effect of the surface tension gradient, which can be present in part of the airway for the entire simulation if the expiration rate is sufficiently small.

![Graphs showing closure zones](image)

Fig. 2B-2. Closure "zones" plotted as a function of end expiratory volume EEV and breathing rate $f$ for (a) variable surface tension (as in Fig. 2-3) and (b) $\gamma = constant = 1$ dyne/cm. Lung volumes at closure corresponding to $(f, EEV)$ coordinates are printed on the graph. At a fixed $f$, e.g., 1 breath/s, closure will not occur if EEV is sufficiently high. As EEV is reduced, however, closure will occur on inspiration; as EEV is further reduced, closure will occur on expiration. Although it is not apparent in the figure, as $f \to 0$, closure will occur on expiration only, because sufficient time will be allowed for bridge formation in that phase, so long as the surface tension is finite. Therefore the closure on inspiration envelope closes as $f \to 0$. 

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On the other hand, variable surface tension can cause closure to occur on inspiration for \((f, EEV)\) settings for which closure would not occur with \(\gamma = 1\) dyne/cm (e.g. \(f=1\) breath/s, \(EEV=0.17\)TLC). This is due to the abrupt rise in surface tension on inspiration mentioned above, and causes the "closure on inspiration" zone to be wider in the variable surface tension case. In either case, closure would first be seen on inspiration as EEV is incrementally reduced (by less than or equal to \(=0.02\)TLC/breath) at a constant breathing rate.

Figure 2B-2 reveals that for closure to occur at a normal adult breathing rate of \(f = 0.25\) breaths/s with \(h_0 = 10\) μm, EEV must be reduced below approximately \(0.23\)TLC, a value below that encountered in normal breathing. If the breathing frequency was further reduced, the closing volume would tend to \(0.26\)TLC as an upper limit. As in the case of closure on expiration, the type of closure mechanism modelled here probably only occurs if the airway lumen area is reduced by excess airway liquid, reduced parenchymal tethering, and/or thickened airway walls. However, if the diameters of small airways fall faster than the cube root of lung volume, as some models [e.g. Wiggs et al., 1990] suggest, closure by liquid bridging will occur at higher lung volumes than we have calculated here.

If surface tension goes to a value sufficiently close to zero (it cannot drop to zero, as this is a characteristic of liquid at its critical point, where it is indistinguishable from a gas [Bangham, 1992, Adamson, 1990]) closure would not occur on expiration unless lung EEV was driven to the lower volume limit shown in Fig. 2-7, where the airway is full of liquid. Barring such low EEV values, closure could only occur on inspiration and would be facilitated by low inspiration rates.

To explain why the amount of gas trapped in an excised lung is more sensitive to the rate of inspiration than that of expiration, it has been hypothesized [Morgan, 1985, Frazer et al., 1976] that liquid bridges form on expiration to low lung volumes, closing the airway and trapping gas in distal airspaces. During the subsequent inspiration, they argue that the
bridges are relatively stable and are pushed distally through the bronchial tree without breaking. The pressure difference across the bridge then causes air to diffuse through it, and as long as the bridge exists, the amount of air diffusing into the airspace during inspiration exceeds that diffusing out during expiration because the bridge thickness is greater in the latter phase of breathing, impeding gas diffusion. They offer this as the reason why the amount of gas trapped increases each breathing cycle, and why the amount of gas trapped is very sensitive to inspiration rate. They have strengthened their thesis by showing that the amount of gas trapped increases as the diffusion coefficient of the gas is raised [Morgan, 1985, and Frazer et al., 1980]. Their hypothesis raises a number of questions. If it is gas diffusion through the meniscus that causes gas to be trapped, could not the lung be degassed with a small, static, negative pressure applied at the trachea, given sufficient time?

To conclude, an abrupt rise in the surface tension at the start of inspiration could promote closure by liquid bridging at that phase in the breathing cycle. Our model result might explain the sensitivity of gas trapping to inspiration rate in that early in inspiration, factors very favorable for liquid bridge formation (high surface tension and large film thickness) exist. As lung volume increases during inspiration, and the liquid layer grows thin, airway closure is averted as there is insufficient liquid to form a bridge in the expanded airway. This "window of opportunity" for liquid bridging during each inspiration might account for the observed rate dependence: a faster inspiration would not allow sufficient time for a liquid bridge to form. Furthermore, if liquid bridging is the dominant closure mechanism, then closure would first occur on inspiration as EEV is incrementally decreased. This matter will be taken up in Chapter 6, where experiments in excised lobes have been carried out to check this hypothesis.

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APPENDIX 2C: ANALYSIS OF CIRCUMFERENTIAL FLOW OVER EPITHELIAL RIDGES

Consider the simple case in which the curvature of the air-liquid interface varies sinusoidally in the azimuthal direction, as it would if epithelial ridges observed by Yager et al. [1989] lined the airway walls. Figure 2C-1(a) shows a schematic cross-section of a constricted airway with twelve epithelial ridges protruding into the lumen.

![Diagram of cross-section of constricted airway with epithelial ridges and liquid layer](image)

(a)

![Diagram showing liquid film flow](image)

(b)

FIG. 2C-1. (a) Schematic of cross-section of a constricted airway with axial epithelial ridges; a liquid layer with thickness $h$ covers the epithelium. (b) an idealized flat liquid film flowing from A towards B.

The epithelium is covered with a liquid film of thickness $h$. In the case of $N$ ridges, let the radius to the free surface be
\[ r = a + \varepsilon \sin(N\theta) \]  

(2.45)

with the \(x\) and \(y\) coordinates of the free surface being

\[ x = r \cos \theta = (a + \varepsilon \sin(N\theta)) \cos \theta = x(\theta) \]  

(2.46)

\[ y = r \sin \theta = (a + \varepsilon \sin(N\theta)) \sin \theta = y(\theta) \]  

(2.47)

The pressure in the film, \(p\), equals the surface tension \(\gamma\) times the curvature of the interface:

\[ p = \gamma \frac{d^2y}{dx^2} \left(1 + \left(\frac{dy}{dx}\right)^2\right)^{-3/2} \]  

(2.48)

where we have neglected longitudinal curvature and

\[ \frac{dy}{dx} = (dy/d\theta)(dx/d\theta)^{-1} \]  

(2.49)

where

\[ \frac{dy}{d\theta} = a \cos \theta + \varepsilon N \cos(N\theta) \sin \theta + \varepsilon \sin(N\theta) \cos \theta \]  

(2.50)

and
\[
\frac{dx}{d\theta} = -a\sin\theta + \varepsilon N \cos(N\theta) \cos\theta - \varepsilon \sin(N\theta) \sin\theta 
\] (2.51)

so that

\[
\frac{d^2 y}{dx^2} = \frac{d}{d\theta} \left( \frac{dy}{d\theta} \right) \left( \frac{dx}{d\theta} \right)^{-1} \left( \frac{dx}{d\theta} \right)^{-1}
\]

\[
= \frac{-a \sin\theta - \varepsilon N^2 \sin(N\theta) \sin\theta + 2 \varepsilon N \cos(N\theta) \cos\theta - \varepsilon \sin(N\theta) \sin\theta}{(dx/d\theta)^2}
\]

\[
- \frac{(dy/d\theta)}{(dx/d\theta)^3} \left[ a \cos\theta - \varepsilon N^2 \sin(N\theta) \cos\theta - 2 \varepsilon N \cos(N\theta) \sin\theta - \varepsilon \sin(N\theta) \cos\theta \right] 
\] (2.52)

Inserting (2.54)-(2.57) into (2.53), we obtain a lengthy expression of the form

\[
p = p(a, N, \varepsilon, \gamma, \theta) 
\] (2.53)

which reduces to \( p = -\gamma / a \) when \( \varepsilon = 0 \).

To calculate an approximate time-scale for flow in the tangential direction, consider the case where \( N=12 \). This is a reasonable value based on the micrographs presented in Yager et al. [1989]. Adjacent maximum and minimum pressure regions in the liquid film, A and B, are shown in Fig. 2C-1(a). We can calculate the pressures at these two points by setting \( dp / d\theta = 0 \) to obtain

\[
p_A = p_{\text{max}} = \gamma (-a + \varepsilon + \varepsilon N^2) / (a - \varepsilon)^2
\] (2.54)

and

\[
p_B = p_{\text{min}} = -\gamma (a + \varepsilon + \varepsilon N^2) / (a + \varepsilon)^2
\] (2.55)

where \( p_A \) and \( p_B \) tend to \(-\gamma / a\) as \( \varepsilon \to 0 \). From these two equations,
\[ \Delta P_{AB} = 2\gamma(\varepsilon^3 N^2 + \varepsilon N^2 a^2 + \varepsilon - a^2 \varepsilon) \div (\varepsilon - a^2 \varepsilon) / ((a - \varepsilon)(a + \varepsilon)^2) \quad (2.56) \]

Idealizing the film segment AB in Fig. 2C-1(a) as a flat, thin liquid film, as shown in Fig. 2C-1(b), we have, in the absence of gravity,

\[ \mu \frac{d^2 u}{dy^2} = \frac{dp}{dx} \quad (2.57) \]

which scales as

\[ \mu \frac{U}{h^2} \approx \frac{\Delta P_{B-A}}{l_{AB}} \quad (2.58) \]

where \( U \) is the characteristic velocity for this tangential flow. From geometry,

\[ l_{AB} = (4\varepsilon^2 + (\pi a / N)^2)^{1/2} \quad (2.59) \]

and taking \( U \propto l_{AB} / \tau \), where \( \tau \) is the time-scale for tangential fluid movement, we have

\[ \tau \propto \mu(4\varepsilon^2 + (\pi a / N)^2)(a - \varepsilon)(a + \varepsilon)^2 / (2\gamma h^2(\varepsilon^3 N^2 + \varepsilon N^2 a^2 + \varepsilon^2 - a^2 \varepsilon)) \quad (2.60) \]

For a liquid layer with \( h=1 \mu m, \mu=0.01 \) dyne-sec/cm\(^2\) (viscosity of water), \( a=0.02 \) cm, \( \varepsilon=20 \mu m, N=12, \) and \( \gamma=1 \) dyne/cm, we obtain \( \tau=0.03 \) s. Using these same parameters and varying the amplitude \( \varepsilon \), we obtain the values in the table below.
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<th>N</th>
<th>ε (cm)</th>
<th>μ (dyne/s/cm)</th>
<th>γ (dyne/cm)</th>
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</tbody>
</table>

Table 2C-1. Time-scales for tangential flow.

From Table 2C-1 and equation (2.60), we observe that

1. \( \tau \propto \frac{\mu}{h^2} \) due to viscous forces.

2. \( \tau \propto \frac{l}{\gamma} \) because surface tension causes the pressure difference that drives the flow.

3. As \( \varepsilon \) increases, \( \tau \) decreases because the pressure difference rises; this is moderated by an increase in \( l_{AB} \); in Table 1, note that \( \tau \) is nearly constant for \( 20 \mu m < \varepsilon < 100 \mu m \).

4. The time-scale for flow in the tangential direction appears to be much smaller than typical respiratory time-scales; the time-scale for tangential flow, however, may be increased by any of these factors:

   (a) a viscosity significantly greater than that of water;

   (b) a surface tension significantly lower than 1 dyne/cm;

   (c) a liquid layer thickness significantly less than 1 \( \mu m \);

   (d) surface tension gradient and surface viscosity effects that immobilize the air-liquid interface (increasing the time-scale by approximately four times);

   (e) a decrease in pressure gradient caused by the reduced difference in curvature as tangential flow proceeds.
NOMENCLATURE

\( a = \text{radius to free surface, cm} \)
\( A = (s^2 - a^2)/2, \text{ cm}^2 \)
\( CC = \text{closing capacity, liters} \)
\( D_s = \text{surfactant surface diffusion coefficient, cm}^2/\text{s} \)
\( E = -\Gamma_m^* \gamma_m \left[ \frac{\partial \gamma}{\partial \Gamma^*} \right]_{\Gamma_m^*} = \text{dimensionless Gibbs elasticity} \)
\( EEV = \text{end expiratory volume, liters} \)
\( f = \text{breathing frequency, breaths/s} \)
\( FRC = \text{functional residual capacity, liters} \)
\( h = s - a = \text{film thickness, cm} \)
\( L = \text{airway half-length, cm} \)
\( \dot{L} = \frac{dL}{dt} = \text{rate of change of } L, \text{ cm/s} \)
\( \ddot{L} = \frac{d^2L}{dt^2}, \text{ cm/s}^2 \)
\( p = \text{pressure in liquid film, dynes/cm}^2 \)
\( r = \text{radial coordinate in airway, cm} \)
\( RV = \text{residual volume, liters} \)
\( s = \text{radius to airway wall, cm} \)
\( t = \text{time, s} \)
\( t_B = \text{time at which Rayleigh condition is satisfied, s} \)
\( t_C = \text{time at which surface tension reaches minimum value, s} \)
\( t_D = \text{time at which sufficient liquid condition for closure is satisfied, s} \)
\( t_E = \text{time at which airway closes, s} \)
\( T_{exp} = \text{time in which the lung is emptied from TLC, s} \)
\( TLC = \text{total lung capacity, liters} \)
\( u = \text{radial velocity, cm/s} \)
\( \bar{V} = \bar{w} - \xi \dot{L} \) = mean axial velocity relative to the airway wall, cm/s

\( V_a = w_a - \xi \dot{L} \) = surface axial velocity relative to the airway wall, cm/s

\( V_{liq} \) = volume of liquid in the airway, ml

\( V_L \) = lung volume, liters

\( V_{LE} \) = lung volume at closure (Fig. 2-2), liters

\( w \) = axial velocity of airway film in fixed reference frame, cm/s

\( \bar{w} \) = mean axial velocity of airway film in fixed reference frame, cm/s

\( z \) = axial coordinate in airway, cm

\( \gamma \) = surface tension, dynes/cm

\( \Gamma \) = dimensionless surfactant surface concentration

\( \Gamma^* \) = dimensional surfactant surface concentration, molecules/m²

\( \Gamma_{max} \) = dimensionless maximum surface concentration

\( \mu \) = viscosity of liquid layer, dyne-s/cm²

\( \xi = z/L \)

\( \rho \) = density of liquid layer, g/ml

\( \psi = (1 + (\partial a / \partial z)^2)^{-1/2} \)

**Subscripts**

\( a \rightarrow (r = a) \)

\( m \rightarrow \text{mean} \)

\( s \rightarrow (r = s) \)

\( z \rightarrow z \text{ held constant during differentiation} \)

\( \xi \rightarrow \xi \text{ held constant during differentiation} \)

\( 0 \rightarrow (t = 0) \)
REFERENCES


Chapter 3

Dynamic Surface Tension of Pulmonary Surfactant: Experiments and Theory

ABSTRACT

A bubble surfactometer was used to measure the surface tension (\(\gamma\)) of an aqueous solution of TA surfactant as a function of bubble area (A) over a range of cycling rates and surfactant bulk concentrations. Depending on cycling frequency and bulk concentration, the \(\gamma\) vs. A loops can exhibit several distinctive features.

A model was developed to explain these data and to predict the dynamics of surface layers of pulmonary surfactant under more general circumstances. In this model, the surfactant is treated as a single component and the surface tension is taken to depend only on the interfacial surfactant concentration \(\Gamma\). Two distinct mechanisms are postulated for exchange of surfactant between the bulk phase and the interface. The first is described by a simple kinetic relation for adsorption and desorption that pertains only when the interfacial surfactant concentration is below its maximum equilibrium value. The second mechanism is that of "squeeze-out" [Goerke and Clements, 1986] by which surfactant molecules are expelled from an interface that has been compressed past the maximum packing state. The model provides good agreement with experimental data for cycling rates from 1 to 100 cycles/min and for concentrations between 7 and 7000 \(\mu\)g/ml.
INTRODUCTION

By their nature, surfactant molecules in solution tend to migrate to interfaces. This reduces the free energy of the surfactant-solvent system and the surface tension of the air-liquid interface. If the interface is perturbed from an equilibrium state, the surfactant concentration and surface tension may change, and subsequent transfer of surfactant to or from the interface may occur so that the free energy of the system can again be minimized.

The airspaces of the lung are coated by a thin film of liquid containing pulmonary surfactant composed of phospholipids (approx. 95%) and various proteins (5%) that are secreted by type II epithelial cells lining the alveolar walls [Tchoreloff et al., 1991, Weibel, 1984]. During breathing, this film is periodically expanded and compressed, resulting in periodic variation in surfactant interfacial concentration that in turn causes the surface tension of the layer to vary in a periodic fashion. This variation of surface tension with lung volume promotes lung stability and reduces the work of breathing [Weibel, 1984]. Moreover, the hysteresis in the surface tension vs. lung volume relationship is a major contributor to hysteresis in lung pressure-volume curves [Smith and Stamenovic, 1986].

To measure how the surface tension varies as a function of pulmonary surfactant surface concentration, various instruments have been used to examine surfactant from excised lungs in vitro. Among these instruments are the Langmuir trough used with a Wilhelmy balance [Adamson, 1990], the captive bubble apparatus [Schürch, 1989], and the bubble surfactometer [Enhorning, 1977]. This last instrument is shown schematically in Fig. 3-1; it consists of a chamber of liquid in which a nearly spherical bubble is formed at the end of a narrow tube and is made to vary in size sinusoidally in time. Knowledge of the bubble volume and the pressure difference across the bubble allow one to calculate the dynamic surface tension through Laplace's Law.
Fig. 3-1. Schematic of bubble surfactometer with spherical bubble of surface area $A$ at atmospheric pressure $p_{atm}$ in surfactant solution of concentration $C$. The bubble radius $R$ is measured optically and is made to vary in time by movement of the piston.

The bubble surfactometer was employed to measure surface tension vs. area characteristics of TA Surfactant (also known as Survanta, Tokyo Tanabe, Tokyo), a modified natural surfactant used clinically to treat respiratory distress syndrome. The experiments were performed over a range of cycling rates and bulk concentrations.

We know of only one theoretical model developed to interpret such data. Horn and Davis [1975] undertook an analytical study to consider how hysteresis evident in surface tension vs. area loops for oscillating bubbles might be caused by (i) diffusion of surfactant between the bulk phase and interface, (ii) sorption between bulk and interface, (iii) viscoelastic behavior in the interface, and (iv) viscoelastic behavior in the bulk. They
concluded that the hysteresis in surface tension vs. area loops (and, hence, in lung pressure-volume loops) is most likely caused by viscoelasticity of the air-liquid interface. However, although both diffusion and sorption were considered as transfer mechanisms, no provision was made for "squeeze-out" phenomena or monolayer collapse at high surface concentrations. Moreover, Horn and Davis do not allow for the variation of kinetic processes with surface concentration.

However, it is believed that monolayers of pulmonary surfactant experience squeeze-out of surfactant during surface compression [Goerke and Clements, 1986]; furthermore, it has been shown that the kinetic processes are highly dependent on the surface concentration. In this regard, Smith and Stamenovic [1986] have performed experiments comparing pressure-volume curves of canine lobes with constant surface tension liquids lining the airspaces to those obtained from normal canine lobes. They present evidence for relatively rapid sorption occurring when the surface tension of the lining layer is above the equilibrium value (which they take as 28 dynes/cm) and much slower sorption occurring when the surface tension is below this value.

In this chapter we propose a simple model that includes the effect of squeeze-out in highly compressed pulmonary surfactant films and accounts for the asymmetry in sorption kinetics between films with high and low surface tensions. The model succeeds in predicting surface tension-area behavior exhibited by TA surfactant that the model of Horn and Davis [1975] could not.

MATERIALS AND METHODS

Experimental technique. TA surfactant was received as a suspension in normal saline (25 mg/ml) (Ross Laboratories, Columbus, OH). Before each experiment, a fresh solution was prepared by diluting the surfactant with 5 mM CaCl₂ [cf. Possmayer et al., 1984] to concentrations between 7 and 7000 μg/ml; all experiments were conducted with
surfactant from a single lot. The solution was vortexed and sonicated, with care being taken not to form foam on the air-solution interface.

A set of experiments was conducted to ascertain whether dilution of surfactant in standard saline (0.15 M NaCl) together with 5 mM CaCl\textsubscript{2} would give different results than with 5 mM CaCl\textsubscript{2} alone. These were performed with a different lot of TA surfactant; in all other regards, however, the experimental techniques were the same. The results indicated no observable difference between the two treatments.

The surface tension-area measurements were made using an Electronetics bubble surfactometer (Albany, NY), shown schematically in Fig. 3-1. A small spherical bubble of air is formed at the end of a 0.4 mm diameter needle immersed in a solution of surfactant. The bubble volume is cycled so that the air-liquid interfacial area changes periodically in time. Measurement of the bubble volume and the pressure difference across the bubble surface allow one to calculate the dynamic surface tension \( \gamma \) through Laplace's Law. The variations in bubble volume are equal to the known piston displacement and the initial bubble volume is measured through calibrated optics. The mean bubble diameter is on the order of 1 mm and remains very nearly spherical for surface tensions down to a few dynes/cm [Hall et al., 1993]. For a known bubble volume, the bubble radius can be calculated directly, assuming that the bubble is spherical.

The system was modified to allow access to the analog signals for transfilm pressure and minimum radius signals versus time. These data were processed using data collection and analysis software (Labtech Notebook, Taunton, MA), an analog to digital converter (12 Bit Dash-8, Metrabyte Corp., Taunton, MA), and a PC (Compu-Add 8086 PC, Austin, TX).

Calibrations of both the surfactometer and the computerized data collection system were performed daily using double-distilled water. Static and dynamic distilled water controls were carried out both prior to and after measurements. Electromechanical phase lag between the analog minimum radius signal from the surfactometer and the true
minimum was determined as a function of frequency using distilled water by applying Laplace's law and assuming a fixed surface tension. All results reported here have been corrected for this effect. All experiments were conducted at 37°C.

In the "static bubble" tests, the bubble volume was rapidly increased from zero to a radius of 0.4 mm, and then fixed (so that the bubble was static after the initial inflation). The surface tension was then measured as a function of time until it relaxed to its equilibrium value. This test was performed for concentrations between 7.3 and 730 µg/ml and provided data on how both the equilibrium surface tension and the time-scale characterizing surface tension variation vary with bulk concentration.

Dynamic measurements with cycling rates ranging from 1 to 100 cycles per minute were performed, varying the bubble radius from a minimum of 0.4 mm to a maximum value, fixed for a particular experiment, between 0.53 mm and 0.59 mm. This corresponds to minimum to maximum bubble area ratio between 0.46 and 0.57. Assuming that the bubble in the surfactometer represents the lining film in a spherical alveolus, and that the alveolar volume varies directly as lung volume V, the ratio of minimum to maximum bubble area, A_min/A_max, scales as (V_min/V_max)^2. For tidal breathing, this yields A_min/A_max=0.92; for a breathing maneuver between TLC and FRC, A_min/A_max=0.63; for a vital capacity (TLC-RV) maneuver, A_min/A_max=0.41, where we have taken values for tidal volume, TLC, RV and FRC for normal men at rest from Taylor et al. [1989] and Weibel [1984]. Therefore the A_min/A_max values we used correspond to breathing maneuvers somewhere between full vital capacity and TLC-FRC breathing.

Analog transfilm pressure and minimum radius signals were sampled at 100 Hz. Results represent steady-state values, defined as those in which the surface tension-area loops no longer changed from one cycle to the next; this typically took less than 30 minutes.

**Theoretical Model.** We assume transport of the surfactant to the surface to be an adsorption-limited as opposed to a diffusion-limited process (see Discussion). As such,
<table>
<thead>
<tr>
<th>Regime (a)</th>
<th>Regime (b)</th>
<th>Regime (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Gamma &lt; \Gamma^*$</td>
<td>$\Gamma^* &lt; \Gamma &lt; \Gamma_{\text{max}}$</td>
<td>$\Gamma = \Gamma_{\text{max}}$</td>
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<tr>
<td>$\gamma &gt; \gamma^*$</td>
<td>$\gamma^* &gt; \gamma &gt; \gamma_{\text{min}}$</td>
<td>$\gamma = \gamma_{\text{min}}$</td>
</tr>
</tbody>
</table>

**kinetic sorption**

\[
\frac{dm}{dt} = k_1 A C (\Gamma^* - \Gamma) - k_2 A \Gamma
\]

<table>
<thead>
<tr>
<th>Regime (b)</th>
<th>Regime (c)</th>
</tr>
</thead>
</table>
| **insoluble monolayer**
\[
\frac{dm}{dt} = 0
\]

**squeeze-out**

\[
\frac{dm}{dt} = (dA/dt) \Gamma_{\text{max}} \quad \text{when } dA/dt < 0
\]

- $\Gamma$ varies due to (1) changes in $A$
- (2) sorption

- $\Gamma$ stays constant at $\Gamma_{\text{max}}$

---

Fig. 3-2. Transfer mechanisms for three monolayer "regimes" considered in the model. In regime (a), the surface concentration is less than the maximum equilibrium value ($\Gamma < \Gamma^*$) and surfactant in the bulk phase can adsorb or desorb to the surface per equation (3.1). In (b), the surface concentration is greater than the equilibrium value, and the monolayer is "insoluble" in that it is tightly packed and unable to accommodate new material from the bulk, but not so tightly packed that it cannot be compressed further; in (c), the surfactant layer loses material as it is compressed past its maximum packing concentration ($\Gamma_{\text{max}}$).
the bulk solution was considered to be well-mixed at all times at concentration C. The kinetics of adsorption and desorption were defined by three surface concentration (Γ) regimes (see Figs. 3-2 and 3-3) defined as (a) Γ less than the maximum equilibrium surface concentration Γ* (the limiting surface equilibrium concentration that is reached as bulk concentration C is increased), (b) Γ greater than this concentration but less than the maximum surface concentration Γmax (the maximum concentration of surfactant obtainable on dynamic compression of the interface), and (c) Γ = Γmax.

For the first regime with Γ<Γ*, adsorption to and desorption from the surface are assumed to follow Langmuir kinetics [Horn and Davis, 1975; Borwankar and Wasan, 1983]:

\[
\frac{dm}{dt} = A \left( k_1 C (\Gamma^* - \Gamma) - k_2 \Gamma \right)
\]  
(3.1)

where:

- A is the area of the bubble air-liquid interface, mm²
- C is the bulk concentration of surfactant, g/liter
- \(k_1\) is the adsorption coefficient, liter/(g-min)
- \(k_2\) is the desorption coefficient, min⁻¹
- \(m=\Gamma A\) is the mass of surfactant in the interface, g
- \(\Gamma\) is the concentration of surfactant in the interface, g/mm²
- \(\Gamma^*\) is the maximum equilibrium surface concentration, g/mm²

For the computations, we divided both sides of (3.1) by \(\Gamma^*\), allowing us to perform the calculations with nondimensional concentrations (\(\Gamma/\Gamma^*\) and \(m/\Gamma^*\)).

Inherent in Langmuir kinetics is the assumption that the interface consists of a given number of adsorption sites [Adamson, 1990] defined by \(\Gamma^*\) and that an adsorbed molecule interacts with the adsorption site but not with the other adsorbed molecules. The maximum
equilibrium surfactant concentration $\Gamma^*$ corresponds to the minimum equilibrium surface tension determined by the static bubble tests described above.

![Graph showing surface tension $\gamma$ vs. bubble area $A$ loop. The dark arrowheads directed tangent to the loop denote the clockwise progression in time. The open arrowheads normal to the loop symbolize surfactant transfer between the interface and the bulk; outward arrows represent desorption, inward arrows adsorption. The three transfer regimes are (a) kinetic adsorption or desorption for $\gamma > \gamma^*$ (between D and A), (b) insoluble monolayer for $\gamma_{\text{min}} < \gamma < \gamma^*$ (segments AB and CD), and (c) squeeze-out desorption (segment BC) as the area is lowered beyond the value associated with point B. In this figure $\gamma_{\text{min}} = 10$ dynes/cm.]

In the second regime with $\Gamma^* < \Gamma < \Gamma_{\text{max}}$, the monolayer is modeled as insoluble, i.e., it does not exchange surfactant with the subphase. In this regime the surface concentration can change only because of changes in bubble area; as the bubble area decreases, the concentration rises as

$$\Gamma = \frac{\Gamma^* A^*}{A}$$  \hspace{1cm} (3.2)
up to a maximum value \( \Gamma = \Gamma_{\text{max}} \). When \( \Gamma \) reaches \( \Gamma_{\text{max}} \) (regime (c)), the surfactant molecules are packed as tightly as possible in the interface, and the surface concentration can rise no higher. The surface tension reaches its minimum value here and any further compression is taken to result in a loss (or "squeezing out") of surfactant to the bulk phase [cf. Goerke and Clements, 1986]. These regimes cover the range from liquid-expanded (\( \Gamma < \Gamma^* \)) to liquid-condensed (\( \Gamma^* < \Gamma < \Gamma_{\text{max}} \)) to solid (\( \Gamma = \Gamma_{\text{max}} \)) and collapsed ("squeeze-out") monolayer states [Tchoreloff et al., 1986, Adamson, 1990].

As in the bubble surfactometer, the volume \( V \) of the bubble is modeled to vary as [Hall et al., 1993]

\[
V = V_0 + \frac{\Delta V}{2}(1 + \cos(2\pi ft))
\]  

(3.3)

where \( f \) = oscillation frequency (cycles/min), and \( t \) = time (min). Therefore the area of the spherical bubble

\[
A = (36\pi)^{1/3} V^{2/3} 
\]  

(3.4)

also varies periodically in time. The numerical simulation of the bubble oscillation was started at \( t = 0 \) with \( A = A_{\text{max}} = (36\pi)^{1/3}(V + \Delta V)^{2/3} \) and \( m_0 \) grams of surfactant at the interface, such that the initial interfacial concentration was \( \Gamma_0 = m_0/A_{\text{max}} \), with surfactant transport to or from the interface defined by the three regimes set forth above. The results were not affected by the initial value chosen for \( m_0 \) since the calculation was continued until a steady state was achieved.

Time-stepping was performed using a third-order Adams-Bashforth technique. Due to the symmetry of the bubble, we took the surface concentration and hence the surface
tension to be uniform over its entire surface, noting, however, that the presence of the needle may introduce some artifact in the experiments not mimicked by the model.

**Isotherm calculation.** The isotherm or equation of state relates the interfacial surfactant concentration to the surface tension at a particular temperature. The isotherm for TA surfactant was obtained by an iterative process that will now be described.

First, an isotherm approximating that for DPPC, based on data from Schurch et al. [1989], was employed to compute surface tensions from the interfacial surfactant concentrations, which were computed as described above. This provided the fourth and last equation needed to model the surface tension vs. area loops for a given $k_1$, $k_2$, and $C$. ($\Gamma^*$ was assigned the value corresponding to the $\gamma^*$ measured in the static bubble tests.) Model computations were then performed to explore the $k_1$-$k_2$ parameter space, and the $k_1$ and $k_2$ values that best matched the experimental data were determined. In practice it was found that the model predictions were insensitive to $k_2$ at high bulk concentrations, and so $k_1$ was determined from high concentration data. Low bulk concentration data was used to determine $k_2$; comparison of experimental data and simulations in which the mass of surfactant in the interface $m$ was too small for squeeze-out to occur were utilized here. Once selected, the $k_1$ and $k_2$ values were checked for consistency with the rest of the model. This was done in both regimes (a) and (b). For the former, the equilibrium form of (3.1)

$$\frac{\Gamma_{eq}}{\Gamma^*} = \frac{k_1C}{k_1C + k_2} = \frac{l}{l + (k_2/k_1C)}$$

must hold. $\Gamma_{eq}$ is the equilibrium surface concentration corresponding to a particular bulk concentration $C$. This equation enabled us to calculate $\Gamma_{eq}/\Gamma^*$ as a function of $C$, given $k_1$ and $k_2$. Because the equilibrium surface tension was measured as a function of $C$ in the static bubble tests, we were able to relate $\Gamma_{eq}/\Gamma^*$ to $\gamma_{eq}$. 

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In regime (b) (Γ > Γ*), (3.5) does not apply and another relation must be employed to check the isotherm. In this "insoluble monolayer" regime, the mass of surfactant in the interface is constant so that

\[ m = AΓ = AΓ^* = \text{constant} \]  \hspace{1cm} (3.6)

Again, Γ* was taken to correspond to the value of γ* measured in the static bubble tests. Hence, to obtain the isotherm in the range Γ* < Γ < Γ_{\text{max}}, the area corresponding to γ = γ* on the deflation limb of a γ-A loop (point A in Fig. 3-3) was measured. Similar measurements were made for smaller areas and surface tensions in the same regime, i.e., at points on the AB segment in Fig. 3-3. This data and (3.6) yield a set of paired Γ/Γ* and γ values for Γ* < Γ < Γ_{\text{max}}. The deflation limb of the loop (AB) was chosen instead of the inflation limb (CD) for reasons that will be explained in the Discussion.

These data, together with those for Γ < Γ*, were fit to a curve, yielding an isotherm of the form γ vs. Γ/Γ*. Surface tension vs. area loops were again calculated for a range of k_1, k_2, C and f values, and the k_1 and k_2 values yielding the best fit to the data were again selected.

This procedure was repeated until agreement between the experimental data and the model was optimized and the isotherm, kinetic constants and equilibrium surface tensions were reasonably self-consistent. The optimum kinetic constants were \(k_1 = 102 \text{ liter/(g-min)}\) and \(k_2 = 1 \text{ min}^{-1}\). The resulting isotherm is shown in Fig. 3-4. A linear regression provided a good fit to the data and a quadratic that passed through γ=70.5 with dγ/dΓ=0 at Γ=0 was connected to the aforementioned line to complete the isotherm. The corresponding equations, shown graphically in Fig.3-4, are

\[ γ_f = -156.2863 \left( \frac{Γ}{Γ^*} \right)^2 + 70.5 \]  \hspace{1cm} (3.7)
for \( 0 \leq \frac{\Gamma}{\Gamma^*} \leq 0.179 \) and

\[
\gamma_f = -55.992 \left( \frac{\Gamma}{\Gamma^*} \right) + 75.515
\] (3.8)

for \( 0.179 \leq \frac{\Gamma}{\Gamma^*} \leq 1.242 \) where \( \gamma \) is in dynes/cm. The subscript \( f \), for "fit", is included to make clear that equations (3.7)-(3.8) represent a curve fit that does not yield \( \gamma \left( \frac{\Gamma}{\Gamma^*} = 1 \right) = \gamma^* = 22.2 \) dyne/cm because the curve was not forced through this point.

Fig. 3-4. Isotherm relating surface tension to normalized surface concentration of surfactant. Circular symbols signify measurements made in regime (b); square symbols represent data from the equilibrium surface tension measurements and equation (3.5). The solid line shows eqs. (3.7)-(3.8).

Instead, the curve fit yields \( \gamma_f \left( \frac{\Gamma}{\Gamma^*} = 1 \right) = 19.5 \) dyne/cm and \( \gamma_f \left( \frac{\Gamma}{\Gamma^*} = 0.952 \right) = 22.2 \) dyne/cm. However, we can "force" the curve fit through \( \gamma (\Gamma = \Gamma^*) = \gamma^* \) by re-scaling \( \Gamma \) in equations (3.7)-(3.8). The result is
\[ \gamma = -141.7024 \left( \frac{\Gamma}{\Gamma^*} \right)^2 + 70.5 \] (3.9)

for \( 0 \leq \Gamma / \Gamma^* \leq 0.188 \) and

\[ \gamma = -53.316 \left( \frac{\Gamma}{\Gamma^*} \right) + 75.515 \] (3.10)

We have not included a new subscript on \( \Gamma \), although it has been re-scaled. Moreover, the subscript on \( \gamma \) has been dropped, although these equations also represent a curve-fit. This is the isotherm we will use in the computations. It is nearly identical to that in eqs. (3.7)-(3.8), but is consistent with our original definitions of \( \gamma^* \) and \( \Gamma^* \), while the previous equations were not.

**Selection of minimum surface tension.** The minimum surface tension seen in the experimental loops varied with bulk concentration, even when the surface concentration was large enough for squeeze-out to occur (cf. Figs. 3-6 through 3-8); a representative value, though, is 10 dynes/cm, which corresponds to \( \Gamma / \Gamma^* = 1.23 \) for the isotherm represented by (3.9)-(3.10). We took these values to correspond to the minimum surface tension and maximum surface concentration, respectively, for all the bulk concentrations. This matter will be considered further in the Discussion.

**RESULTS**

**Static tests.** The results of the static bubble tests are shown in Fig. 3-5. The curves for different concentrations of TA surfactant each begin at a relatively high surface tension and then decrease to their equilibrium values. The surface tensions for the two lowest concentrations (7.34 and 73.4 \( \mu g/ml \)) decrease exponentially in time, with time
constants 18 and 12 minutes, respectively. The time-scale characterizing the (presumably exponential) surface tension equilibration at the highest concentration (734 μg/ml) was too small to be measured at the sampling rate we used.

![Graph showing surface tension vs. time for different concentrations](image)

**Fig. 3-5.** Surface tension vs. time results for static bubble tests at bulk concentrations ranging over three orders of magnitude. Equilibrium surface tensions are 22, 27, and 49 dynes/cm for C = 734, 73.4, and 7.34 μg/ml, respectively.

Figure 3-5 also shows that the equilibrium surface tension decreases as the bulk concentration of TA surfactant increases. The equilibrium data were used to generate the isotherm relating interfacial surfactant concentration to surface tension as described above.

**Dynamic tests.** Figures 3-6 through 3-9 show selected surface tension vs. bubble area loops measured over a wide range of bulk concentrations, oscillation frequencies and bubble area ratios. The data clearly demonstrate that, for sufficiently high bulk concentration of surfactant (Figs. 3-6 through 3-8), a minimum surface tension is reached on compression that remains approximately constant until compression is finished and re-
expansion begins (as along BC in Fig. 3-3). This is consistent with previous observations [Tchoreloff et al., 1991, Enhorning, 1977]. In some cases, however (e.g. Fig. 3-8), there is a slight upward drift in γ once the minimum value has been reached. Also apparent are random fluctuations in γ along the minimum surface tension region at the bottom of the loop (esp. apparent in Fig. 3-7) which may correspond to "clicking" described by Schürch et al. [1989] in which the surface tension of a compressed interface increases abruptly; these are especially obvious at lower frequencies and higher bulk concentrations.

The loops at higher bulk concentration (Figs. 3-6, 3-7, and 3-8) all exhibited a minimum surface tension plateau consistent with monolayer collapse [Tabak et al., 1977] and considerable hysteresis. This behavior was not apparent at lower concentrations (Fig. 3-9), however, where there was little hysteresis and the lowest surface tension occurred only at minimum area and increased with decreasing bulk concentration. The low concentration results also exhibited minimal frequency dependence.

Frequency has several effects on loop shape that are most apparent at the higher concentrations (Figs. 3-6 through 3-8). First, as the cycling rate is increased, the maximum surface tension attained rises. Second, the area at which the minimum surface tension is first reached during interfacial compression decreases with increasing cycling rate (esp. apparent in Fig. 3-8). Third, and perhaps most interesting, is that \( \partial \gamma / \partial A \) at the start of surface expansion (i.e., the slope along CD in Fig. 3-3) is independent of cycling rate (Figs. 3-7, 3-8) and generally exceeds \( \partial \gamma / \partial A \) at the early stages of area contraction (slope along AB in Fig. 3-3). These observations, in part, formed the basis for the model formulation.

**Theoretical Model Results.** Figures 3-10 to 3-13 show the model predictions of the experimental loops in Figs. 3-6 to 3-9. The model is able to reproduce many of the features in the experimental loops. First, the model correctly predicts the effect of bulk concentration on loop shape. For the higher concentration data, it also mimics the experimental observation that \( \partial \gamma / \partial A \) at the start of surface expansion (i.e., the slope along
Fig. 3-6. Experimental surface tension vs. area loop for C=7300 μg/ml at
(A) f=10 cpm and (B) 100 cpm. Loop directions are clockwise.
Fig. 3-7. Experimental surface tension vs. area loop for C=730 μg/ml at f=1 and 10 cpm. Loop directions are clockwise.

Fig. 3-8. Experimental surface tension vs. area loops for C=73 μg/ml at f=1, 10 and 100 cpm. Loop directions are clockwise.
Fig. 3-9. Experimental surface tension vs. area loop for C=7.3 μg/ml at (A) f=1 cpm, (B) 10 cpm and (C) 100 cpm. Loop directions are clockwise.
Fig. 3-9.(continued). For caption, see previous page.
CD in Fig. 3-3) is independent of cycling rate and exceeds $\partial \gamma / \partial A$ during the early stages of area contraction. The feature of the model responsible for the replication of this behavior is the lack of desorption occurring until the surface tension exceeds the minimum equilibrium value (i.e. the existence of regime (b) in Figs. 3-2 and 3-3). Moreover, the greater the cycling frequency (or the lower the value of $k_1 C / f$), the greater the maximum surface tension and the smaller the bubble area at which the minimum surface tension is reached (see Figs. 3-11 and 3-12).

At lower bulk concentrations (Figs. 3-9, 3-13) the model correctly predicts that the hysteresis in the loops is less, the minimum surface tension plateau is absent, and the frequency dependence is negligible. It also provides reasonable predictions for the minimum surface tension achieved at minimum area. The desorption constant $k_2$, which pertains to regime (a), was essential for reproducing this behavior. The effect of increasing $k_2 / k_1 C$ is to reduce the amount of surfactant in the interface; this may eliminate or will at least reduce squeeze-out; in the former case, increasing $k_2$ causes the minimum surface tension to rise.

DISCUSSION

We have examined the dynamic behavior of TA surfactant over a range of frequencies and bulk concentrations. Previous investigations have been conducted to determine the effects of dynamic compression on the surface tension of lung surfactants and their analogues (e.g. [Fuchimukai et al., 1987, Keough et al., 1988, Tchoreloff et al., 1991, Schurch et al., 1992, and Rana et al., 1993]). In these studies, however, no model was proposed to elucidate the mechanisms responsible for the observed behavior. We have developed a theoretical model to analyze similar data under a variety of experimental conditions with the goal of better understanding the processes by which surfactant
Fig. 3-10. Computed surface tension vs. bubble area loops for C=7340 μg/ml at 10 (solid line) and 100 (dashed line) cpm. k₁=102 liter/(g-min), k₁C=750 min⁻¹, k₂=1 min⁻¹, γ_min=10 dyne/cm, γ*=22.2 dyne/cm, A_min=2 mm², A_max=3.8 mm². Same A_min/A_max, bulk concentration and oscillation frequencies as in Fig. 3-6. Loop directions are clockwise.

Fig. 3-11. Computed surface tension vs. bubble area loops for C=734 μg/ml at 1 (solid line) and 10 (dashed line) cpm. k₁=102 liter/(g-min), k₁C=75 min⁻¹, k₂=1 min⁻¹, γ_min=10 dyne/cm, γ*=22.2 dyne/cm, A_min=2 mm², A_max=4.35 mm². Same A_min/A_max, bulk concentration and oscillation frequencies as in Fig. 3-7. Loop directions are clockwise.
Fig. 3-12. Computed surface tension vs. bubble area loops for \( C = 73.4 \ \mu g/ml \) at 1 (solid line), 10 (dashed line) and 100 (dash-dot line) cpm. \( k_1 = 102 \ \text{liter/(g-min)} \), \( k_1C = 7.5 \ \text{min}^{-1} \), \( k_2 = 1 \ \text{min}^{-1} \), \( \gamma_{\text{min}} = 10 \ \text{dyne/cm} \), \( \gamma^* = 22.2 \ \text{dyne/cm} \), \( A_{\text{min}} = 2 \ \text{mm}^2 \), \( A_{\text{max}} = 4.35 \ \text{mm}^2 \). Same \( A_{\text{min}}/A_{\text{max}} \), bulk concentration and oscillation frequencies as in Fig. 3-8. Loop directions are clockwise.

Fig. 3-13. Computed surface tension vs. bubble area loops for \( C = 7.34 \ \mu g/ml \) at 1 (solid line), 10 (dashed line) and 100 (dash-dot line) cpm. \( k_1 = 102 \ \text{liter/(g-min)} \), \( k_1C = 0.75 \ \text{min}^{-1} \), \( k_2 = 1 \ \text{min}^{-1} \), \( \gamma_{\text{min}} = 10 \ \text{dyne/cm} \), \( \gamma^* = 22.2 \ \text{dyne/cm} \), \( A_{\text{min}} = 2 \ \text{mm}^2 \), \( A_{\text{max}} = 3.55 \ \text{mm}^2 \). Same \( A_{\text{min}}/A_{\text{max}} \), bulk concentration and oscillation frequencies as in Fig. 3-9. Loop directions are clockwise.
molecules enter and leave the interface. The model has been shown to provide reasonable agreement with experimental measurements performed over three orders of magnitude of concentration and two orders of magnitude of oscillation frequency.

One crucial assumption in the theoretical model is that TA surfactant can be treated as a single component, even though it is known to be a mixture of lipids and proteins. Thus, Goerke and Clements [1986] and Longo et al. [1993] describe squeeze-out as a selective ejection of anionic lipids and fatty acids from the compressed monolayer, leaving a DPPC-rich film at the interface. Nonetheless, the simple model yields satisfactory agreement with the experimental data, suggesting that the important processes are captured by the simulation.

Other important assumptions in the theoretical model, adopted to best fit the experimental data, include (i) that there exists a maximum interfacial surfactant concentration to which the surface can be dynamically packed, and at which further interfacial compression will result in squeeze-out or collapse of the interface, (ii) that transport of surfactant to the interface is adsorption- rather than diffusion-limited, (iii) that when the interfacial surfactant concentration is less than the maximum equilibrium value, adsorption and desorption are controlled by Langmuir kinetics, (iv) that for interfacial surfactant concentrations between the maximum equilibrium value \( \Gamma^* \) and the maximum packing concentration \( \Gamma_{\text{max}} \), surfactant in the interface behaves as an insoluble monolayer, with no adsorption or desorption taking place. Additional support for each of these assumptions/findings is given below.

**Squeeze-out and \( \Gamma_{\text{max}} \).** The experimental data (Figs. 3-6 through 3-8) clearly demonstrate that when the surfactant film is compressed beyond a certain point, the surface tension remains nearly constant as the area is further reduced. Tchoreloff et al. [1991] found a similar result for dipalmitoylphosphatidylcholine (DPPC), attributing the phenomenon to "squeeze-out" of the interfacial material. Using a Langmuir-Blodgett
technique, they demonstrated that following squeeze-out a sublayer of surfactant forms immediately adjacent to the interface.

**Sorption and Diffusion.** The time-scale for adsorption in our dynamic model scales as $1/\kappa_1 C$. If, in fact, the surfactant transfer to the interface were diffusion-limited, the time-scale would vary as $1/C^2$ [cf. Jiang and Chiew, 1993]. This can be shown by relating the interfacial concentration to the bulk concentration through a length scale

$$L \approx \frac{\Gamma_{eq}}{C}$$

(3.11)

If this length scale is determined by diffusion, then

$$L \propto \sqrt{D \tau}$$

(3.12)

where $\tau$ is the diffusional time scale. Combining (3.9) and (3.10) yields

$$\tau \propto \frac{1}{D} \left( \frac{\Gamma_{eq}}{C} \right)^2$$

(3.13)

Thus for adsorption-limited processes, the time for adsorption scales as $1/C$ while for diffusion-limited processes, this time varies as $1/C^2$. By comparison of the data in Figs. 3-6 through 3-9 with the model predictions shown in Figs. 3-10 through 3-13, it is clear that the data correlate better as a adsorption-controlled rather than a diffusion-controlled process.

In the static bubble tests, where the surface tension of a freshly-formed bubble relaxes to its equilibrium value in time, we would expect diffusional time scales to dominate, because a sublayer of surfactant has not yet formed adjacent to the interface. However, the time constants characterizing the relaxation shown in Fig. 3-5 do not vary as $1/C^2$. 

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Perhaps this is because at lower bulk concentrations, the length scale $L$ (3.9) is much greater than the dimensions of the solution container in the surfactometer. As a result, the diffusion process is cut short, with the measured time constant at the lowest concentration not as low as it would be if a solution of infinite extent were measured. If this is the case, the measured equilibrium surface tensions at low bulk concentrations may have been overestimated.

Other investigators [Schuch et al., 1992] have demonstrated that equilibration time varies as $C^{-2}$. We believe that the dynamic process is adsorption-limited because the surfactant that is squeezed out remains adjacent to the surface as a reserve that can resupply surfactant to the interface [Tchoreloff et al. 1991]. Thus after a diffusion-limited transient equilibration period during which this subsurface layer is formed, there would be no diffusive barrier to adsorption.

**Transfer regimes (a) and (b).** The third and the fourth assumptions are related as these describe the nature of the adsorption and desorption processes. For surface concentrations less than the maximum equilibrium surface concentration $\Gamma^*$, we assume that the dynamics of adsorption and desorption are controlled by equation (3.1), which is the simplest kinetic equation consistent with the Langmuir isotherm [Chang and Franses, 1992]. We have made the simplifying assumption that below the maximum equilibrium surface concentration, $k_1$ and $k_2$ are constant, while above this concentration they drop to zero. This abrupt change in kinetics accounts for the sharp "nose" in the upper right-hand corner of the $f=1$ cpm loop in Fig. 3-11; a more gradual transition in the kinetics would smooth this out. However, as our coarse, stepwise approximation seems to describe the rest of the data reasonably well, it is difficult to justify a more complicated adsorption/desorption model. Additional support is provided by Goerke and Clements [1986], who report that for surface tensions above 25 dynes/cm, surface relaxation toward equilibrium occurs very rapidly (in seconds) while for surface tensions lower than this, the
Fig. 3-14. (A) Pressure-volume curve for excised canine lobe undergoing intermittent inflation and deflation. The horizontal isopleth corresponds to the amplitude change in pressure at constant volume over a 20 minute equilibration period; differences in amplitude reflect differences in film kinetics through the pressure-volume cycle. The dashed line shows the quasi-static pressure-volume curve. (B) Corresponding Surface tension-volume curve. $\gamma=28$ dyne/cm is taken to be the equilibrium surface tension.

From Smith and Stamenovic [1986].
relaxation process is very slow (in hours). Tabak et al. [1977] have noted similar behavior for DPPC.

This asymmetry in kinetics is made very clear by the experimental result of Smith and Stamenovic [1986]. They introduced liquids of constant surface tension into excised dog lobes to infer how surface tension in untreated lobes varies during the breathing cycle. This allowed them to deduce the alveolar surface tension as a function of lung volume and transpulmonary pressure. Their results for stepwise expiration and inspiration (Fig. 3-14) indicate that for surface tensions below the equilibrium value the monolayer kinetics are much slower than those above. Our model would predict no change in surface tension during the 20 minute delay for any initial surface tension below $\gamma^*$, and a reduction in surface tension to the equilibrium value for an initial surface tension greater than $\gamma^*$. Apart from the very small changes in $\gamma$ measured during the 20 minute wait periods for initial surface tensions less than $\gamma^*$, our theoretical model agrees very well with their experimental result.

**Monolayer rupture on bubble expansion.** From Figs. 3-10 through 3-13, it is apparent that the model predicts larger $\partial \gamma / \partial A$ at the start of bubble expansion (AB in Fig. 3-3) than at the start of contraction (CD in Fig. 3-3); this was also a characteristic of the experimental loops (Figs. 3-6 through 3-8). In the model, this occurs because the percentage of interfacial area change is greater at lower surface areas, so, for the same change in area, the concentration change along CD is greater than that along AB. It is also apparent, however, that the $\partial \gamma / \partial A$ slopes along CD predicted by the model are not as great as those measured experimentally. This discrepancy may be caused by rupture of the surface layer on expansion, leaving condensed "icebergs" of surfactant on an "open sea" of water [Goerke and Clements, 1986]. Such breakage would cause the surface tension to rise sharply as water, with its high surface energy, entered the interface.

This hypothesis can be tested against the hypothesis on which the model is based, i.e. that the surfactant layer is uniformly spread for the entire $\gamma$-A cycle and is insoluble on
segments AB and CD in Fig. 3-3. If an isotherm is constructed using the γ-A relationship at the start of bubble expansion (CD in Fig. 3-3), it can be compared with that derived from data obtained during bubble compression as was described in the Methods section above. The γ vs. Γ/Γ* curve derived using the data along CD is significantly steeper than that employed in the model, suggesting that the packing and unpacking of the surfactant layer is not a reversible process. This shortcoming of the theoretical model, which assumes uniform spreading of surfactant through the entire γ-A cycle, is manifest by the difference between the predicted and measured CD slopes.

Nevertheless, the model assumption that no sorption takes place during expansion between points C and D manages to duplicate the observed rate independence of the γ-A loop early in bubble expansion. If sorption started at C, the CD slope would vary with the cycling rate.

Monolayer collapse and re-spreading. A precise description of the collapse process of lung surfactant extract and pure phospholipids DOPC and DPPC has been provided by Tchorellof et al. [1991]; they employed differential scanning calorimetry (DSC), a Langmuir trough, Langmuir-Blodgett film techniques and electron microscopy to analyze film compression and collapse at several temperatures.

They remark that depending on the monolayer temperature and ratio of lipids, highly compressed lipid films either collapse into three-dimensional structures or squeeze components into the bulk phase; at temperatures above the main transition temperature (obtained through DSC) the monolayer is in a "liquid" state and compression does not result in a 3-D collapsed structure (also called "highly condensed stacked bilayers"); instead, extra material is squeezed out of the monolayer and into the bulk phase. This squeezing may be selective and favor the expulsion of lipids other than DPPC. Lung surfactant extract, a combination of phospholipids and proteins, has less 3-D collapsed structures evident than pure DPPC films.
Tchoreloff et al. also report that when lung surfactant extract films were compressed to near-zero surface tensions and then expanded, effective respreading did not occur until the surface tension increased to around 30 dynes/cm; here again there is evidence that certain mechanisms that act to reduce the surface tension (be they sorption or spreading) do not come into play until the surface tension has risen to approximately its equilibrium value. This characteristic may be essential for promoting uniform recruitment of collapsed alveoli; an abrupt rise in surface tension on expansion will increase the amount of work required for further local expansion, encouraging subsequent work (i.e. expansion) to be performed on more compliant areas, until all areas are equally expanded.

Surface viscosity effects. Hall et al. [1993] show that the effect of surface dilatational viscosity is zero when the bubble is at its minimum area (point C in Fig. 3-3) because the rate of dilatation is zero at the extremes of bubble area. However, they maintain that surface tensions determined at points other than the minimum and maximum areas may be inaccurate because of appreciable surface dilatational viscosity effects. However, our results show a lack of frequency dependence late in compression and early in expansion (e.g. Figs. 3-7 and 3-8), when surface concentration is maximum and interfacial viscous effects would be most apparent; this suggests that surface viscosity is not significant in the experiments we have performed. In this regard, Edwards et al. [1991] comment on the difficulty of distinguishing the effects of dilatational viscosity from other mechanisms without a surfactant transport model like the one describe here.

Minimum surface tension. In our simulations we did not permit the surface tension to fall below 10 dynes/cm, i.e. we set \( \Gamma_{\text{max}} \) to correspond to this surface tension for all the bulk concentrations. However, it is clear from the experimental data that the level of the minimum surface tension plateau is sensitive to the bulk concentration. While it would be simple to vary \( \Gamma_{\text{max}} \) (and hence \( \gamma_{\text{min}} \)) with \( C \) to better fit the experimental data, it is desirable to minimize the number of adjustable parameters in the model; it seems
reasonable that there is one $\Gamma_{\text{max}}$ for all the concentrations, but the surface tension likely depends on both $\Gamma$ and $C$ [Defay et al., 1966].

Moreover, Fig. 3-8 shows, for the $\gamma$-A loops at 1 and 10 cpm, that the minimum surface tension may be achieved early in the compression phase (at point B in Fig. 3-3), and the surface tension may rise on subsequent compression, forming a less than perfect "plateau." Such behavior is not accounted for by the present model.

**Bubble surfactometer limitations.** One potential artifact of the experiments is leakage of surfactant out the tube that pierces the bubble (Fig. 3-1). If the tube is an escape route for highly compressed films, the measured surface tensions would be higher than if the bubble were completely closed. If the alveoli are open to the alveolar ducts during breathing, then this opening in the surfactometer bubble may be a useful physiological analogue. Scarpelli [1988], however, argues that bubbles form in the alveoli during breathing, and are essential for proper lung function.

No provision was made in our experiments to measure leakage of surfactant through the tube shown in Fig. 3-1. However, as our measurements were made at steady state, and (i) there did not appear to be greater discrepancies between experimental data and model predictions at low frequencies than at high, and (ii) that the low frequency, high concentration loops (e.g. Figs. 3-6 and 3-7) were rate independent along BCD (Fig. 3-3), where leakage would most likely occur, such leakage does not appear to have been a problem, unless it occurred on a time-scale much smaller than that corresponding to our maximum cycling rate.
REFERENCES


Chapter 4

Airway Closure by Compliant Collapse

ABSTRACT

A computational model that predicts airway lumen diameter vs. lung volume and the lung volume at which the airway will collapse has been developed. Parenchymal tethering acting outward on an airway is quantified using the approach of Lai-Fook et al. [1977] and is balanced by the inward collapsing pressure caused by surface tension of the liquid lining layer. The airway itself is assumed to have negligible stiffness. Airway collapse is taken to occur at the lung volume at which the parenchymal tethering is insufficient to maintain the balance of forces. The model indicates that compliant collapse is the dominant closure mechanism for liquid layer thicknesses below a certain threshold value that depends on the minimum surface tension; for a minimum surface tension of 1 dyne/cm, the model predicts that compliant collapse will govern airway closure for initial (TLC) film thicknesses less than approximately 10 μm.

An alternative model using a tube law for pulmonary veins [Yen and Foppiano, 1981] is also proposed but not pursued because of its speculative nature and questionable relevance to the airways.
INTRODUCTION

In Chapter Two we focused on how airway closure might occur by liquid bridge formation, but mentioned that closure might be caused by "compliant collapse" of the airway. It is well-known that veins collapse at negative transmural pressures [Kamm, 1987, Shapiro, 1977] and it is often assumed that airways behave in the same way, with "airway collapse" and "airway closure" frequently treated as synonyms.

However, the mechanical properties of airways in the terminal bronchiole region, where airway closure is believed to occur [Hughes et al., 1970], are not well known. There is reason to believe, however, that because these small airways lack cartilage, they require parenchymal tethering to remain patent and so collapse near zero transpulmonary pressure [Greaves et al., 1986, Yen and Foppiano, 1981].

Because of the lack of data on the mechanical properties of the peripheral airways, in this chapter we will consider two models which treat limiting cases. The first considers the parenchymal tethering of the airway to be the only factor promoting airway patency: any airway stiffness is neglected. The second model employs data from pulmonary veins that relates the vessel diameter to the transmural pressure at various transpulmonary pressures. Both models yield information on how airway size varies as a function of lung volume, surface tension, and liquid layer thickness; both models also indicate that there is a lung volume below which the inward collapsing pressure in the liquid layer cannot be balanced by parenchymal tethering or airway stiffness. Comparison of the first model with the liquid bridging model developed in Chapter Two reveals that, under the given assumptions, compliant collapse is the dominant closure mechanism unless the liquid film is abnormally thick.
PART I: CYLINDRICAL AIRWAY OF NEGLIGIBLE STIFFNESS TETHERED BY PARENCHYMA

Fig. 4-1. Schematic of cylindrical hole cut in parenchyma. \( R \) = radius before cut, \( R + U \) = radius after cut. \( p_{tp} \delta p \) = radial traction exerted by parenchyma on cut-out tissue. Before cut, \( \delta p = 0 \); after cut, \( \delta p = p_{tp} \).

Methods. Let us consider the stability of a single cylindrical airway of negligible stiffness that is maintained patent by radial traction from the surrounding parenchyma. The traction varies with lung volume and may as a first approximation be taken as equal to the transpulmonary pressure \( p_{tp} \) [Greaves et al., 1986]. Lai-Fook et al. [1977] measured this traction indirectly by cutting cylindrical holes in the parenchyma of excised dog lobes (Fig. 4-1). They measured the hole diameters along the deflation limb of the lung pressure-volume curve and showed that the relative expansion of such holes was independent of \( p_{tp} \) for \( 0 < p_{tp} < 20 \) cm H\(_2\)O (Fig. 4-2), as would be expected of a linearly elastic material in which the shear modulus \( G \) is taken to be.
\[ G = \kappa p_p \]  

(4.1)

with \(0.5 < \kappa < 0.7\) and radial deformation \(u\) given by

\[ u = R \frac{\delta p}{2G} \]  

(4.2)

We will employ this result and consider a cylindrical airway of zero stiffness lined with liquid and embedded in the parenchyma as shown in Fig. 4-3. The pressure in the

![Graph](image)

**Fig. 4-2.** Measurements of elastic recoil \(U\) for cylindrical holes cut in excised dog lobes as a function of transpulmonary pressure; \(R=\text{pre-cut radius (}=2.2\ \text{mm in a frozen collapsed lobe)}\). From Lai-Fook et al. [1977].
Fig. 4-3. Schematic of an airway lined with liquid of surface tension $\gamma$ and embedded in parenchyma exerting radial traction $(p_{ip} - \delta p)$ on airway. $s =$ airway radius, $a =$ radius of free surface, $R =$ airway radius when $|p_{liq}| = \gamma / a = p_{ip}$.

The liquid layer is negative with respect to that in the airway and the surrounding parenchyma due to the curvature and tension of the air-liquid interface. Taking the airway pressure to be zero, we have

$$p_{liq} = -\frac{\gamma(a)}{a}$$

(4.3)

where the surface tension $\gamma$ depends on $a$ because of the effect of surfactant; longitudinal curvature of the interface will be neglected for now. For equilibrium, the inward force caused by the surface tension and curvature is balanced by the outward traction.
\[
\frac{\gamma(a)}{a} = p_{ip} - \delta p
\]  

(4.4)

Solving for \(\delta p\) from (4.1) and (4.2), (4.4) becomes

\[
\frac{\gamma(a)}{a} = p_{ip} - \frac{2k \rho_{ip} (s - R)}{R}
\]  

(4.5)

where we have taken \(u = s - R\). Given (i) a relationship between \(a\) and \(s\), (ii) \(L\), \(R\), and \(p_{ip}\) as a function of lung volume, (iii) a value for \(\kappa\), and (iv) \(\gamma(a)\), we can solve for the interface radius \(a\) as a function of lung volume.

We will consider a single cylindrical airway of length \(2L\) (to be consistent with Fig. 2-1) in which liquid is conserved, so that

\[
V_{liq} = 2\pi L (s^2 - a^2) = \text{constant}
\]  

(4.6)

and so for any set amount of liquid, \(a\) determines \(s\). Next, we take the "uncut" parenchymal dimension \(R\) and the airway half-length \(L\) to vary as the cube root of lung volume:

\[
R = R_0 (V_L / TLC)^{1/3}
\]  

(4.7)

\[
L = L_0 (V_L / TLC)^{1/3}
\]  

(4.8)

As in Chapter Two, we take \(L_0 = 0.075\) cm (the zero subscript refers to \(t=0\), or TLC). \(R_0\) is calculated from (4.5) at the start of each simulation to agree with the specified liquid layer and parenchymal properties:
\[ R_0 = \frac{s_0}{l + \frac{(p_{ip})_0 - \gamma_0 / a_0}{2\kappa(p_{ip})_0}} \] 

(4.9)

The pressure-volume curve of the lung has an exponential form during deflation [Davis et al., 1975]; we begin using an exponential relationship in which \( p_{ip} = 30 \) cm H₂O at TLC and \( p_{ip} = 0 \) at 0.15TLC:

\[ p_{ip} = -784.48 \ln \left( \frac{1.02047 - V_L / TLC}{0.87047} \right) \text{ dyn/cm}^2 \] 

(4.10)

The lung volume corresponding to \( p_{ip} = 0 \) (\( V_L / TLC = 0.15 \)) was chosen based on data presented for rabbit [Sharp and Hammond, 1990] and dog lungs [Hughes et al., 1972]. Refinements of the above equation that consider the inflection point and departure from exponential form in the neighborhood of \( p_{ip} = 3 \) cm H₂O [Davis et al., 1975] will be considered later. We will take \( \kappa = 0.7 \), a value cited by Stamenovic and Wilson [1992] for normal lungs. Finally, we take the surface tension to either (i) remain constant with \( a \), or (ii) vary per the equation of state based on DPPC data presented in Fig. 2-3.

As in the Chapter 2 calculations, we begin at TLC. Let us consider the function \( f \) where

\[ f = \frac{\gamma}{a} - p_{ip} + \frac{2\kappa p_{ip} (s - R)}{R} \] 

(4.11)

Any \( a^* \) for which \( f(a^*) = 0 \) is a solution of the equilibrium equation (4.5). We will plot \( f \) vs. \( a \) for various lung volumes to determine how \( a^* \) depends on parameters \( V_L \), \( \gamma \), and initial liquid layer thickness \( h_0 = s_0 - a_0 \).

To determine whether these are stable solutions, consider the cross-sectioned airway in Fig. 4-3; a liquid layer configuration at equilibrium would be stable if an increase in \( a \)
resulted in an increase in the inward collapsing pressure that exceeds the increase in radial traction. (In fact, for constant surface tension, an increase in $a$ results in a decrease in both the collapsing pressure and the traction, but the airway is stable if the drop in collapsing pressure is less than that in the traction.) That is, the airway is stable if

$$\frac{d}{da}\left(\frac{\gamma}{a}\right) > \frac{d}{da}(p - \delta p)$$

(4.12)

This implies that if

$$\frac{df}{da} = \frac{d}{da}\left(\frac{\gamma}{a}\right) - \frac{d}{da}(p - \delta p) > 0$$

(4.13)

the solution is stable, and if

$$\frac{df}{da} < 0$$

(4.14)

the solution is unstable. Stamenovic and Wilson [1992] have employed a similar approach to examine parenchymal stability.

**Results.** We begin by considering a constant surface tension of 1 dyne/cm. The curves in Fig. 4-4 show two solutions at each lung volume for $0.185 \leq V_L / TLC \leq 1.00$. Based on (4.13)-(4.14), there is one stable solution and one unstable solution, the former corresponding to the solution with the greater value of $a^*$, with $df/da > 0$. We will restrict our interest to this stable solution.
Fig. 4-4. \( f \) (defined by (4.11)) vs. free surface radius \( a \) for \( V_L/TLC=0.18, 0.20, 0.4, 0.6, 0.8 \) and 1.0. Any \( a^* \) for which \( f(a^*) = 0 \) is a solution of the equilibrium equation (4.5) at the corresponding lung volume. Of the two solutions at each lung volume for \( V_L/TLC>0.19 \), only the one with \( df/da > 0 \) is stable. For \( V_L/TLC \leq 0.18 \), there is no equilibrium solution. \( \gamma = 1 \) dyne/cm, \( h_0 = 10 \) \( \mu \)m.

Figure 4-4 shows that for lung volumes below approximately 0.19TLC the curve lifts off the abscissa, and there are no physical solutions to the equilibrium equation (4.5). This implies that below a certain lung volume, the parenchymal tethering is unable to support an airway in a cylindrical configuration and so the airway "collapses" or changes shape in some way. This threshold volume increases strongly with increasing surface tension and weakly with increasing liquid layer thickness.

The time-scale for collapse of the airway once the equilibrium solution is lost can be approximated by balancing the inward driving force of the liquid layer pressure with the inertia of the surrounding parenchyma. As \( p_{lp} \) tends to zero, this yields
\[ \tau \propto \sqrt{\frac{\rho a_0^3}{\gamma_{\text{min}}}} \quad (4.15) \]

where we have taken the parenchymal mass to consist of the annulus of tissue of outer radius \( 2a_0 \), inner radius \( a_0 \), and length \( 2L \). Taking the parenchymal density to be somewhere between 0.2 and 1.0 g/cm\(^3\) [Fredberg and Holford, 1983], \( a_0=0.02 \) cm and \( \gamma_{\text{min}}=1 \) dyne/cm, \( \tau \) is of order several milliseconds, much smaller than a human breathing time-scale. Thus we will treat the maximum lung volume at which no solution to the equations exists as the collapsing volume \( V_{\text{cc}} \).

Figure 4-5 shows how the equilibrium free surface radius \( a \) varies with lung volume for the simulation shown in Fig. 4-4. As lung volume falls, so does \( a \), with increasing steepness until the solution vanishes at \( V_L/TLC=V_{\text{cc}}/TLC=0.19 \).

Fig. 4-5. Equilibrium free surface radius \( a^* \) vs. normalized lung volume for variable (Fig. 2-3, with \( \Gamma_0=1.0 \)) and constant (\( \gamma=30 \) dyne/cm) surface tensions. The variable surface tension result is virtually identical to that obtained with \( \gamma=1 \) dyne/cm=constant. TLC dimensions are \( s_0=0.025 \) cm, \( L_0=0.075 \) cm \( a_0=0.024 \) cm.
Fig. 4-6. Dimensionless lung volume at closure vs. airway liquid film thickness at TLC for $\gamma = 1$ dyne/cm. $V_{cc}$=lung volume at compliant collapse; $V_{LE}$=lung volume at liquid bridging (cf. Fig. 2-7). For the liquid bridging simulations, $T_{exp} = 3$ s. The volume at closure is determined by compliant collapse for $h_0 \leq 10$ $\mu$m and by liquid bridging for $h_0 > 10$ $\mu$m. $s_0$=0.025 cm, $\kappa$=0.7.

Figure 4-6 provides a comparison between $V_{cc}$ and the lung volume at closure by liquid bridging, $V_{LE}$ (presented in Chapter Two) as a function of initial film thickness $h_0$ for a constant surface tension of $\gamma = 1$ dyne/cm, $s_0$ = 0.025 cm, $\kappa$ = 0.7, and $T_{exp}$=3 s. As was the case in Fig. 2-7 an almost identical result would be obtained for $V_{LE}$ if the variable surface tension shown in Fig. 2-3 were employed. This is because at low lung volumes the surface tension is the same in both cases, and at higher lung volumes, the higher surface tension active in the surfactant case has a small effect because the tethering is dominant. The lung volume at closure caused by compliant collapse increases slightly with $h_0$; $V_{LE}$ is much more sensitive to this parameter. The dominant closure mechanism is compliant collapse for $h_0 \leq 11$ $\mu$m and liquid bridging for $h_0 \geq 11$ $\mu$m. Moreover, as $h_0 \to 0$ the liquid bridging model predicts that closure will not occur for
lung volumes greater than zero while that for compliant collapse predicts \( V_{cc} = 0.16 \text{TLC} \). As both \( h_0 \to 0 \) and \( \gamma \to 0 \) the compliant collapse model predicts that lung volume at closure tends to 0.15TLC, the lung volume at which \( p_{lp} = 0 \).

If the compliant collapse model described here is incorporated into the liquid bridging model described in Chapter Two, we can examine how the liquid bridging and compliant collapse mechanisms interact. For very thick films, we would expect a bridge to form before the lung volume drops to values where the airway is weakly tethered and collapse can occur. And for very thin films, we anticipate that compliant collapse will be the dominant closure mechanism, as liquid bridging would only be able to occur at very low lung volumes. Therefore, in these limits the interactive effect of the two mechanisms should be small. In between, however, the two mechanisms will combine to yield a lung volume at closure higher than either one model would predict. This is shown in Figure 4-6, which reveals a smooth transition between the two mechanisms with compliant collapse as the cause of closure for \( h_0 \leq 11 \mu \text{m} \) and liquid bridging as the controlling mechanism for thicker films. In combining the compliant collapse and liquid bridging models, we use a modified version of (4.5) at each node that takes into account both the radial and transverse curvature of the air-liquid interface (cf. (2.30)):

\[
\frac{\gamma}{a} \frac{\partial}{\partial z} \left( \psi \frac{\partial a}{\partial z} \right) \
\]

\[
\left( p_{lp} - \frac{\gamma}{a} \frac{\partial}{\partial z} \left( \psi \frac{\partial a}{\partial z} \right) \right) \
\]

\[
R \left( 1 + \frac{\gamma}{a} \frac{\partial}{\partial z} \left( \psi \frac{\partial a}{\partial z} \right) \right) \
\]

\[
(4.16) 
\]

The \( s \) values were then averaged over all the nodes to obtain a mean value which was assigned to each node. This is equivalent to assuming that the airway wall exhibits a large stiffness to axial bending. This simplified the calculation and eliminated the need to specify boundary conditions for \( \partial s / \partial z \) and \( s \) at the tube ends.
Fig. 4-7. Dimensionless lung volume at closure vs. airway liquid film thickness at TLC for $\gamma = 30$ dyne/cm. For the liquid bridging simulations, $T_{exp} = 3$ s. The dominant closure mechanism is compliant collapse for $h_0$ less than approximately 20 $\mu m$ and liquid bridging for larger values of $h_0$.

If we perform the same calculations with a higher surface tension of 30 dynes/cm, we obtain the result shown in Fig. 4-7, which reveals much higher lung volumes at closure and a compliant collapse regime dominant for $h_0$ less than approximately 21 $\mu m$. The lung volume at closure as $h_0 \rightarrow 0$ is approximately 0.40TLC. Figure 4-5 shows how the radius $a$ varies with lung volume when $\gamma=30$ dynes/cm and $h_0=10$ $\mu m$. Because of the greater collapsing pressure, the airway diameter falls more steeply than in the variable surface tension (or $\gamma=1$ dyne/cm) case, and collapse occurs at more than twice the lung volume (approximately 0.47TLC).
PART II: AIRWAY MODELED AS A PULMONARY VEIN

One of the few studies on the mechanical properties of the small airways is that of Martin and Proctor [1958]. They dissected airways from excised dog lungs and found that small airways (o. d. 2 mm) were much more compliant than medium (o. d. 5 mm) and large (segments of trachea) airways, apparently because the small airways possess less cartilage and more smooth muscle than their larger counterparts [Forrest and Lee, 1991]. Yen and Foppiano [1981] have carried out similar experiments in pulmonary veins. They also found that compliance decreased with diameter for pulmonary veins in the 100-1200 mm diameter range.

Seeing that data for small pulmonary veins is more plentiful than that for small airways, and that there may be similarities between these two pulmonary "tubes", as both contain smooth muscle, collagen, and elastin [Forrest and Lee, 1991, Fung, 1981, and Burton, 1972], let us consider how the small airways might behave if they had the same properties as pulmonary veins of the same size. Yen and Foppiano [1981] have measured the relationship between transmural pressure and diameter of pulmonary veins of the cat. They found that over a diameter range of 100-1200 μm, the diameter varies approximately linearly with the "transmural" pressure difference \( (p_v - p_{pl}) \):

\[
\frac{s}{s_{10}} = 1 + \alpha (p_v - p_{pl} - 9810) \tag{4.17}
\]

where \( p_v = \) venous pressure (dyne/cm²), \( p_{pl} = \) pleural pressure (alveolar and airway pressures were zero, so \( p_{ip} = -p_{pl} \)), \( \alpha = \) compliance coefficient (cm²/dyne), and \( s_{10} = \) the vein (inner) radius at \( (p_v - p_{pl}) = 10 \) cm H₂O=9810 dyne/cm². (We have added the -9810 term to (4.17) to correct the equation given by Yen and Foppiano [1981].) The reasons for the use of \( (p_v - p_{pl}) \) as the transmural pressure are given by Yen, Fung and Bingham [1980]. Yen and Foppiano made measurements at \( p_{ip} = 5, 10, 15 \) and \( 20 \) cm H₂O, not
including $p_{lp}=0$ to "avoid the possibility of airway collapse at very small transpulmonary pressures which could lead to distortion in the external pressure environment of the blood vessels studied." This statement lends support to the approach undertaken in previous section. It is unfortunate that no data are presented for $p_{lp}=0$, as this is the region of greatest interest when modeling airway closure. Such data would help differentiate between the contributions of vessel stiffness and parenchymal tethering at low lung volume.

Fung [1984] points out that pulmonary veins are able to withstand negative transmural pressures of large magnitude because they are supported by tension in the surrounding interalveolar septa. This tethering prevails as long as the lung is inflated and the alveoli are open, and tends to distend the vessel. The walls of pulmonary veins have an exponential stress-strain relationship which causes the incremental Young's modulus to increase as the vessel is distended; this rise in modulus in turn causes the critical buckling pressure to increase. Hence vessel stiffness is greatly increased by parenchymal tethering. Although we lack data on vessel compliance in the neighborhood of $p_{lp}=0$, we can explore an upper limit of vessel stiffness in the neighborhood of $p_{lp}=0$ by taking the compliance at that pressure equal the compliance at $p_{lp}=5$ cm H$_2$O.

**Methods.** Taking the vein to be an airway, we substitute $p_v$ with $p_{liq}$, which from (4.3) is $\gamma / a$. Thus the equilibrium condition (4.17) can be written

$$\frac{\gamma}{a} = p_{lp} - \frac{s-s_{10}}{\alpha s_{10}} - 9810$$

(4.18)

As in the previous section, solutions to this equation will be stable if

$$\frac{d}{da} \left( \frac{\gamma}{a} \right) > - \frac{1}{\alpha s_{10}} \frac{ds}{da}$$

(4.19)
We now define a new $f$ as

$$f = \frac{\gamma}{a} \left( p_{ip} - \frac{s - s_{10}}{\alpha s_{10}} - 9810 \right)$$  \hspace{1cm} (4.20)

and plot it versus $a$ with lung volume as a parameter. However, we must first specify how $s_{10}$ varies with lung volume. Yen and Foppiano [1981] do not provide this information. We will take

$$s_{10} = (s_{10})_0 \left( \frac{V_L}{TLC} \right)^{1/3}$$  \hspace{1cm} (4.21)

although this probably underestimates the true value. We can now calculate the $s_{10}$ value at TLC to agree with $\alpha$ and the TLC values for $\gamma$, $a$, $s$, and $p_{ip}$:

$$(s_{10})_0 = \frac{s_0}{1 + \alpha \left( -\frac{\gamma_0}{a_0} + \left[ p_{ip} \right]_0 - 9810 \right)}$$  \hspace{1cm} (4.22)

We employ conservation of liquid (4.6), the airway length-lung volume relationship in (4.8), and the $p_{ip}$-$V_L$ curve (4.10) to plot $f$ vs. $a$.

**Results.** A result obtained with a constant surface tension of 30 dynes/cm, $\alpha = 1.02 \times 10^{-5}$ cm$^2$/dyne (as measured for Yen and Foppiano for veins in the 400-800 $\mu$m diameter range), $s_0 = 0.025$ cm and $h_0 = 10$ $\mu$m is presented in Fig. 4-8. There are two solutions for each volume, and (4.19) implies that only the solution with $df/da > 0$ is stable. This equilibrium $a$ value decreases steadily with lung volume and disappears at a volume just below 0.20 TLC.

For lower surface tensions, lower lung volumes can be reached before the solution disappears. However, it is likely that the vessel compliance, which Yen and Foppiano
found to be constant over the range $5 \text{ cm H}_2\text{O} < p_{tp} < 20 \text{ cm H}_2\text{O}$, increases significantly as the distending pressure tends to zero. Such an increase in compliance will promote airway collapse at lung volumes higher than those computed here.

Fig. 4-8. $f$ (defined by (4.20)) vs. free surface radius $a$ for $V_L/\text{TLC}=0.1$, 0.2, 0.3, 0.5, 0.7 and 1.0. Any $a^*$ for which $f(a^*) = 0$ is a solution of the equilibrium equation (4.18) at the corresponding lung volume. Of the two solutions at each lung volume for $V_L/\text{TLC}>0.19$, only the one with $df/da > 0$ is stable. For $V_L/\text{TLC}<0.19$, there is no equilibrium solution. $\alpha = 0.011981 = 1.02 \times 10^{-5} \text{ cm}^2/\text{dyne}$, $\gamma = 30 \text{ dyne/cm}$, $h_0 = 10 \mu\text{m}$.

Figure 4-9 shows how the equilibrium radius $a^*$ varies as a function of lung volume both for the $\gamma=30$ simulation shown in Fig. 4-8 and for another simulation with $\gamma=1$ dyne/cm. These curves differ in many ways from those presented in Fig. 4-5 for the model presented in Part I. First, there is little difference between the curve for $\gamma=\gamma(\Gamma)$ and that for $\gamma=30 \text{ dyne/cm}=\text{constant}$. Second, the curves have a sigmoid shape instead of the monotonically increasing slope with decreasing lung volume characteristic of the curves in Fig. in Fig. 4-5.
Fig. 4-9. Equilibrium free surface radius $a^*$ vs. normalized lung volume for variable ($\Gamma_0=1.0$) and constant ($\gamma=30$ dyne/cm) surface tensions. TLC dimensions are $s_0=0.025$ cm, $L_0=0.075$ cm, $a_0=0.024$ cm. Airway has been modeled as a pulmonary vein with $\alpha = 1.02 \times 10^{-5}$ cm$^2$/dyne.

Fig. 4-10. Lung volume corresponding to compliant collapse (cc) or liquid bridging (LE) vs. liquid film thickness at TLC. Results for constant surface tensions of 1 and 30 dyne/cm.
Figure 4-10 shows that the $V_{cc}$ values calculated are linearly related to the initial film thickness and that both $V_{cc}$ and $V_{LE}$ tend to zero as $h_0 \to 0$. For a given surface tension, the $V_{LE}$ vs $h_0$ slope is steeper than that for $V_{cc}$ vs. $h_0$, and the lines do not cross as they did in Figs. 4-6 and 4-7. This would not be the case if the simulation took account of the increase in vessel compliance at low lung volume.

DISCUSSION

Two simple models of the compliant collapse mechanism have been presented. The first considers a balance between parenchymal tethering and the inward collapsing pressure caused by surface tension. The second balances the same inward collapsing pressure with the elasticity of the airway. Both models predict a lung volume below which the balance of forces cannot be maintained. It is presumably at this volume that some type of airway collapse would occur.

The models show two very different ways in which the lumen radius $a$ varies with lung volume during expiration. In Fig. 4-11 we plot the $a$ vs. $V_{L}/TLC$ results for the two models at two surface tensions and include for comparison $a$ vs. $V_{L}/TLC$ curves that assume (i) a constant amount of airway liquid confined in a tube whose inner diameter and length vary as the cube root of lung volume and (ii) a constant amount of airway liquid and tissue confined in an airway whose outer diameter (i. e. the outer diameter of the adventitia) and length vary as the cube root of lung volume. In this latter case we have used the model of Wiggs et al. [1990, 1992] to estimate the cross-sectional area of the wall of a sixteenth-generation airway.
Fig. 4-11. Variation of free surface radius $a$ with normalized lung volume for (a) a liquid-lined airway with inner diameter and length varying as the cube root of lung volume, (b) an airway of negligible stiffness embedded in parenchyma with $\gamma = \gamma(\Gamma)$, (c) an airway modeled as pulmonary vein with $\gamma = \gamma(\Gamma)$ and $\alpha = 1.02 \times 10^{-5}$ cm$^2$/dyne=constant, (d) an airway modeled as pulmonary vein with $\gamma = 30$ dynes/cm=constant and $\alpha = 1.02 \times 10^{-5}$ cm$^2$/dyne=constant, (e) a liquid-lined airway with outer (adventitial) diameter and length varying as the cube root of lung volume, and (f) an airway of negligible stiffness embedded in parenchyma with $\gamma = 30$ dynes/cm=constant. For all simulations, $a_0 = 0.024$ cm, $s_0 = 0.025$ cm, and airway length = 2L$_0$ = 0.150 cm. For part I simulations, $\kappa = 0.7$.

The leftmost curve (a) reveals how $a$ would vary in a non-compliant but shrinking tube ($s \propto V_L^{1/3}$, $L \propto V_L^{1/3}$ as in the model developed in Chapter Two) as lung volume falls. The curve corresponds to a liquid lining layer that remains cylindrical, with closure occurring when the airway is full of liquid. In reality, the liquid layer would not remain cylindrical, and so closure would occur at a higher lung volume than that shown. It is demonstrated in Chapter Two that the lung volume at closure would be determined by the liquid layer properties and expiration rate, but would not exceed 0.26TLC.
Curve (e) is obtained by a method identical to that for (a) except that in the former case it is the *outer* diameter of the airway that is taken to fall as the cube root of lung volume. In such case the void volume (i.e. the lumen) rapidly diminishes with lung volume as the tissue volume must remain constant. Moreover, the liquid layer dynamics discussed in relation to curve (a) also pertain here, and could move curve (e) even farther to the right if the minimum value of $a$ was plotted versus lung volume.

Curves (b) and (f) delimit a range of curves with negligible wall stiffness, but are supported by parenchymal tethering, which counteracts the collapsing effect of surface tension. The result is highly dependent on surface tension; in the limit as $\gamma \to 0$, closure will occur at $V_L/TLC=0.15$, the point at which $p_{tp}$ is taken to be zero. For higher surface tensions, the $a$ vs. $V_L$ curve steepens and closure occurs at higher volumes, as the parenchymal tethering falls with lung volume while the collapsing pressure may increase. The collapsing volume for curve (f) ($\gamma=30$ dyne/cm) is more than twice that obtained with curve (b) ($\gamma=\gamma(1)$ or $\gamma=1$ dyne/cm=constant).

Finally, curves (c) and (d), obtained using the model developed in part II, have a different shape than the other curves and an almost negligible dependence on surface tension. The form of these curves rests on the assumptions made about the compliance at low transpulmonary pressures and the volume dependence of $s_{10}$; it is a great shortcoming of this model that we are left to speculate about parameters and relationships that have a decisive effect on the model result. Furthermore, although there may be similarities between small pulmonary veins and airways of equal diameter, their mechanical properties may be quite different. Both contain smooth muscle, but apart from that little seems to be known. In light of these deficiencies, it seems best to turn our attention to the parenchymal tethering model developed in Part I, for which more relevant and complete data are available (while recognizing that this model neglects airway wall properties which are likely the only structures promoting airway patency around $p_{tp}=0$).
In this model we employed the data and analysis of Lai-Fook et al. [1977] to consider how a liquid-lined airway embedded in parenchyma would change shape and eventually collapse as lung volume is reduced. We reasoned that once the parenchymal tethering cannot balance the inward collapsing pressure caused by surface tension, the airway collapses rapidly, on a time-scale given by (4.15). This allows us, for specified liquid layer and parenchymal properties, to calculate the "collapsing volume" by determining the minimum lung volume at which a balance of forces (4.5) is possible. This yielded the curves in Figs. 4-6 and 4-7, which reveal how collapsing volume varies with initial film thickness and surface tension.

The liquid bridging closure mechanism described in Chapter Two is also considered in Figs. 4-6 and 4-7, in the former figure the combined effect is shown. It is apparent that for low film thicknesses, the compliant collapse mechanism governs the closure process. As film thickness increases past a certain threshold, however, the liquid bridging mechanism takes control. This supports a hypothesis advanced in Chapter Two, viz. that liquid bridging may only be an important closure mechanism in diseased lungs with excess airway liquid.

Raising the airway surface tension causes the airways to collapse at higher lung volumes; comparison of Figs. 4-6 and 4-7 makes this clear. Enhorning [1988] has reasoned that peripheral airways may be more prone to collapse than the alveolar spaces because (i) the mean curvature is usually larger in the airways, (ii) surfactant is secreted in the alveoli and hence $\gamma$ should be lowest there, and (iii) the alveolar film is more compressed than the airway film, causing $\gamma$ in the alveoli to fall faster (and maybe farther) than that in the airways. It was shown in Fig. 2-6(b) that the larger the airway surface tension, the greater the magnitude of the negative pressure in the liquid layer that tends to cause compliant collapse. The high values of $V_{cc}$ in Fig. 4-7 are a result of these large negative pressures.
Fig. 4-11. Deflation limb of the lung volume vs. transpulmonary pressure curve for constant surface tension lobe ($\gamma = 32$ dyne/cm curve adapted from Stamenovic and Smith [1986] and D. Stamenovic [personal communication]) and lobe with exponential $p_{tp}-V_L$ dependence for $0 < p_{tp} < 30$ cm H$_2$O (eq. (4.10)).

It should be noted that the results obtained with the compliant collapse model developed in Part I are sensitive to the pressure-volume curve that is used, and especially to the lung volume at which the transpulmonary pressure goes to zero. In (4.10) this is taken to be 0.15TLC. If the liquid lining the airways and airspaces possesses a constant surface tension, the $p_{tp}-V_L$ curve does not fit an exponential form like that in (4.10). Smith and Stamenovic [1986] have measured $p_{tp}-V_L$ relationships in such lobes, and a representative curve is shown in Fig. 4-11. For a given lung volume, the transpulmonary pressure required to hold the constant surface tension ($\gamma = 32$ dyne/cm) lobe open is greater than that for the normal lobe, represented by (4.10). Deflation of lobes with constant, high surface tension to zero transpulmonary pressure results in complete
collapse, so that no gas is trapped in the lobe, i.e. $V_L \to 0$ as $p_{tp} \to 0$. (The curves in Smith and Stamenovic [1986] do not fully detail the limit where $p_{tp} \to 0$, but Fig. 4-11 fairly represents the measured curves in this region [D. Stamenovic, personal communication].) The lack of gas trapping does not necessarily imply the absence of airway closure, as alveolar collapse can precede airway closure, driving out alveolar gas before airway closure can trap it. In this regard, Greaves et al. [1986] assert that although airways and airspaces both collapse near zero transpulmonary pressure, airway closure normally precedes alveolar collapse; perhaps this is because the airway surface tension exceeds that in the alveoli. The terminal bronchioles readily collapse because they lack cartilage, but the same is true of the alveolar septa [Greaves et al., 1986], which will promptly buckle if a higher than normal surface tension imposes a compressive stress on them; such higher than normal surface tensions would certainly be expected to prevail in airspaces coated with constant surface tension liquid. Hence a plausible explanation for the absence of gas trapping in constant surface tension lobes is a reversal of the normal sequence of airway closure, as is believed to occur in some diving mammals. Such mammals are believed to possess peripheral airways lined with cartilage, so that alveolar collapse precedes airway closure, and on slow deflation the excised lung empties completely, trapping no gas [Greaves et al., 1986].

We have taken the linear relationship between $u$ and $\delta p$ (4.2) to hold for the full range $0 < u < U$. Lai-Fook et al. [1977] performed a (presumably more accurate) nonlinear analysis that yielded a nonlinear $u$ vs. $\delta p$ relation which matched the linear relation (and the data) at $u=0$ and $u=U$, but gave greater $u$ values in between. (No experimental measurements were made for $0 < u < U$, so there is presently no way of telling which analysis provides the best match to the data.) It would be simple to replace the linear relation (4.2) with the nonlinear result of Lai-Fook et al.; we would not expect, however, that it would qualitatively affect the results or even produce a significant quantitative effect.
The same holds for the incorporation of precise $p_{tp}-V_L$ curves that include the inflection point at $p_{tp} = 3 \text{ cm H}_2\text{O}$. It is interesting that this inflection point is often identified as the onset of airway closure [Demedts et al., 1975]. Indeed, the tethering model implies that the airways will lose their patency as $p_{tp}$ tends to zero, and it is at the inflection point that the $p_{tp}-V_L$ curve "turns the corner" in the final approach towards $p_{tp}=0$. The present model implies that airway closure would not occur in a normal lung until $p_{tp} = 1 \text{ cm H}_2\text{O}$ and therefore may seem inconsistent with the assumption that closure begins at higher transpulmonary pressures. Perhaps this discrepancy may be attributed to inhomogeneity of the lung; if, for example, a lung does not contract uniformly on expiration, the region of greatest compliance will have its dimension $R$ fall faster than indicated by (4.7). In such a case, the airways enclosed in this region would be expected to close before those in less compliant regions. (It is somewhat surprising that the present model should underestimate the transpulmonary pressure at which closure begins, as we have neglected airway wall stiffness.) Alternatively, the inflection point on the lung $p_{tp}-V_L$ curve may be caused by factors other than airway closure. In this regard, preliminary numerical simulations of alveolar duct mechanics which do not account for airway closure also exhibit an inflection point in the $p_{tp}-V_L$ curve in the neighborhood of $p_{tp}=3 \text{ cm H}_2\text{O}$ [R. C. Schroter, personal communication].

Both the parenchymal and vein models take the airway lumen to be circular. This is likely true at high lung volumes, but becomes questionable as lung volume is reduced, and is clearly false when the airway has collapsed. If the out-of-roundness or epithelial wrinkling is slight, the time-scale for circumferential liquid movement (see Appendix 2C) will be small and the liquid layer will flow to form a uniform radius $a$. If, however, the out-of-roundness or ridging is severe, the air-liquid interface will not be circular. In such cases there will still be a net inward collapsing pressure, but exactly how it will balance the recoil force (owing to parenchymal tethering and/or tube elasticity) is difficult to say.
The analysis of Halpern and Grotberg [1992, 1993] also assumes that the airway remains circular as it collapses.

A more complete model would include the effects of stiffness, tension, mass, viscoelasticity and thickness of the airway wall. Halpern and Grotberg [1992, 1993] have developed a model that includes all these effects. The model provides insight into the roles played by the various parameters, but the values assigned to each parameter are somewhat speculative, as the mechanical properties of the peripheral airways are not well characterized. Moreover, no provision is made for parenchymal tethering or the variation of airway dimensions that accompany expiration. This last fact makes direct comparison between their model and ours difficult.

Lambert [1991] states that parenchymal tethering, smooth muscle, and the basement membrane underlying the epithelial cells all contribute to the stiffness of the peripheral airways. He argues that this last component may lend significant stiffness to the airway because it is composed of collagen, the stiffest type of airway soft tissue. On this basis, the airway is modeled as a thin-walled linearly elastic tube and the basement membrane is "geometrically confined" by the surrounding smooth muscle. It is demonstrated that the greater the number of ridges or folds in the basement membrane, the greater the collapsing pressure the airway can withstand.

Ultimately, accurate simulations of airway collapse should also take into account the non-circular cross-section of the airway and buckling of the airway wall at low lung volume. Until that time, the approach presented in Part I of this chapter provides an approximation of the upper limit of lung volume at which airway collapse will occur.
REFERENCES


Chapter 5

Simulation of Airway Closure by Liquid Bridging in a Physical Model

ABSTRACT

The time-scale of liquid bridge formation in a branching network of tubes has been measured in a physical model. The branching network simulates four generations of pulmonary airways; two immiscible liquids of equal density are used to model airway liquid and air. The measurements are compared with time-scales computed from a one-dimensional numerical model of closure in a single cylindrical airway [Johnson et al., 1991]. The computed and measured results are in reasonably close agreement although the latter stages of closure proceed more slowly than predicted. The effect of slight airway curvature and neighboring airways do not appear to significantly influence the closure time-scale.

INTRODUCTION

It has been shown that pulmonary airways close at low lung volume, leaving gas in airspaces distal to the closure site "trapped" [Engel et al., 1975] until re-opening occurs. It is believed that closure occurs due to collapse of the airway wall and/or the formation of liquid plugs or "bridges" that block the airway lumen [Kamm and Schroter, 1989].

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Liquid bridging occurs for the same reason that a cylindrical stream or column of liquid breaks up into individual droplets with aggregate surface area less than that of the original column. Such a column is unstable to small radial perturbations; if perturbations are present, a stream or column will separate into a series of droplets if its length exceeds its circumference. This instability, first discussed by Lord Rayleigh [Rayleigh, 1879], also applies to a liquid annulus of uniform thickness: if the axial length of the annulus exceeds its inner circumference, the instability will cause a flow that drives the liquid layer away from its initial shape toward a liquid bridge or unduloidal surface configuration. The latter forms if there is insufficient liquid to form a bridge [Johnson et al., 1991]. For a straight tube with length-to-diameter ratio in the range found in the pulmonary airways, it has been found that closure will occur if \( V_{\text{liq}}/s^3 > 5.6 \) where \( V_{\text{liq}} \) is the quantity of liquid lining the airway wall and \( s \) is the airway radius [Kamm and Schroter, 1989].

In previous studies, airway closure has been studied by numerical analysis in the idealized configuration of a cylindrical tube with zero-flow boundary conditions at both ends [Johnson et al., 1991, Halpern and Grotberg, 1992 & 1993, and Otis et al., 1993]. In reality, the individual segments of the airway tree are curved and the possibility exists for movement of wall liquid between neighboring generations. The present study was motivated by a need to explore the effect on closure time of a more realistic geometry.

For this purpose we performed experiments in a large-scale laboratory model of a branching network in which liquid bridges can form (Fig. 5-1). The time-scale for bridge formation was measured and is compared with the results from the axisymmetric numerical model of bridge formation in a finite-length cylindrical tube [Johnson et al., 1991].
Fig. 5-1. Schematic of four-generation Plexiglas branching network with associated tubing and valves. Valve A is the inlet through which the low-viscosity core liquid is introduced. The generation number (1-4) of each airway is noted. Once the low-viscosity core liquid has passed through the eight distal valves B, these valves and the inlet valve A are closed.

MATERIALS AND METHODS

A symmetrical, large-scale model of four generations of the bronchial tree, shown schematically in Fig. 5-1, was employed in the experiments. It was constructed by Hammersley et al. [1986, 1992] with airway dimensional ratios $L_{aw}/2s=3.0$, $s_p/s_d=1.33$, $R/s_d=7$ and branch angle $70^\circ$. The diameter of the first-generation airway is 2.5 cm. The branching network is made of Plexiglas, machined and polished to give maximal optical clarity and minimal distortion; Plexiglas has a refractive index of $n_2=1.49$. Fluid is
supplied and drained from the network through tubing and valves shown schematically in Fig. 5-1. The fluid used to line the tube walls in the network, modeling airway liquid, was a silicone oil (Dow Corning 200 Fluid) with a kinematic viscosity of $10^4$ centistokes, refractive index $n_1=1.40$ and specific gravity 0.960. The core liquid, modeling air, was a mixture of ethanol and water, with a kinematic viscosity of 1.7 centistokes and specific gravity equal to that of the oil to eliminate the effects of gravity. Food coloring was added to the core liquid to provide contrast. The interfacial tension between the core and wall liquids was measured with a ring tensiometer (du Noüy Tensiometer #70535, Cenco Instruments, Chicago, IL) and found to be 35 dynes/cm.

This network was completely filled with the high-viscosity oil before the low viscosity liquid was introduced to the network through valve A (Fig. 5-1). A positive, constant pressure was maintained at A while the low viscosity liquid purged oil from generations 1-4 of the network. Equal hydraulic resistances distal to each generation 4 airway equalized the flow rates through each branch of the tree, and a thin film of oil was left on the walls of the tubes. The thickness of the film was controlled by the speed at which the core liquid was introduced into the network; an analogous problem in a straight tube was treated experimentally by Taylor [1961].

Once the core had been purged, the valves feeding and draining the network, A and B, were closed and the liquid film on the walls, initially of approximately uniform thickness in a given airway, began to redistribute in order to reduce the interfacial area. If sufficient wall liquid was present to form a bridge, the time required for the bridge to form was measured, and its position recorded. The closure process in one airway is illustrated in Fig. 5-2, where the wall liquid thickens near the airway midsection until a bridge forms at time $t = t_c$ (Fig. 5-2(c)). Photographs (NIKON Nikkormat 35 mm SLR camera with Kodak Ektachrome 400 HC) of each airway in generations 2 and 3 (measurements were not made in generations 1 or 4 to avoid effects of surrounding tubing) were taken as the
closure process proceeded, beginning with a snapshot of the airway immediately after the core of low-viscosity liquid passed through (t=0) (Fig 5-2(a)) and continuing through the course of bridge development (e.g. Fig. 5-2(b)-5-2(d)).

The photographs were analyzed in one of two ways, either scanned and processed digitally (SCANFRESCO software, developed at MIT, with user interface by Celadon Inc., Cambridge, MA) to measure the interfacial radius \( a \) in each airway, or were projected onto a wall and measured directly. Measurements from the photographs were corrected for the error due to refraction through the Plexiglas and wall liquid; it can be shown that the measured (apparent) value of \( a \) must be multiplied by \( n_2/n_1 \) to obtain the true, corrected value. Closure time \( (t_c) \) was determined as the instant at which opposite sides of the film first came into contact (Fig. 5-2(c)).

We define a disturbance amplitude \( \varepsilon \) such that

\[
\varepsilon = 1 - \frac{a_{min}}{a_0}
\]  

(5.1)

where \( a_{min} \) is the radius of the free surface at the axial position where the bridge forms, and \( a_0 \) is the radius of the interface at time zero; \( \varepsilon \) grows with time, starting at some small initial value at \( t=0 \) and reaching 1 at closure (\( t=t_c \)). The interface radius \( a_0 \) is measured from the initial snapshot (Fig. 5-2(a)) and a value of \( a_{min} \) is measured in each subsequent photograph. Therefore for each photo there corresponds a value of \( \varepsilon \) and time to closure (\( t_c-t \)). Specification of \( \varepsilon \) and the physical properties (\( \mu, \rho \)) and dimensions (\( L, s, a_0 \)) of the liquid layer suffice to compute the time to closure from the numerical model. In this way the model of Johnson et al. [1991] and the experiment may be directly compared.
Fig. 5.2. Closure process in a generation 2 airway. (a) Initial snapshot (t=0) taken immediately after the core of dark, low-viscosity liquid has passed through (from right to left), leaving a film of clear, high-viscosity liquid on the tube walls; (b) photo at t=770 s with t=0.23; the Rayleigh instability causes the film thickness to be non-uniform; (c) a bridge forms, closing the tube at t=t=1355 s; (d) the bridge evolves to have a more uniform curvature and greater thickness (at t=1375 s).
RESULTS AND DISCUSSION

The purpose of these experiments was to determine if factors such as airway curvature and neighboring bifurcations had a significant influence on the time it takes for a liquid bridge to form. The comparison of experimental times and numerical predictions shown in Fig. 5-3 suggests that, while these factors exert some influence, the effects of airway geometry are not dominant. In general, the numerical model underestimates the closure time, a tendency that is especially evident near the end of the closure process ($t_c - t \leq 600$ s) where the data suggest a curve that is concave upward.

![Graph showing comparison of predicted and measured closure times](image)

Fig. 5-3. Comparison of the measured and predicted closure times. Predicted times were computed from the 1-D model described in [Johnson et al., 1991]. Measured times correspond to the time it takes to produce closure ($t_c - t$) from a specified perturbation measured at time $t$. The symbols specify generation number and experimental run number.
There are a number of factors that could produce the observed discrepancies. One is the exchange of liquid between adjacent airways. In general, liquid would be expected to flow from parent to daughter due to the smaller radius, and therefore lower pressure, in the daughter branch (note that the ratio of initial film radius $a_0$ to airway radius $s$ was nearly constant through the generations 2-4; hence the smaller $s$ values in the smaller daughter airways would make the $a_0$ values there less also). These tendencies might be expected to exert the greatest influence during the early growth of the instability since the thickness of the communicating film tends to decrease as time progresses. The observation that differences between theory and experiment are greatest near the end of the process suggests that this effect is not dominant, although it is difficult to rule out completely. Also, in the competition for liquid between neighboring branches, one might expect that those airways in which the initial perturbation is greatest would exhibit the fastest growth during the early stages of the instability and therefore tend to draw liquid from neighboring films. If this occurred, some branches would close more rapidly while others would progress toward closure more gradually. Since all airways seem to exhibit the same tendency, this mechanism also seems unlikely.

The effect of curvature may play a role, but it is difficult to see why it should have a greater influence during the later stages of closure. It is interesting to note that, despite airway curvature, the initial distribution of liquid around the circumference is remarkably uniform as can be seen in Fig. 5-2. Even the axial curvatures in the vicinity of the bifurcation have little influence over the film thickness, except at the carina where the thickness approaches zero.

Another influence is the possible presence of trace contaminants which might be present at the interface. Such impurities might act as a surfactant and reduce the interfacial tension. As the instability proceeds, motion of the interface is such that surface impurities will tend
to accumulate in the region where the film is thickening, producing a nonuniform surfactant
distribution and therefore a surface tension gradient. Such gradients will tend to oppose the
growth of the instability and increase the time to closure by a factor of four as shown by
Otis et al. [1993]. Since this effect requires the establishment of concentration gradients, it
would exert an increasing effect as the instability proceeds, consistent with the experimental
observation. Although it is not possible to quantify this effect in the experiments since the
concentration and physico-chemical nature of surface-active impurities in the film are
unknown, the experimental observations are consistent with this hypothesis.

These experiments also provide information concerning the magnitude of the initial
perturbation that should be used in the numerical simulations. Previously [Johnson et al.,
1991, Otis et al., 1993], a sinusoidal perturbation with amplitude $\varepsilon=0.001$ was arbitrarily
chosen for use in the simulations. Using the time between the start of an experiment and
the establishment of a disturbance of measurable amplitude as a means of estimating the
*actual* initial perturbation gives estimates in the range of $\varepsilon=0.02$ to $\varepsilon=0.2$. Due to the
somewhat idealized geometry of the model, it is likely that perturbations in the lung are at
least of comparable magnitude.

Another factor not yet discussed concerns the similarity between these experiments and
the instability that presumably occurs in the peripheral airways of the lung. Clearly,
pulmonary airways are compliant and the physical model is not; this gives rise to
differences in the rate of closure as discussed in Halpern and Grotberg [1992]. There is
also the question of proper scaling with respect to inertial effects. The appropriate
Reynolds number for this type of flow in a single cylindrical airway of length $L_{aw}$ has been
determined by Johnson et al. [1991]:

\[
Re = \left( \frac{\rho a_0 \gamma}{9 \mu^2} \right)^{1/2} \left( \frac{h_0}{a_0} \right)^{5/2} \left( \frac{\lambda^2 - 1}{\lambda^4} \right)^{1/2}
\] (5.2)
where $\lambda = L_{aw}/(2\pi a_0)$. Here we take $L_{aw}$ equal to three times the tube diameter. For a tube in generation $3$ of the branching network, with the fluid properties given earlier and $h_0/a_0=0.39$, $Re=7\times10^{-4}$, indicating that inertial effects are negligible in the experiment. In the terminal bronchioles of the lung, $Re$ can vary over a wide range, depending on the properties and dimensions of the liquid layer. With $\gamma=20$ dynes/cm, $\rho=1$ g/ml, $\mu=0.01$ dyne-s/cm$^2$, $a_0/s=0.8$ and $s=0.025$ cm, the relation above gives $Re=0.3$. In this case, the inclusion of inertia in the calculation slightly increases the computed closure time, by $8\%$. For a thicker film, e.g., $a_0/s=0.7$, and all other parameters as above, $Re=1.2$ and inertial terms play a larger role, extending the computed time to closure by over $80\%$.

Alternatively, if the surface tension is reduced ten-fold (as by pulmonary surfactant) and the viscosity is increased a hundred-fold (as by airway mucus), $Re$ is reduced to $0.001$ when $a_0/s=0.8$, implying that inertia is unimportant. Therefore the experiment, performed at approximately this Reynolds number, most effectively models closure in airways in which the airway geometry and airway liquid properties cause $Re$ to be significantly less than one.

The primary purpose of these experiments, however, was to provide some validation of the numerical simulations in a geometry that better mimics that of the lung rather than to produce perfect similarity. In that regard, it appears that geometry plays a minor role and that factors such as slight airway curvature and neighboring airways do not significantly influence the time-scale of airway closure by liquid bridging.

**NOMENCLATURE**

- $a$ radius to free surface, cm
- $h$ film thickness on airway wall (s-a), cm
- $L_{aw}$ length of a single airway branch, cm
\( n_1 \) index of refraction of wall liquid (silicone oil)
\( n_2 \) index of refraction of Plexiglas
\( R \) radius of curvature of airway centerline in bifurcation, cm
\( Re \) Reynolds number
\( s \) radius of airway, cm
\( t \) time, s
\( V_{\text{liq}} \) volume of liquid lining the airway wall, ml
\( \gamma \) interfacial tension between wall and core liquids, dyne/cm
\( \lambda \) \( L_{aw}/(2\pi a_0) \)
\( \mu \) viscosity of wall liquid, dyne-s/cm\(^2\)
\( \rho \) density of wall liquid, g/ml

**Subscripts**

0 \( \Rightarrow \) \text{t=0}

\( p \Rightarrow \) parent

\( d \Rightarrow \) daughter
REFERENCES


Chapter 6

Assessment of Airway Closure and Re-opening with the Alveolar Capsule Oscillation Technique

ABSTRACT

An alveolar capsule oscillation technique has been employed to measure the acoustic impedance of the terminal airways of excised canine lobes. This technique allows one to determine the lobar pressure and volume at which the airways proximal to the capsule close and re-open. Three protocols were performed to determine (i) the lobe pressure and volume at which the airways close and re-open, (ii) the effect of expiration rate on closing volume and pressure, (iii) the effect of lobe perfusion on airway closure and re-opening, (iv) the phase in the breathing cycle at which airway closure occurs and (v) the site of airway closure. The mean transpulmonary pressure at closure in unperfused lobes was slightly less than zero ($p_{tp} = -2.5$ cm H$_2$O); the corresponding mean re-opening pressure was $p_{tp} = 14$ cm H$_2$O. A perfused lobe closed at slightly higher transpulmonary pressure ($p_{tp} = 0$ cm H$_2$O) but opened at approximately the same pressure as the unperfused lobes. The expiration rate was varied between 1 and 20% TLC/s and appeared to have no effect on the closing volume and pressure. Closure usually took place on expiration but appeared to occur on inspiration in special breathing maneuvers. Analysis of the measured acoustic impedances and re-opening pressures suggests that closure occurred in the respiratory bronchiole and alveolar duct region. Re-opening was usually signalled by a sudden decrease in capsule impedance on inspiration; however, stepwise decreases in impedance were often seen, suggesting a sequential popping open of series and/or parallel arrangements of closed airways.

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INTRODUCTION

Various techniques have been employed to determine the lung volume corresponding to airway closure. The nitrogen washout test [West, 1987] has been used widely to make this type of measurement. Engel et al. [1975] employed radioactive xenon gas to determine both the site of airway closure and the lung volume at which it occurs. These methods are limited, however, in their spatial resolution. They are "macroscopic" in that they provide an averaged result over a portion of the lung, not detailed data from a particular acinus. To better understand the mechanisms responsible for airway closure, examination of the process in individual airways is required.

In this chapter we present a direct method for assessing airway closure and re-opening events in specific acini of an excised lung; the method also allows one to estimate the site of airway closure. The alveolar capsule, which has been used widely to monitor alveolar pressures in airspaces close to the pleura [Fredberg et al., 1984], is employed. The apparatus developed to perform this operation will now be described.

APPARATUS AND METHODS

Figure 6-1 shows a schematic of the alveolar capsule oscillation apparatus. An excised canine lobe, cannulated at the main bronchus, was attached to tubing A through which air was passed to inflate the lobe. Small capsules (5 mm diameter base) were glued to the pleural surface at C and a perforation of this surface through the capsule bore was made, allowing the airspace under the perforation to communicate with a small loudspeaker D (30 mm diameter, Phillips) through polyethylene tubing (1.45 mm i. d.) E. At various degrees of lung inflation, the loudspeaker was driven at a set frequency and the resultant signal at miniature transducers F and G (ICS model 33NA002D) compared. Using transmission
line theory [Franken et al., 1981, Fredberg et al., 1984], the input impedance seen from the puncture \((Z_c)\) through the alveolar capsule can be calculated. This impedance can be used to gauge whether the airways to which the capsule is connected are open or closed.

![Diagram of alveolar capsule oscillation apparatus](image)

Fig. 6-1. Schematic of the alveolar capsule oscillation apparatus.

The deflation and inflation rates were measured by a screen pneumotachograph \(H\) (16 mm i. d.) with an attached transducer (Validyne MP45, ±5 cm H\(_2\)O), and changes in the lobe volume were obtained by integrating the flow signal. The transpulmonary (or translobe) pressure, \(p_{tp}\), was measured near the main bronchus by the transducer \(J\) (Validyne MP45, ±30 cm H\(_2\)O). The pressure signals read by the transducers were low-pass filtered at 25 Hz and digitized using an analog-to-digital converter board on an IBM AT compatible computer.

**Theory.** The acoustic input impedance seen through the capsule, \(Z_c\), is equal to the load impedance on the catheter \(E\), which for low frequencies [Fredberg et al., 1984] is
\[
Z_c = \frac{P_c}{V_c} = \frac{Z_{\text{char}} \sinh(jkL)}{P_l / P_c - \cosh(jkL)} = R_c + jX_c
\] (6.1)

(this relation is derived in Appendix 6A) where \(P_l\) and \(P_c\) are the pressures measured by the transducers at the loudspeaker and capsule, respectively, \(\dot{V}_c\) is the flow rate through the capsule, \(L\) is the length of tubing between the loudspeaker and capsule, \(Z_{\text{char}}\) is the characteristic impedance of the polyethylene catheter, \(k\) is the wavenumber, and \(R_c\) and \(X_c\) are the input resistance and reactance, respectively. For a loudspeaker oscillation frequency of 10 Hz (used in all experiments that employed the speaker), speed of sound in air of 340 m/s, and \(L = 1.0\) m, \(\cosh(jkL)\) has a magnitude of approximately one. When closure occurs, the magnitude of the pressure ratio \(P_l / P_c\) also tends to one, making for a very high \(|Z_c|\); because of noise in the pressure signal, however, the pressure ratio fluctuates about one, causing the calculated impedance to vary wildly. For this reason, the capsule impedance was recorded continuously during each maneuver, and a large and noisy impedance magnitude was taken to indicate closure.

**Maneuvers.** Three types of maneuver (MA, MB and MC) were performed. In MA (4 lobes), shown schematically in Fig. 6-2, constant flow rate deflation from total lobe capacity (TLC, corresponding to \(p_{l_b}=25\) cm H\(_2\)O) to a minimum volume corresponding to \(p_{l_b}=-15\) cm H\(_2\)O was followed by a dwell time at minimum volume, and then a re-inflation to TLC. As shown in the figure, the difference between TLC and minimum volume is called the Vital Capacity (VC); we will refer to the minimum volume as (RV)\(_e\), i.e. the residual volume of the excised lobe, to distinguish it from residual volume (RV), a term reserved for the volume of air remaining in a lung after a maximal expiration in vivo in a close-chested animal [West, 1987]. The deflation rate was systematically varied from 7 to 70 ml/s, yielding, for the four lobes tested, a range of characteristic expiration time \(T_{\text{exp}}=\text{TLC}/(\text{expiration rate})\) between 5 and 160 seconds. Approximately fifteen maneuvers were performed on each lobe, and the pressures and volumes corresponding to airway
closure and re-opening were recorded. The speaker oscillation frequency was set at 10 Hz, enabling us to track impedance changes with 0.1 second resolution. The goal of this maneuver was to measure closing and opening pressures and volumes as a function of expiration rate and compare the results with those obtained from the models in Chapters Two and Four. The dwell time at minimum volume was included to aid in flow rate calibration and was accomplished by clamping the tubing on both sides of the pneumotach (Fig. 6-1). A membrane pump was used to re-inflate the lobe, and the inspiration rate tended to decrease with increasing lung volume (see Fig. 6-2). The mean inspiration rate, however, varied little from maneuver to maneuver and lobe to lobe; the average rate during the first half of the volume inspired was approximately 10 ml/s.

![Graph](image-url)

**Fig. 6-2.** Change in lobe volume ($\Delta V_L$) and transpulmonary pressure ($p_{tp}$) vs. time for MA. At $t=0$, $p_{tp}=25$ cm H$_2$O and $V_L$=TLC. Typical airway closure (dark circle) and re-opening (open circle) sites are shown. The expiration rate was constant for a given maneuver and was varied over a range of values in a given lobe. Maneuver DO8-2.

In MB, shown schematically in Fig. 6-3, sinusoidal fluctuations with periods of 2, 5, and 15 seconds were superimposed on the deflation flow. To accomplish this, an
oscillating bellows was connected in parallel with the pump used to deflate the lobe. The objective of this maneuver was to test the hypothesis advanced in Appendix 2B: that is, if liquid bridging is the dominant closure mechanism, then airway closure may first occur on inspiration as end expiratory volume (EEV) is incrementally reduced.

A third maneuver, MC, was carried out in which the lobe pressure was varied cyclically during deflation as in MB, and the capsule pressure was measured at G (Fig. 6-1) with no speaker oscillations; the pressures at the main bronchus and the capsule were then plotted against one another, and the point at which the capsule pressure did not change in response to variations in main bronchus pressure was taken to signal airway closure.

![Graph showing change in lobe volume (ΔV_L) vs. time for MB. At t=0, V_L = TLC; for t>0, lobe volume varies sinusoidally with time, with incrementally decreasing end expiratory volume (EEV). Maneuver RK4-9.](image)

**Fig. 6-3.** Change in lobe volume (ΔV_L) vs. time for MB. At t=0, V_L = TLC; for t>0, lobe volume varies sinusoidally with time, with incrementally decreasing end expiratory volume (EEV). Maneuver RK4-9.

**Preparation of lobes.** Mongrel dogs were anesthetized with pentobarbital sodium (30 mg/kg), heparinized (5000 U) and exsanguinated via a femoral artery catheter. The chest was opened and the lungs were removed and separated into lobes. The main
bronchus was cannulated, and plugged until use. In the case of the one perfused lobe tested in MA, the lobar artery and vein were also cannulated. The lobes were then floated in a tray with saline, covered, and refrigerated until use. They were used anywhere from 2 to 36 hours after removal from the chest. During each maneuver, the lobes were periodically sprayed with saline to keep the pleural surfaces moist.

Placement of capsules. Once a lobe was attached to the apparatus, it was inflated to TLC and checked for leaks by clamping the tubing near the main bronchus and monitoring the pressure (pTP) for drift. Capsule sites on the pleural surface were chosen carefully, so that the tissue supporting the capsule and the attached catheter would suffer minimal distortion during the maneuver. Rubbing alcohol was applied with cotton swabs to clean these sites, and the lobe pressure was reduced to 4 cm H2O (FRC) at which time cyanoacrylate adhesive (Pattex, Henkel KgaA, Düsseldorf) was applied sparingly to the capsule base, which was then pressed against the pleural surface until the adhesive held. A conical pin with maximum diameter 0.8 mm was used to puncture the pleural surface through the capsule bore, after which the catheter E was attached to the capsule (Fig. 6-1). In general, three capsules were placed on each lobe and all capsules were connected to the same loudspeaker.

Perfused lobe preparation. One of the lobes subjected to MA had its vasculature perfused during the tests. In this case, the lobe had its main artery and vein cannulated, and perfusion with Dextran (Rheomacrodex 10%, Pharmacia AB, Budapest) was begun before the capsule was attached. Dextran was chosen because its solute content should discourage excessive filtration of liquid from the blood vessels to the interstitium and airspaces. A second perfusate, a mixture of Dextran and histamine, was to be introduced to the vasculature after the Dextran alone had been tested. The perfusion rate was scaled to the lung size, and set at 10 ml/min using a peristaltic infusion pump (Gilson Minipuls 3). The venous outlet pressure was maintained at 5 cm H2O. Once Dextran had flushed out the capillaries, the pump was turned off and the capsules were attached per the previous
procedure. The perforation of the pleural surface, however, had to be made using a hot needle (Electroskapel II, Medicor Co., Budapest) that cauterized the hole, preventing local edema. Failure to use the hot needle resulted in foam leaking out through the capsules.

The lobe was subjected to three maneuvers at three different expiration rates before the infusion pump was turned back on. Then three more maneuvers were performed while Dextran was perfused. Following this, histamine (Chinoin, Budapest) infusion (8 μg/ml) was started. All maneuvers were then delayed for fifteen minutes to allow the histamine to have its effect. The tube leading to the main bronchus was clamped so that air could not escape from the lung and the transpulmonary pressure was monitored. Airway constriction caused by histamine would be expected to cause the transpulmonary pressure to rise, but no such rise was apparent and it was concluded that the histamine had little or no effect in this lobe.

![Graph](image)

*Fig. 6-4. Impedance magnitude vs. lung volume during MA. TLC corresponds to ΔVL=0. Maneuver DO10-19, capsule 1. Texp=25 s.*

**Measurement of total lobe capacity (TLC).** After the last maneuver was performed on a lobe, the capsules were plugged and pип was reduced to -15 cm H₂O. The
tube attached to the cannula A (Fig. 6-1) was clamped and disconnected from the rest of the apparatus. Then the lobe, cannula, tubing, and clamp were (i) weighed and (ii) immersed in water to determine their volume. Subsequent measurement of the cannula, clamp, and tube masses and volumes allowed the amount of gas in the lobe to be calculated. TLC was then calculated by adding this quantity of trapped gas to the vital capacity of the last maneuver.

RESULTS

**Maneuver A.** Four lobes (see Table 6.1) were tested for a total of 59 maneuvers, resulting in approximately 180 capsule impedance measurements. A typical impedance signal versus lung volume is shown in Fig. 6-4. As the lobe volume decreased, the impedance magnitude gradually rose from a TLC value of \( |Z_c| = 300 \text{ cm H}_2\text{O-s/liter} \) with increasing steepness to reach a noisy plateau with a mean \( |Z_c| = 8 \times 10^4 \text{ cm H}_2\text{O-s/liter} \), which we took to signal closure of the airway between this airspace and the trachea.

<table>
<thead>
<tr>
<th>Lobe</th>
<th>Dog</th>
<th>Dog mass, kg</th>
<th>lobe perfused</th>
<th>Total lobe capacity, ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>DO5</td>
<td>1</td>
<td>25.0</td>
<td>no</td>
<td>1270</td>
</tr>
<tr>
<td>DO7</td>
<td>2</td>
<td>21.4</td>
<td>no</td>
<td>790</td>
</tr>
<tr>
<td>DO8</td>
<td>2</td>
<td>21.4</td>
<td>no</td>
<td>920</td>
</tr>
<tr>
<td>DO10</td>
<td>3</td>
<td>18.9</td>
<td>yes</td>
<td>300</td>
</tr>
</tbody>
</table>

Table 6.1. Characteristics of dog lobes used in MA experiments.

The closure event was taken to correspond to the point at which (i) the impedance signal first became noisy and/or (ii) the first abrupt rise in \( |Z_c| \) occurred; these two events normally coincided, but are stated separately to eliminate spurious noisy signals with low \( |Z_c| \) that might occur. The rationale for associating this impedance signal with closure is that (i) a noisy impedance signal implies, through (6.1), that the flow through the capsule has been blocked, (ii) the impedance at the plateau level has a magnitude that is
approximately equal to the capacitive impedance of the airspaces peripheral to the most peripheral airways, as will be shown below, and (iii) the abrupt transition between smooth and noisy signals at high and low lung volumes, respectively, corresponds to the abrupt physical transition in the airway tree we would expect to mark an airway closure event, as modeled in Chapters Two and Four.

Figure 6-5 shows how the impedance magnitude varied with time during the maneuver shown in Fig. 6-4. Both closure (completed at approximately $t = 45$ s) and final re-opening (at approximately $t = 67$ s) occur abruptly. At the beginning of inspiration from low lung volume (at $t = 57$ s), the impedance fell rapidly, soon to be followed by a rapid rise to the previous value until a final, definite re-opening occurred at $t=67$ s. The brief plunge in impedance at the onset of inspiration was seen often in these tests, and was attributed to irregularities in the apparatus and not to airway re-opening.

Figure 6-4 shows that on inspiration, the airway remained closed until the lobe volume was 0.15 liters below TLC, at which time the impedance fell sharply, signalling a sudden re-opening of the airway. Re-opening generally occurred in a more discrete, less gradual fashion than closure, always took place at a higher transpulmonary pressure than closure, and exhibited poor repeatability. It often occurred in stepwise fashion, as shown in Fig. 6-6; approximately 25% of the maneuvers had multistep re-openings where the two largest steps were of comparable magnitude.

The time-domain plot corresponding to Fig. 6-6 is shown in Fig. 6-7. The impedance magnitude rose gradually on expiration, then leaped upward at $t = 120$ s, after which the signal was noisy. The mean magnitude of this noisy signal continued to rise until expiration was complete; it remained relatively constant until inspiration started, when a stepwise decrease occurred. Two more stepwise decreases followed, the last occurring at $t = 290$ s.

The opening and closing volumes shown in Fig. 6-2 were measured for each maneuver and each capsule. As stated above, the closure event was recorded at the
pressure and volume at which (i) the impedance signal first became noisy and/or (ii) the first abrupt rise in impedance magnitude occurred, as a point B in Fig. 6-6. Alternatively, re-opening was taken to occur when the impedance signal ceased to be noisy and/or the impedance magnitude dropped abruptly. For stepwise re-opening, the re-opening event was taken to have occurred at an average volume and pressure weighted by the position of the two largest steps, as at point C in Fig. 6-6. A more complete characterization would take into account the individual steps. For the present purposes, however, the opening events are lumped together to yield an average opening pressure and volume.

Fig. 6-5. Impedance magnitude vs. time for maneuver shown in Fig. 6-4. Maneuver DO10-19, capsule 1. \( \text{T}_{\text{exp}}=25 \) s.
Fig. 6-6. Impedance magnitude vs. lung volume for MA with two-step re-opening. TLC corresponds to $\Delta V_L = 0$. Closing volume was taken to correspond to the volume at B, where closure was fully accomplished. In cases of multistep re-opening, the re-opening volume was taken to correspond to point C, midway between the two largest stepwise decreases in impedance. Maneuver DOS-7, capsule 3. $T_{\text{exp}} = 180$ s.

Fig. 6-7. Impedance magnitude vs. time with two-step re-opening. (This is the time domain plot corresponding to Fig. 6-6.) Expiration ends at $t = 160$ s, inspiration starts at $t = 215$ s.
Figures 6-8 through 6-11 show the results from the four lobes tested; the first three figures present data for unperfused lobes, while Fig. 6-11 pertains to the perfused lobe. The mean and standard deviation of the measured CV/TLC and OV/TLC values are given for each lobe; moreover, the median, skewness (SK), and kurtosis (K) are presented to quantify any non-normality of the distributions. The expiration rate seems to have a negligible effect on the measured closing and opening volumes. In general, the closing volumes for the unperfused lobes were less than 0.05TLC, while those for the perfused lobe were greater, with greater scatter, and a mean value of approximately 0.10 TLC. In each lobe there was some overlap between the opening and closing volumes, but the mean opening volume was always higher than the mean closing volume. Intercapsule variation in opening and closing behavior reflected inhomogeneities in the lobe: for example, some capsules had relatively large opening volumes (e.g. capsule 2 in Fig. 6-9) or large closing volumes (e.g. capsule 3 in Fig. 6-11). Intracapsule variation, on the other hand, measures the repeatability of an opening or closing event in a certain acinus. The overall variation from both these sources was appreciable and accounts for the significant scatter in the data.

To put the closure results in terms of the absolute lung volumes used in Chapters Two and Four, we will calculate an absolute closing volume or "closing capacity," defined as CC=(RV)\textsubscript{e}+CV [cf. West, 1984] where (RV)\textsubscript{e}=TLC-VC. As gas trapping caused VC to decrease in successive maneuvers (see Discussion), (RV)\textsubscript{e} steadily rose, making CC drift upward in successive maneuvers.

Figures 6-12 to 6-15 present the normalized closing capacity, CC/TLC, as a function of expiration rate. The values were insensitive to expiration rate over the range measured and CC/TLC ranged from 0.05 to 0.48, with a mean value of 0.24. There is significant scatter in the data, caused chiefly by the upward drift in (RV)\textsubscript{e}. Nevertheless, the data are presented for completeness. The earliest measurements on each of these plots, before significant gas trapping had occurred, yielded a mean CC/TLC value of around 0.09.
Fig. 6-8. Normalized closing and opening volumes vs. $T_{\text{exp}}$ for lobe DO5. CV and OV are defined in Fig. 6-2. For CV/TLC, mean=0.04, median=0.03, st. dev.=0.03, SK=1.81, K=1.93. For OV/TLC, mean=0.29, median=0.27, st. dev.=0.14, SK=0.34, K=-0.72.

Fig. 6-9. Normalized closing and opening volumes vs. $T_{\text{exp}}$ for lobe DO7. For CV/TLC, mean=0.03, median=0.03, st. dev.=0.01, SK=0.29, K=-1.11. For OV/TLC, mean=0.25, median=0.16, st. dev.=0.18, SK=0.75, K=-0.60.
Fig. 6-10. Normalized closing and opening volumes vs. $T_{\text{exp}}$ for lobe DO8. For CV/TLC, mean=0.02, median=0.02, st. dev.=0.01, SK=0.75, K=0.09. For OV/TLC, mean=0.12, median=0.12, st. dev.=0.06, SK=1.42, K=4.11.

Fig. 6-11. Normalized closing and opening volumes vs. $T_{\text{exp}}$ for lobe DO10. For CV/TLC, mean=0.05, median=0.03, st. dev.=0.05, SK=3.26, K=10.6. For OV/TLC, mean=0.36, median=0.39, st. dev.=0.15, SK=0.17, K=-0.55.
Fig. 6-12. Normalized closing capacity vs. $T_{exp}$ for lobe DO5. Mean CC/TLC=0.29, median=0.28, st. dev.=0.06, SK=-0.05, K=-1.28.

Fig. 6-13. Normalized closing capacity vs. $T_{exp}$ for lobe DO7. Mean CC/TLC=0.25, median=0.27, st. dev.=0.12, SK=-0.11, K=-1.25.
Fig. 6-14. Normalized closing capacity vs. T_{exp} for lobe DO8. Mean CC/TLC=0.21, median=0.22, st. dev.=0.09, SK=0.05, K=-1.37.

Fig. 6-15. Normalized closing capacity vs. T_{exp} for lobe DO10. Mean CC/TLC=0.22, median=0.19, st. dev.=0.10, SK=0.80, K=-0.36.
Because of the enormous scatter in Figs. 6-12 to 6-15 introduced by gas trapping, we will follow the lead of previous investigators [Cavagna et al., 1967, Macklem et al., 1969] who have presented closing pressures instead of closing volumes or capacities. If the closing and re-opening pressures are plotted vs. $T_{exp}$ (Figs. 6-16 to 6-19), the scatter is reduced and there is virtually no overlap between the closing and re-opening data points, due to the shape of the $p_{tp}$-$V_L$ loop (cf. Fig. 6-20). For the three unperfused lobes, the mean closing pressure was -2.3 cm H$_2$O. For the perfused lobe, it was 0.0 cm H$_2$O. Moreover, the impedance signals from the perfused lobe were easier to interpret than those from the others, as the transitions from open to closed and closed to open states were more abrupt.

![Graph showing closing (dark symbol) or opening (open symbol) pressure vs. $T_{exp}$ for lobe DO5.](image)

**Fig. 6-16.** Closing (dark symbol) or opening (open symbol) pressure vs. $T_{exp}$ for lobe DO5. For opening pressure, mean=15.31 cm H$_2$O, median=15.0 cm H$_2$O, std. dev.=3.34 cm H$_2$O, SK=-0.24, K=-0.65. For closing pressure, mean=-1.79 cm H$_2$O, median=-2 cm H$_2$O, std. dev.=1.14 cm H$_2$O, SK=-0.20, K=-0.20. Circle, square and diamond symbols for capsules 1, 2 and 3.
Fig. 6-17. Closing (dark symbol) or opening (open symbol) pressure vs. $T_{exp}$ for lobe DO7. For opening pressure, mean=16.17 cm H$_2$O, median=16.3 cm H$_2$O, std. dev.=2.95 cm H$_2$O, SK=-0.02, K=0.78. For closing pressure, mean=-2.04 cm H$_2$O, median=-2 cm H$_2$O, std. dev.=2.24 cm H$_2$O, SK=-0.26, K=-0.75. Circle, square and diamond symbols for capsules 1, 2 and 3.

Fig. 6-18. Closing (dark symbol) or opening (open symbol) pressure vs. $T_{exp}$ for lobe DO8. For opening pressure, mean=11.48 cm H$_2$O, median=13 cm H$_2$O, std. dev.=2.91 cm H$_2$O, SK=-1.00, K=-0.29. For closing pressure, mean=-3.10 cm H$_2$O, median=-3 cm H$_2$O, std. dev.=1.7 cm H$_2$O, SK=0.35, K=-0.91. Circle, square and diamond symbols for capsules 1, 2 and 3.
Fig. 6-19. Closing (dark symbol) or opening (open symbol) pressure vs. $T_{\text{exp}}$ for lobe DO10 (perfused). For opening pressure, mean=13.25 cm H$_2$O, median=14 cm H$_2$O, std. dev.=2.99 cm H$_2$O, SK=-1.19, $K$=1.94. For closing pressure, mean=-0.06 cm H$_2$O, median=0.2 cm H$_2$O, std. dev.=1.84 cm H$_2$O, SK=-1.27, $K$=1.89. Circle, square and diamond symbols for capsules 1, 2 and 3.

It should be noted that the pressure $p_{\text{lp}}$ is often changing very rapidly at the time closure occurs; this is apparent from the steep slope of the pressure curve in Fig. 6-2 in the neighborhood of $p_{\text{lp}}=0$. For the expiration rates and inspiration rates measured, however, our 0.1 s resolution was sufficient to determine the closing and opening pressures.

Figure 6-20 shows a MA pressure-volume curve with symbols marking the points at which closure and re-opening of the three capsules occurred. It is evident that the closing and opening volumes overlap, while the pressures do not. A region of negative compliance is apparent on inspiration at AB. This is probably caused by re-opening of a large airway which temporarily causes the main bronchus pressure to fall as the airspace distal to the opened site re-inflates.
Fig. 6-20. Change in lobe volume vs. transpulmonary pressure for typical MA. The negative $p_{tp}-V_L$ slope between A and B is indicative of unstable behavior, probably re-opening of a large airway. Dark and open circles on loop show positions at which the three capsules closed and re-opened, respectively. Capsule numbers are indicated. Maneuver DO10-10. $T_{exp}=50$ s.

Fig. 6-21. Volume expired and capsule impedance magnitude as a function of time for MB. An airway proximal to the capsule closes on expiration and remains closed as lung volume continues to oscillate. Maneuver RK2-1, capsule 2. Oscillation period=5 s.
**Maneuver B.** A variety of interesting behavior was seen here, and several representative cases will be shown. For the maneuver shown in Fig. 6-21, lung volume reduction from TLC was begun at \( t=0 \); by \( t=100 \) s, the volume had fallen by approximately 0.6 liters from its TLC value. For every cycle up to approximately \( t=130 \) s, the impedance rose on expiration and fell by nearly the same amount during inspiration. For times greater than approximately \( t=132 \) s, however, the impedance remained at a high and noisy value, relatively unaffected by the ongoing oscillation in lung volume. This represents a case in which the airway closed near the end of expiration and remained closed during successive oscillations.

![Graph](image)

Fig. 6-22. Volume expired and capsule impedance magnitude as a function of time for MB. An airway attached to the capsule closes on expiration and re-opens on inspiration, over and over again. Lobe volume is represented by the thicker of the two lines. Maneuver RK4-7, capsule 1, oscillation period=16 s.

Figure 6-22, on the other hand, shows re-opening behavior on inspiration following the closure on expiration. In this figure closure occurs near the end of expiration at \( t = 134 \)
s, 148 s, and 165 s. Full re-opening occurs at \( t = 142 \) s and \( t = 159 \) s; subsequent re-openings at \( t = 172 \) s and \( t = 189 \) s are partial in that the impedance falls, but not back to the baseline level. This stepwise re-opening will be considered in the Discussion.

Maneuvers conducted at the smallest oscillation period, 2 s, gave signals that often appeared to involve two closure and re-opening events per cycle. An example is shown in Fig. 6-23. Here again, as expected, the impedance maxima correspond to volume minima for \( t \leq 159 \) s; for greater times, there are brief excursions between high and low impedances, with closure appearing to occur on both expiration and inspiration.

The impedance magnitudes corresponding to closure (approximately \( 10^5 \) cm H\(_2\)O-s/liter) agree with those found in MA. It is surprising that re-opening occurred in MB, as the MA results indicate that high pressures are necessary to re-open closed airways. Perhaps the short closure dwell time in MB facilitated re-opening.

Only unperfused lobes were used in this maneuver as attempts to test perfused lobes proved unsuccessful, resulting in alveolar and airspace edema.

Fig. 6-23. Volume expired and capsule impedance magnitude versus time for MB. Two closing/re-opening events per cycle are evident for \( t \geq 161 \) s. Maneuver RK4-15, capsule 1, 2 s oscillation period.
Fig. 6-24. Alveolar pressure vs. tracheal (main bronchus) pressure for MC. The bellows volume was oscillated at 1 Hz. The maneuver started with $p_{tr}$ oscillating about 10 cm H$_2$O; the oscillations were felt by the transducer at the alveolus, so $p_{alv}$ also experienced the same oscillation about 10 cm H$_2$O. (The phase difference was caused by frequency response differences between the transducers used to measure $p_{alv}$ and $p_{tr}$.) As the mean $p_{tr}$ was reduced, $p_{alv}$ also fell, continuing to track $p_{tr}$ until $p_{tr}$ fell below zero. For $p_{tr}$<4 cm H$_2$O, the alveolar pressure did not change although the $p_{tr}$ continued to oscillate; this indicates closure of all intervening airways.
Maneuver C. Only one lobe was tested with this simple, intuitive approach. Figure 6-24 shows that as the mean pressure in the main bronchus ($p_{tr}$) was reduced, the mean pressure at the capsule ($p_{alv}$) also fell; the bellows imposed a constant volume displacement, and the corresponding change in pressure each cycle decreased as the lobe deflated from TLC because the pulmonary compliance increases with decreasing lung volume. The main bronchus and alveolar pressure excursions were nearly equal until the main bronchus pressure reached approximately 0 cm H$_2$O. At that point the variation in $p_{alv}$ was reduced with respect to variations in $p_{tr}$; as $p_{tr}$ was further reduced, the oscillation in $p_{tr}$ had less and finally no effect on $p_{alv}$, indicating complete closure of the intervening airways. The alveolar space does not appear to be completely isolated from the main bronchus until $p_{tr} = -5$ cm H$_2$O.

DISCUSSION

Effect of expiration rate in MA. We did not explore the range of relatively fast expirations ($T_{exp} < 5$ s) modeled in Chapter Two (cf. Fig. 2-7) because such high rates made it difficult to control the lobe pressure. It is also possible that expiratory flow limitation, discussed in Chapter Two, would complicate such results.

Over the range of expiration rates we did test ($5$ s $< T_{exp} < 160$ s), however, there was no obvious dependence of closing pressure or volume (or opening pressure or volume) on expiration rate. This implies that the closing mechanism acts over a time-scale that is much smaller than the expiration time-scales used in our tests.

Time-scales for closing and opening events. While both closure and re-opening occur very rapidly compared to the breathing time-scale, closure seems to be a more gradual event than re-opening. Fredberg and Holford [1983] have modeled airway re-opening and the associated sounds as an unstable event in which there is a non-equilibrium transition between the closed and open states characterized by a time-scale
\[ \tau \propto a_0 \left( \frac{\rho}{\kappa_E} \right)^{1/2} \] (6.2)

where \( \kappa_E^{-1} \) is the specific elastance of a small airway, approximately equal to the elastance of the lung

\[ \kappa_E^{-1} = \frac{l}{V_L} \frac{\partial V_L}{\partial p_{lp}} \] (6.3)

This can be measured off the \( V_L-p_{lp} \) curves obtained in the experiments. A representative value on re-opening is \( \kappa_E^{-1} = 8 \times 10^{-5} \text{ cm}^2/\text{dyne} \). Taking \( a_0 = 0.02 \text{ cm}, \quad 0.2 < \rho < 1.0 \text{ g/cm}^3 \) for the parenchymal density [Fredberg and Holford, 1983] gives \( 8 \times 10^{-5} < \tau < 1.8 \times 10^{-4} \text{ s} \). This is about an order of magnitude faster than the compliant collapse time-scale we calculated in Chapter Four; both these time-scales are too small to resolve with our 10 Hz oscillation frequency. However, Fig. 6.5 illustrates a case in which time-scale for closure is within the range of our measurement. Gaver et al. [1990] calculate re-opening times of less than 0.1 s provided that the airway liquid has the viscosity of water and show that more viscous lining layers can increase this time-scale significantly. The fact that the re-opening time-scales we measured were so small suggests that the liquid lining in closed airways is water-like, as was assumed in the airway closure model presented in Chapter Two.

In this regard, the characteristic time-scale for liquid bridge formation, once the Rayleigh and sufficient liquid conditions (see Chapter Two) have been met, can be shown to scale as

\[ \tau_{lb} \propto \frac{\mu a_0}{\gamma} \left( \frac{a_0}{h_0} \right)^3 \] (6.4)
This value is highly dependent on the ratio of initial liquid layer thickness, $h_0$, to the transverse free surface radius $a_0$ (see Fig. 2-1). The actual time required for bridge formation also depends logarithmically on the initial perturbation, and the closure process accelerates as the instability grows. For the purposes of comparison, however, let us calculate a representative range of closure times: for a viscosity $\mu$ equal to that of water, a surface tension $\gamma$ of 1 dyne/cm, and $a_0=200 \, \mu$m, $\tau_{lb}$ ranges between $2 \times 10^{-4}$ and 1.6 seconds as $(a_0 / h_0)$ varies between 1 and 20. Hence for very thick liquid films the liquid bridge time-scale may be comparable to those for compliant collapse and re-opening, but for thin films the liquid bridging time-scale is significantly larger.

**Effect of trapped gas in Maneuver A.** Figure 6-25 shows that the VC obtained in MA for lobes DO5, DO7, and DO8 decreased with increasing maneuver number. That is, the reduction in lung volume obtained by decreasing the transpulmonary pressure from 25 cm H$_2$O to -15 cm H$_2$O decreased as the number of cycles increased. This effective stiffening of the lobe is thought to have been caused by gas trapping at low lung volume: at minimum volume, the pleural surfaces of the aforementioned lobes appeared increasingly rough and "bubbly" with each successive maneuver. A patchwork of collapsed and air-filled subpleural spaces were evident. The perfused lobe DO10, however, developed neither the patchy appearance characteristic of gas trapping nor a significant reduction in VC. Hence it seems reasonable to associate the reduced VC with an increase in the amount of trapped gas at minimum lung volume.

If the airways that closed at low lung volume did not readily open on re-inflation, the lung volume corresponding to $p_{tp}=25$ cm H$_2$O would be less after re-inflation than initially. Based on our observations of almost no airways remaining closed (2/177) after re-inflation to $p_{tp}=25$ cm H$_2$O, in spite of substantial gas trapping at low lung volume, we inferred that gas trapping at low lung volume did not change the number of airways open at $p_{tp}=25$ cm H$_2$O, and hence did not change the lobe volume corresponding to this pressure. This
means that increased cycling caused airways to close at higher and higher lung volumes, but that the closed airways nearly always re-opened on re-inflation to \( P_{10} = 25 \) cm H\(_2\)O. The pressure-volume curves corresponding to the first and last maneuvers in lobe DO8 are shown in Fig. 6-26. It is apparent that \((RV)_{e}\) has increased by approximately 230 ml over the course of 16 maneuvers.

The reasons for the increasing non-uniformity in closure behavior and increasing tendency to trap more and more air on increased cycling are unknown; however, it is known that the lobe can be restored to an almost initial condition by placing the lobe in a chamber, drawing out the surrounding air with a vacuum pump, and letting the trapped gas expand and escape [J. J. Fredberg, personal communication]. Because we had no vacuum pump available, this was not attempted.

Fig. 6-25. Vital capacity vs. maneuver number for the four lobes tested in MA. The unperfused lobes DO5, DO7 and DO8 all evidenced significant gas trapping, the VC falling by 27, 36, and 27% respectively. VC for the perfused lobe DO10 fell by only 6%.
Fig. 6-26. Lobe volume vs. lobar pressure for the first and last maneuvers in lobe DO8. The decrease in volume change for a given pressure change (i.e. the decrease in compliance) is caused by trapped gas in the lobe. Note that the region of negative compliance present in the first maneuver is absent in the last. Maneuvers DO8-1 and DO8-16.

Closing pressures. The model presented in Part I of Chapter Four predicts that, for finite surface tensions, collapse will always occur for $p_{tp}>0$, as the parenchymal shear modulus is taken to vanish as $p_{tp} \to 0 \ (4.1)$. Seeing that the mean closing pressures in all four MA lobes were less than or equal to zero, it seems the airways or parenchyma possess some inherent stiffness or "elastic resistance to collapse" [Cavagna et al., 1967] not accounted for in our model. This stiffness allows the airways to remain patent for small negative transpulmonary pressures. Macklem [1971] states that "transpulmonary pressure must become negative for airways to close," and that the transpulmonary pressure corresponding to closure approaches zero as the lung ages.

In the unperfused lobes used in MA, we found the mean closing pressure to be -2.3 cm H₂O. This agrees very well with the measurements of Cavagna et al. [1967], who measured the transpulmonary pressure corresponding to closure in living cats, dogs, and
rabbits (in both open- and close-chested configurations). They found that the airspaces and trachea are in communication for transpulmonary pressures greater that approximately -2 cm H\textsubscript{2}O, but not below this value. This agreement between their measurements and ours lends support to the airway closure criteria we have adopted, which is based on the measured acoustic impedance signal.

The data presented in Figs. 6-16 to 6-19 show that closure occurs at \( p_{\rho} = 0 \) for the one perfused lobe tested (DO10) and a slightly lower value in unperfused lobes (DO5, DO7, and DO8). The reason the closing pressure was greater in the perfused lobe may be that perfusion caused (i) the liquid layer to thicken, (ii) the surface tension in the airways to rise, and/or (iii) changes in the dimensions or mechanical behavior of the airways walls. Cook et al. [1959] have shown that lung compliance is reduced during pulmonary edema, largely as a result of increased surface forces, which they attribute to increased curvature of the air-liquid interface and not to increased surface tension. They, together with Hughes and Rosenzweig [1970] maintain that edema will increase the lung volume (and hence transpulmonary pressure) at which the airways and airspaces collapse. However, Hughes and Rosenzweig also maintain that edema will tend to increase the amount of gas trapping in a lobe. As the perfused lobe we tested experienced almost no gas trapping, and no excess liquid was evident at the capsule, it is hard to draw definite conclusions.

It is noteworthy, however, that the perfused lobe DO10 behaved much like the constant surface tension lobes tested by Smith and Stamenovic [1986] and discussed in Chapter Four. These constant surface tension lobes revealed no gas trapping on repeated cycling, presumably because the airspaces collapsed before the airways. If the filtration of perfusate into the airspaces in lobe DO10 caused the surface tension there to be higher than normal, the airspaces would tend to collapse at a higher than normal lung volume, perhaps at a higher lung volume than airway closure, thereby eliminating the possibility of gas trapping. Moreover, if perfusate in DO10 also caused the airway surface tension to rise, airway closure would be expected to occur at a higher than normal lung volume (or
transpulmonary pressure), which it did. This appears to be the best explanation of the observed difference between the perfused and unperfused lobe closure behavior.

**Re-opening pressures.** Gaver et al. [1990] used a laboratory model to measure the pressure required to re-open a collapsed tube. The opening pressure was approximately \(8\gamma/s\) where \(\gamma\) is the surface tension of the liquid layer and \(s\) is the uncollapsed tube radius. The mean opening pressure measured in MA was 14 cm H\(_2\)O. Taking \(\gamma=22\) dynes/cm (cf. Chapter Three and Greaves et al. [1986]), the approximate equilibrium surface tension, the correlation of Gaver et al. implies that the mean radius of the closed airways was

\[
s = \frac{8\gamma}{P_{\text{open}}} = 0.0128 \text{ cm}
\]

(6.5)

or an airway diameter of approximately 250 \(\mu\)m. This compares favorably with the minimum diameter for canine alveolar ducts given by Greaves et al. [1986] and is about half the terminal bronchiole value given by Horsfield [1986]. (Horsfield's study was performed at an inflation pressure of 25 cm H\(_2\)O, with a resin injection pressure of 30 cm H\(_2\)O [Horsfield, 1982]. Hence we would expect the dimension at \(P_{\text{op}}=14\) cm H\(_2\)O to be somewhat smaller.) In any case, the re-opening pressure data seems to indicate that closure occurred in the smallest peripheral airways.

**Stepwise re-opening.** The stepwise reduction in capsule impedance on inspiration shown in Figs. 6-6 and 6-7 may be explained by the popping open of closed airways in series and/or parallel arrangements. Consider Fig. 6-27. If closure sites A, C and D are closed, and D opens first, the impedance measured through the capsule will drop slightly because the compliance of the gas region to which the capsule is attached has been increased. A larger decrease in impedance will accompany the opening of C, and an even larger decrease will mark the opening of A.

**Location of closed airways.** To estimate the site of closure in the bronchial tree, we can compare the magnitude of the mean impedance measured through the capsule with
the value predicted by the lumped parameter model in Fig. 6-28. This figure shows an analog circuit in which $R_1$ represents flow resistance through the capsule and subpleural alveolar groups, $R_2$ is the flow resistance through the conducting airways, and $C$ is the compliance of the airspaces (gas, tissue, and surface contributions) in communication with the capsule; the active element corresponds to the loudspeaker. The impedance through this circuit is

$$Z_c = R_c + jX_c = \left( R_1 + \frac{R_2}{1 + \left( \frac{1}{R_2} \right)^2} \right) - j \frac{R_2^2 C \omega}{1 + \left( \frac{1}{R_2} \right)^2} \quad (6.6)$$

Fig. 6-27. Schematic of alveolar capsule and adjoining airspaces. Potential closure sites are shown in airways (A, B, C, D) and in one airspace (E). The airspace closure site E represents a closed collateral ventilation path.
Fig. 6-28. Analog model of alveolar capsule oscillation apparatus and attached airspaces. $R_1$ represents DC resistance through capsule and subpleural alveoli; $R_2$ represents DC resistance through conducting airways; $C$ represents compliance of all airspaces in communication with the capsule.

When closure occurs, $R_2 \rightarrow \infty$ and the impedance magnitude jumps to approximately 50,000 to 150,000 cm H$_2$O-s/liter (cf. Figs. 6-4, 6-6, 6-21, and 6-22). The flow resistance through the capsule is small in comparison, being approximately 2000 cm H$_2$O-s/liter (with 1 mm i. d. and 0.5 mm length). Taking this value to be representative of $R_1$, the impedance magnitude at closure reduces to

$$|Z_c| = \frac{1}{\omega C}$$  \hspace{1cm} (6.7)

For a speaker oscillation frequency of 10 Hz, and $|Z_c| = 50,000$ cm H$_2$O-sec/liter, $C = 3 \times 10^{-7}$ liter/cm H$_2$O. Taking the lobar compliance to be 0.056 liter/cm H$_2$O (a representative value from the $p_{pl}-V_L$ curves obtained in MA), the ratio of compliance of the closed region to the compliance of the whole lobe is $C_{closed} / C_{lung} = 5.4 \times 10^{-6}$.

Assuming that the lung is homogeneous, we take this fraction to equal the fraction of lung volume subtended by the closed airway. Horsfield [1986] reports that there are approximately 150,000 airway endings (or alveolar ducts) in the dog lung. Neglecting the dead space, we set the number of endings contained in the closed space divided by the total
number of endings equal to the compliance (or volume) fraction calculated above. That is, we take

\[
\frac{C_{\text{closed}}}{C_{\text{lung}}} = \frac{V_{\text{closed}}}{V_{\text{lung}}} = \frac{(#\text{endings})}{(\text{total#endings})}
\] (6.8)

This enables us to estimate the order of airway in which closure occurs. For the numbers given above, we obtain a value of 0.8 endings in the closed space. This implies that closure takes place in a respiratory bronchiole (order 2). The total number of endings used here is probably an overestimate, as our measurements were on a lobe, not a whole lung. If the impedance is halved, the corresponding number of endings is doubled, and the estimated closure site moves to order 3.

If we use a dichotomous branching model [Weibel, 1984] to make the same estimate, we have

\[
\frac{C_{\text{closed}}}{C_{\text{lung}}} = \frac{V_{\text{closed}}}{V_{\text{lung}}} = 2^{-Z}
\] (6.9)

where \(Z\) = the generation of the closed airway, with \(Z=0\) corresponding to the lobar bronchus. For the compliance fraction given above, \(Z=17.5\), also corresponding to the respiratory bronchioles. Here also halving the impedance magnitude reduces the generation by one. We have neglected the gas compliance in the closed region because its specific compliance,

\[
C = -\frac{I}{V} \frac{\partial V}{\partial p} = -\frac{I}{p} = 9.7 \times 10^{-4} \text{ (cm H}_2\text{O)}^{-1}
\] (6.10)
is about seventy times less than the specific compliance of the lobe, which is around 0.07 (cm H\textsubscript{2}O\textsuperscript{-1}.

Our analysis of the impedance magnitude characterizing closure and the magnitude of the re-opening pressure both indicate that closure occurs in the smallest, most peripheral airways. This is consistent with the histologic studies of Hughes, Rosenzweig, and Kivitz [1970] which demonstrated closure of the most distal airways at low lung volume, and with our airway closure models presented in Chapters Two and Four.

*Limitations of the alveolar capsule technique.* One possible limitation of the capsule oscillation technique is that when extra liquid is present in the airspaces and airways the capsule bore itself may close, yielding a false indication of airway closure. This liquid may originate from edema from the pleural perforation. This is unlikely, however, because the capsule bore is larger than that of the surrounding airways.

Moreover, because the capsule is attached to the pleural surface at p\textsubscript{bp}=4 cm H\textsubscript{2}O (see "Placement of capsules" above) and is much more rigid than the pleural surface, it would be expected to constrain the pleural surface at transpulmonary pressures above and below this value. This may affect the closure and re-opening behavior of nearby airways.

*Re-opening on inspiration.* The possibility of liquid bridging occurring during inspiration was considered in Appendix 2B. Modeling (cf. Fig. 2B-2) indicates that under the proper conditions, closure might occur on inspiration; simulations suggest that at very low breathing frequencies closure on inspiration would not occur, but as the breathing frequency is increased, there exists a "window" or "envelope" (Fig. 2B-2) within which closure on inspiration can occur. In Fig. 6-23, the cause of the two closing/re-opening events occurring each cycle is unknown. It is interesting, however, that (i) one of the re-opening events consistently occurred on inspiration, (ii) closure first occurred on inspiration, (iii) this behavior was not seen at lower oscillation frequencies, where the model indicates such behavior would not exist, and (iv) the incremental decrease in end expiratory volume in this experiment was approximately 0.2% TLC, implying that the end
expiratory volume could fall well within the relatively wide "closure on inspiration envelope" (with a maximum width of approximately 3% TLC) in Fig. 2B-2(a).

The simulations performed in Appendix 2B considered a single sinusoidal variation in lung volume from TLC, instead of the "cyclic deflation" performed in MB and shown in Fig. 6-23. Moreover, the airway geometry and liquid layer properties used in the Chapter Two simulations certainly do not correspond exactly to the appropriate values for the excised lobe used. For these reasons, we would expect to see differences between the model and experimental results; it is interesting, however, that there is some qualitative agreement. Further research is required to determine what relationship might exist between these experimental and computational model results.

*Liquid bridging closure mechanism.* It is unclear whether or to what extent liquid bridging may have occurred in the airways of the excised lobes, but it is known that closure occurred at higher and higher lung volumes with increasing maneuver number. The closing pressure did not display a uniform a tendency: in some lobes it increased with increasing maneuver number, while in others it decreased or stayed nearly constant. It is possible that after closure occurs several times, airway liquid may become especially thick at certain locations, due to flow towards the negative pressure behind the highly curved air-liquid interface at the closure site; thus the airway liquid film, initially of fairly uniform thickness, could develop local thick spots where liquid bridging would occur at higher and higher lung volumes as more liquid accumulated. Exactly why placing the lobe in a vacuum chamber would undo this behavior (see "Effect of trapped gas in Maneuver A" above) may have to do with the fully expanded lung (effected by re-opening pressures possibly as high as one atmosphere, $p_{ip} = 1000 \text{ cm H}_2\text{O}$) maximally expanding virtually all airways and airspaces, allowing the airway liquid layer thickness to become more uniform if the sufficient liquid and Rayleigh conditions (see Chapter Two) in these hyper-extended airways are not met. Perhaps evaporation of part of the liquid layer at this low pressure also plays a role. While these explanations are speculative, it is plausible that the
vacuum chamber treatment affects the liquid layer; on the other hand, it is difficult to imagine such a treatment having any effect on the mechanical properties of the parenchyma and airways, except indirectly through modification of the liquid layer. In conclusion, while the present method has provided much useful information about airway closure, certainty about the mechanisms responsible for closure awaits the development of tools that allow true visualization of the process.
APPENDIX 6A: DERIVATION OF CAPSULE IMPEDANCE EQUATION (6.1).

Equation (6.1), the low-frequency estimate of catheter load impedance, is often cited [e.g. Fredberg et al., 1984, Franken et al., 1983, 1985] without derivation. A derivation is included here for completeness and to illuminate the theory on which the experiments are based.

Fig. 6A-1. Schematic of model cylindrical catheter of length L and cross-sectional area A₀.

Consider plane waves in a cylindrical tube of uniform cross-sectional area A₀ (Fig. 6A-1). The pressure

\[ p(x,t) = \{Ae^{jkt} + Be^{-jkt}\}e^{j\omega t} \]  

(6.11)

is a solution of the wave equation

\[ \frac{\partial^2 p}{\partial x^2} = \frac{1}{c^2} \frac{\partial^2 p}{\partial t^2} \]  

(6.12)
which is the first-order equation of acoustic motion [Morse and Ingard, 1968] with \( c = \omega / k \) where \( c \) is the speed of sound in air. The acoustic momentum equation, which to leading order [Morse and Ingard, 1968] is

\[
\rho \frac{\partial u}{\partial t} = -\frac{\partial p}{\partial x}
\]  

(6.13)

implies that the velocity has the form

\[
u(x,t) = \left\{ Ce^{j\lambda x} + De^{-j\lambda x} \right\} e^{j\omega t}
\]  

(6.14)

Moreover, the acoustic impedance in the tube at \( x=L \) is defined to be

\[
Z_L = \left( \frac{p}{V} \right)_{x=L} = \left( \frac{p}{uA_0} \right)_{x=L} = \frac{P_2 e^{i\omega t}}{uLA_0}
\]  

(6.15)

where \( V \) is the volumetric flow rate and \( u_L \) is the mean axial velocity in the tube at \( x=L \).

From (6.11),

\[
\frac{\partial p}{\partial x} = jk\left\{ Ae^{j\lambda x} - Be^{-j\lambda x} \right\} e^{j\omega t}
\]  

(6.16)

and from (6.14),

\[
\frac{\partial u}{\partial t} = j\omega u
\]  

(6.17)

so that (6.13), evaluated at \( x=L \), is equivalent to
\[ u_L = -\frac{k}{\rho \omega} \left( A e^{jkL} - B e^{-jkL} \right) e^{j\omega t} \]  (6.18)

To solve for the constants A and B in (6.11), we employ the boundary conditions

\[ p_{x=0} = (A + B) e^{j\omega t} = P_1 e^{j\omega t} \]  (6.19)

\[ p_{x=L} = (A e^{jkL} + B e^{-jkL}) e^{j\omega t} = P_2 e^{j\omega t} \]  (6.20)

Inserting (6.18) into (6.15),

\[ Z_L = \frac{\rho \omega}{k A_0} \frac{P_2}{(A e^{jkL} + B e^{-jkL})} \]  (6.21)

We can eliminate A and B in this equation by setting \( A = P_1 - B \) and \( B = \frac{P_2 - P_1 e^{jkL}}{e^{-jkL} - e^{jkL}} \) (from (6.19) and (6.20)), which yields

\[ Z_L = \frac{\rho c}{A_0} \frac{\sinh(jkL)}{P_1 / P_2 - \cosh(jkL)} \]  (6.22)

where we have taken \( c = \omega / k \). The characteristic impedance \( Z_{\text{char}} \) of the cylindrical tube is defined to be the input impedance looking into an infinite length of tube [Keefe, 1984]. By calculating the acoustic impedance at \( x=0 \), and letting \( L \to \infty \), it can easily be shown that \( Z_{\text{char}} = \frac{\rho c}{A_0} \). Therefore (6.22) becomes

\[ Z_L = \frac{Z_{\text{char}} \sinh(jkL)}{P_1 / P_2 - \cosh(jkL)} \]  (6.23)
which is identical to (6.1) if the capsule position is taken to correspond to \( x=L \). That is, \( Z_L \), the load impedance on the catheter, will equal \( Z_c \), the impedance seen through the capsule, if the capsule is attached to the catheter at \( x=L \).

The relationship derived above for the load impedance is correct for low frequencies, i.e., those frequencies for which the acoustic wavelength is much greater than the catheter length, so that \( \omega \ll c/L \). In our experiments, with \( \omega = 10 \) Hz, \( c = 340 \) m/s, and \( L = 1 \) m, this condition is satisfied. This also implies that any phase difference between \( P_1 \) and \( P_2 \) will be small. For a more general analysis, see Franken et al. [1980, 1983].
APPENDIX 6B: SUMMARY OF MANEUVER A DATA

CC=Closing Capacity=(RV)_{e}+CV; CV=Closing Volume (see Fig. 6-2); OV=Opening Volume (see Fig. 6-2); P_{c}=transpulmonary (trans-lobe) pressure at closure; P_{o}=transpulmonary (trans-lobe) pressure at re-opening; (RV)_{e}=Residual Volume of excised lobe; TLC=Total Lobe Capacity (volume of air in lobe at P_{tp}=25 cm H_{2}O); VC=Vital Capacity (Fig. 6-2).

Numeric subscripts refer to capsule number.

<table>
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<tr>
<th>Maneuver</th>
<th>Man. #</th>
<th>VC (ml)</th>
<th>TLC (ml)</th>
<th>(RV)_{e} (ml)</th>
<th>exp. rate (ml/s)</th>
<th>T_{exp} (s)</th>
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Table 6B-1(a). Measured and calculated parameters for lobe DO5.

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<th>(VC-CV)_{2} (ml)</th>
<th>(CV)_{2} /TLC</th>
<th>(CC)_{2} (ml)</th>
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Table 6B-1(b). Measured and calculated parameters for lobe DO5.
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<th>(VC-CV)$_3$ (ml)</th>
<th>(CV)$_3$/TLC</th>
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<th>(CC)$_3$/TLC</th>
<th>(Pc)$_3$ (cm H$_2$O)</th>
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<th>(OV)$_1$/TLC</th>
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Table 6B-1(c). Measured and calculated parameters for lobe DO5.

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<th>(OV)$_2$/TLC</th>
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Table 6B-1(d). Measured and calculated parameters for lobe DO5.
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<th>exp. rate (ml/s)</th>
<th>(T_{\text{exp}}) (s)</th>
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Table 6B-2(a). Measured and calculated parameters for lobe DO7.

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Table 6B-2(b). Measured and calculated parameters for lobe DO7.

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Table 6B-2(c). Measured and calculated parameters for lobe DO7.

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Table 6B-3(a). Measured and calculated parameters for lobe DO8.

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Table 6B-3(b). Measured and calculated parameters for lobe DO8.
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Table 6B-3(c). Measured and calculated parameters for lobe DO8.

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Table 6B-3(d). Measured and calculated parameters for lobe DO8.
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Table 6B-4(a). Measured and calculated parameters for lobe DO10.

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Table 6B-4(c). Measured and calculated parameters for lobe DO10.

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Table 6B-4(d). Measured and calculated parameters for lobe DO10.
REFERENCES


Chapter 7

Summary and Conclusions

The previous chapters have described theoretical and experimental studies undertaken to elucidate the mechanisms responsible for airway closure. We will now briefly summarize the most important findings from each of the chapters and conclude with a discussion of relevant future research topics.

AIRWAY CLOSURE BY LIQUID BRIDGING (CHAPTERS TWO AND FIVE)

This airway closure mechanism, first described by Macklem et al. [1969, 1971], has been the subject of several previous studies. The focus of the present work was to include the effect of surfactant in the theoretical model developed by Johnson et al. [1991]. It was found that pulmonary surfactant discourages liquid bridge formation in airways by (i) reducing the mean surface tension and (ii) introducing surface tension gradients. It was demonstrated that surface tension gradients increase the time required to form a bridge to a degree that depends on the Gibbs elasticity of the surfactant. The greater surfactant effect, though, was the drastic lowering of the mean surface tension, which decreases the driving force for both bridge formation and compliant collapse; it also discourages liquid filtration into the airways from the interstitium. Moreover, the simplified model of bridging in a single, straight airway provides a satisfactory prediction of the time-scale characterizing liquid bridge formation in a model bronchial tree with curved, tapered, and bifurcating airways.

Liquid bridging is promoted by thick liquid layers, high surface tension, low liquid viscosity, and any reduction in lumen area, as would result from thickened airway walls or
increased airway compliance. It was seen that for liquid bridging to occur at normal lung volumes, the amount of airway liquid required would be significantly higher than the amount believed to normally reside in airways—hence it is possible, if not probable, that the mechanism is only significant in diseased lungs, and contributes to the observed increase in residual volume in such cases.

**PULMONARY SURFACE TENSION/SURFACTANT TRANSPORT (CHAPTER THREE)**

It has been shown that several distinctive characteristics of surface tension vs. surface area loops measured in a bubble surfactometer are captured by a simple model of surfactant transport. Transfer of surfactant between the air-liquid interface and the bulk is shown to be kinetically-controlled, and the surfactant is taken to consist of a single component. The model accounts for the asymmetry in sorption kinetics observed between high and low surface tension films; three separate transfer regimes are considered.

The surfactant tested and modeled in Chapter Three is a modified pulmonary surfactant, and as such was not able to achieve the very low ($\approx 1$ dyne/cm) minimum surface tensions characteristic of pulmonary surfactant *in vivo*.

**THEORETICAL MODELING OF AIRWAY COMPLIANT COLLAPSE (CHAPTER FOUR)**

Two models of airway compliant collapse were developed in Chapter Four. The first (Part I) explores the limit of airway closure behavior when the parenchyma is the airway's only means of structural support. The second model (Part II) considered the airway to have the same mechanical properties as a pulmonary vein of equal diameter. The latter approach was difficult to implement because critical data (i.e. venous compliance at zero
transpulmonary pressure and the volume dependence of the venous radius at \( p_{v-ppl}=10 \text{ cm H}_2\text{O} \) were not available. Both models, however, predicted a minimum lung volume below which the balance of forces (outward recoil caused by tethering and/or wall stiffness vs. the inward collapsing pressure caused by surface tension) could not be maintained. As the time-scale governing the collapse process is thought to be small compared to the characteristic breathing time-scale, this minimum lung volume was taken to correspond to the lung volume at which compliant collapse would occur.

The model in Part I predicts that compliant collapse will always occur for transpulmonary pressures greater than or equal to zero, and that the lung volume at compliant collapse is very sensitive to the surface tension of the liquid layer, but relatively insensitive to liquid layer thickness. Moreover, it was shown that the dominant closure mechanism is determined by the amount of liquid in the airway: if the liquid layer thickness is greater than a threshold value, liquid bridging will be the dominant closure mechanism. Otherwise, the airways will close by compliant collapse.

As the liquid bridging model in Chapter Two likely overestimates the airway stiffness, while the compliant collapse model in Part I of Chapter Four underestimates it, these two models may be used to bound the closure behavior of a particular airway.

**ASSESSMENT OF AIRWAY CLOSURE BEHAVIOR IN EXCISED CANINE LUNGS (CHAPTER SIX)**

Here we employed an alveolar capsule technique to measure closing and opening pressures and volumes. The measured closing pressures were less than those predicted by the model in Part I of Chapter Four, presumably because the model neglected airway wall stiffness. Also, the measured absolute closing volumes initially were less than what our liquid bridging model would predict for a film thickness of 10 \( \mu\text{m} \) and minimum surface tension of 1 dyne/cm. However, as we had no way of measuring the liquid layer thickness
or surface tension in the airways, it is hard to say exactly what the model would predict for the lobes tested. Furthermore, the measured closing volumes rose with increasing maneuver number, and there is reason to believe liquid bridging played a role in this.

The magnitudes of both the capsule impedance during closure and the mean re-opening pressure indicate that closure occurred in the respiratory bronchiole or alveolar duct region. Abrupt changes in capsule impedance marked the closure and re-opening events, and re-opening was often marked by stepwise decreases in capsule impedance, suggesting a sequential popping open of series and/or parallel arrangements of closed airways.

FUTURE RESEARCH TOPICS

The present studies represent an attempt to consider certain limiting cases of the closure process, developing models that can be deployed to predict and understand conditions in normal and diseased lungs. Many interesting and difficult questions remain, however. Listed below are several relevant topics worthy of future research.

Liquid bridge movement/rupture after formation. It is unknown how a liquid bridge, once formed in an airway, moves and/or breaks in subsequent breaths. Related issues of how a bridge moves through a bifurcation and the role played by pulmonary surfactant in such movement are of importance in understanding the re-opening process and the relationship between airway closure and gas trapping.

Incorporation of airway wall properties into the compliant collapse model. Measurement of terminal airway lumen diameter vs. transmural pressure at a range of transpulmonary pressures would provide a "tube law" formulation that would allow an analysis of compliant collapse that takes account of both parenchymal tethering and airway wall stiffness. The latter is believed to be important, but is presently neglected in the model in Chapter Four, Part I.
Refinements of the surfactant transport model. Accounting for differential squeeze-out in multicomponent surfactant mixtures, monolayer rupture on expansion, a more gradual transition between the three transfer regimes, and the variation of the minimum surface tension achievable with bulk concentration would all help increase the versatility and predictive power of the theoretical model presented in Chapter Three.

Improved visualization techniques. Development of tools that employ confocal microscopy, micro-bronchoscopy or other novel imaging techniques that allow one to look inside a lobe and see airway closure take place would undoubtedly be of great benefit in better understanding airway closure.

Airway re-opening. Several important questions are: Why is multistep closure not seen as frequently as multistep re-opening? How does the re-opening process propagate through the lung? How are re-opening events related to "crackles" heard by auscultation?

Differences in closure behavior between perfused and unperfused lobes. Relevant questions are: Was the difference in airway closure behavior between perfused and unperfused lobes in Chapter Six significant? How does perfusion alter the airway and airspace liquid layer properties and how are airway closure and re-opening characteristics affected?

REFERENCES


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