An estimation of mechanical stress on alveolar walls during repetitive alveolar reopening and closure

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Chen ZL, Song YL, Hu ZY, Zhang S, Chen YZ. An estimation of mechanical stress on alveolar walls during repetitive alveolar reopening and closure. J Appl Physiol 119: 190–201, 2015. First published May 28, 2015; doi:10.1152/japplphysiol.00112.2015.—Alveolar overdistension and mechanical stresses generated by repetitive opening and closing of small airways and alveoli have been widely recognized as two primary mechanistic factors that may contribute to the development of ventilator-induced lung injury. A long-duration exposure of alveolar epithelial cells to even small, shear stresses could lead to the changes in cytoskeleton and the production of inflammatory mediators. In this paper, we have made an attempt to estimate in situ the magnitudes of mechanical stresses exerted on the alveolar walls during repetitive alveolar reopening by using a tape-peeling model of McEwan and Taylor (35). To this end, we first speculate the possible ranges of capillary number (Ca) = μU/γ (a dimensionless combination of surface tension γ, fluid viscosity μ, and alveolar opening velocity U) during in vivo alveolar opening. Subsequent calculations show that increasing respiratory rate or inflation rate serves to increase the values of mechanical stresses. For a normal lung, the predicted maximum shear stresses are <15 dyn/cm² at all respiratory rates, whereas for a lung with elevated surface tension or viscosity, the maximum shear stress will notably increase, even at a slow respiratory rate. Similarly, the increased pressure gradients in the case of elevated surface or viscosity may lead to a pressure drop >300 dyn/cm² across a cell, possibly inducing epithelial hydraulic cracks. In addition, we have conceived of a geometrical model of alveolar opening to make a prediction of the positive end-expiratory pressure (PEEP) required to splint open a collapsed alveolus, which as shown by our results, covers a wide range of pressures, from several centimeters of water, strongly depending on the underlying pulmonary conditions. The establishment of adequate regional ventilation-to-perfusion ratios may prevent recruited alveoli from reabsorption atelectasis and accordingly, reduce the required levels of PEEP. The present study and several recent animal experiments likewise suggest that a lung-protective ventilation strategy should not only include small tidal volume and plateau pressure limitations but also consider such cofactors as ventilation frequency and inflation rate.

atelectrauma; shear stress; pressure gradient; respiratory rate; lung recruitment; ventilator-induced lung injury

ATELECTRAUMA, DUE TO REPEATED opening and closing of collapsed small airways and alveoli, has been widely recognized as one of the main determinants of ventilator-induced lung injury (VILI) in the ventilatory management of patients with acute respiratory distress syndrome (ARDS) or acute lung injury (ALI). Muscedere and colleagues (38) ventilated isolated, nonperfused, lavaged rat lungs with small tidal volumes at different positive end-expiratory pressures (PEEPs): PEEP = 0, PEEP < infection point (Pinf), and PEEP > Pinf, and found that sites of atelectrauma lied in the respiratory and membranous bronchioles, as well as alveolar ducts. Furthermore, the site of lung injury was dependent on the level of PEEP. In the PEEP = 0 group, there was significantly greater injury to the respiratory and membranous bronchioles, which may manifest as epithelial denudation and/or necrotic debris in the airways, whereas the group ventilated with PEEP = 4 cmH₂O has a significantly greater percentage of alveolar ducts with hyaline membrane formation but no increase in the extent of injury to respiratory or membranous bronchioles. Experimental data collected by Shinya Tsuchida et al. (56) further suggested that distal airway injury associated with atelectasis was generalized throughout the lung and not localized to the regions that are atelectatic. In contrast, alveolar injury, resulting from atelectasis, did not occur in atelectatic (dependent) regions but instead, occurred in remote nonatelectatic (nondependent) alveoli. From the anatomical observations, alveolar opening and closing may also occur at the subalveolar level, with folds of the epithelial surfaces into the pulmonary capillaries and with pleating of the alveolar septa in alveolar corners (22, 23, 61).

A summary of possible atelectrauma sites is shown in Fig. 1. Peripheral airway walls held in apposition by a layer of adhesive lining fluid are forced open by the progression of a finger of air through the collapsed configuration (Fig. 1A). As the meniscus progresses, a dynamic wave of mechanical stresses, characterized by large wall shear and normal stresses, may be imparted on the airway epithelial cells. Figure 1B shows the opening of alveolar folds and pleats at high inflation pressure. The infolded surfaces are separated in a peeling motion, which may generate appreciable shear stress to disrupt cell membranes when the viscosity of lining fluid is elevated in the diseased lungs. The third possible case is schematically shown in Fig. 1C, where a collapsed and fluid-filled alveolus (a3) is peeled apart at different angles (θ) by the joint action of advancing meniscus and juxtaposed, air-filled alveoli (a1 and a2) during inflation. Likewise, the magnitudes of the shear stresses associated with peeling motion depend on viscosity (μ) and surface tension (γ) of the lining fluid, as well as the peeling velocity (U). Gaver et al. (18) and Saffman and Taylor (46) defined a parameter capillary number (Ca) = μU/γ that is a nondimensional combination of three of these properties to represent the relative importance of surface tension to viscous forces in determining the dynamic responses of these types of systems.
A comparison of the experimental and theoretical observations made by Bilek et al. (5) and Kay et al. (31) demonstrated that among four potentially injurious components of the stress cycle associated with airway reopening (shear stress, pressure, shear stress gradient, and pressure gradient), the pressure gradient was the most predominant mechanism for the observed cellular damage. Nevertheless, several recent studies have shown that shear stress plays an important role in inducing signal transduction and alterations in cytoskeletal (CSK) keratin intermediate filaments (KIFs) networks. Ridge et al. (45) demonstrated that in alveolar epithelial cells (AECs), subjected to shear stress (15 and 30 dyn/cm²) for 24 h, there was an increased solubility of both K8 and K18 protein compared with control cells. They also demonstrated that AEC exposed to 30 dyn/cm² for 0, 4, and 24 h exhibited a time-dependent increase in the soluble (disassembled) keratin protein. Furthermore, with the exposure of AEC to shear stress (30 dyn/cm²) for 24 h, the KIF network was disorganized with the formation of large juxtanuclear aggregates of keratin and numerous keratin particles.

For AEC devoid of microtubules and microfilaments, Sivaramakrishnan et al. (48) showed that 15 dyn/cm² for 4 h induced a structural remodeling of AECs, with a more homogeneous distribution of the KIF network from the nucleus to the cell periphery compared with static-control conditions. They also found that shear stress applied across the surface of AECs induced a substantial increase in the mean storage modulus of both K8 and K18 protein compared with control cells. They also demonstrated that AEC exposed to 30 dyn/cm² for 0, 4, and 24 h exhibited a time-dependent increase in the soluble (disassembled) keratin protein. Furthermore, with the exposure of AEC to shear stress (30 dyn/cm²) for 24 h, the KIF network was disorganized with the formation of large juxtanuclear aggregates of keratin and numerous keratin particles.

Multiple repetitive reopening events could span a commensurate period of time, thus inducing mechanical cellular injury. Motivated by these excellent studies reviewed above, we are intensely curious to know about a rough magnitude of mechanical stress on the alveolar wall during cyclic opening and closure of alveoli in both physiological and pathological conditions. More importantly, we have made an attempt to relate the magnitude of mechanical stresses to clinical ventilator settings, such as respiratory frequency, PEEP, and inspiratory time or flow rate, which has implications for designing a “lung-protective” ventilator strategy to moderate or avoid VILI (4, 14). On the basis of an idealized airway model that combined in vitro culture of a pulmonary epithelial cell with semi-infinite air bubbles progressing in a parallel-plate chamber, Bilek and colleagues (5) obtained a set of regression formulas that can theoretically predict the stress magnitudes and gradients during the experimental airway opening for very small Ca. However, the magnitudes of mechanical stresses generated during the repetitive opening and closure of alveoli and alveolar folds and pleats have received little theoretical or experimental attention.

Therefore, the purpose of the present study includes the following: 1) to make a theoretical prediction of the mechanical stress magnitudes during steady-state alveolar opening; 2) to estimate the critical opening pressures for alveoli; and 3) to identify the specific physical characteristics of the lining fluid and ventilator parameters that may have a significant influence on the severity of atelectrauma. To achieve these goals, we first briefly summarized the investigation of a small airway opening by Gaver et al. (16) and the peeling model of a flexible strip by McEwan and Taylor (35). Next, we made a rough estimation of the possible ranges of Ca for an in vivo alveolar opening in both normal and disease conditions. Our results show that the accompanying shear stress and pressure gradient during alveolar reopening may range from several to thousands of dynes per square centimeter and that increased respiratory rate will lead to an increase in the magnitudes of these stresses. Finally, we developed a geometric model that made it possible to estimate the opening pressures for alveoli. We believe that these preliminary studies provide a conceptual framework that
may be helpful toward a better understanding of mechanisms for alveolar reopening and consequently, improve the lung-protective ventilation strategy to avoid atelectrauma as much as possible.

METHODS

Airway opening in Fig. 1A and alveolar opening in Fig. 1, B and C, share similar mechanisms; that is, the collapsed airway or alveolar walls are peeled apart by an advancing air-fluid interface or meniscus. According to the fluid dynamic analysis on airway opening by Gaver and colleagues (5, 16), the geometry of the meniscus mainly depends on the dimensionless Ca. As shown in Fig. 2, the first distinct feature is that the fraction of the channel occupied by the bubble after the meniscus has passed decreases as Ca increases. The second one is that the increase in Ca causes a more radial-wall deflection with wall buckling inward downstream of the meniscus tip.

On the other hand, what is significantly different from airway opening (Fig. 1A) is that the opening of alveolus a3 (Fig. 1C) still includes the contribution of the variable tension within the shared alveolar walls, which is exerted by the adjacent alveoli a1 and a2 during inflation. This kind of architectural interdependence may modulate the shape of the moving meniscus and as will be discussed below, has a direct influence on the critical alveolar opening pressures. For the case of Ca << 1, surface tension is a predominant factor for alveolar opening, with the critical opening pressures determined by the Law of Laplace, and for the case of large Ca, the contribution of viscous stress to alveolar opening is non-negligible, and therefore, we combine a peeling model created by McEwan and Taylor (35) and a proposed geometric model to calculate the critical alveolar opening pressures.

**Model introduction.** McEwan and Taylor (35) investigated the peeling of a completely flexible sheet attached to a plane rigid surface by a fluid of Newtonian viscosity \( \mu \), surface tension \( \gamma \), and initial thickness \( h_0 \), as shown in Fig. 3. The sheet is peeled apart with tension \( T \) at an angle \( \theta \). The motion is assumed to be steady and two dimensional. As the liquid layer separates at the meniscus M, part of it sticks to the surface and part to the sheet, but the total quantity/unit area, adhering to both surfaces, is equivalent to that far upstream of the separation line. McEwan and Taylor (35) defined \( m \) as the ratio of the thickness of the layers of fluid adhering to the moving surface to the width of the gap at the meniscus.

Jensen et al. (30) have also used the similar geometric model to describe the reopening of a collapsed lung airway. They split the entire flow domain into three asymptotic regions: upstream of the bubble tip (region I), the neighborhood of the bubble tip (region II), and far downstream of the bubble tip (region III), as illustrated in Fig. 3. Apparently, it is in region II that the airway epithelial cells are particularly at risk of being damaged due to the greatest mechanical stresses and spatial gradients in these stresses generated by the progression of the separation meniscus. Therefore, our study is mainly focused on region II. In effect, the flow here can be considered as a low Reynolds number valve, which determines the fluid-flow velocity of the entire system. Furthermore, when the meniscus, advancing at speed \( U \), separates the flexible sheet from the rigid surface, the shear stress on the fluid, pressure gradient in the fluid, and peeling angle can be estimated by Eqs. 1–3, respectively.

\[
\tau(x, y) = \frac{6\mu U(h - h_0)}{h}(2y - h) \quad (1)
\]

\[
\frac{dp}{dx} = 12\mu U \frac{(h - h_0)}{h^3} \quad (2)
\]

\[
\left[\zeta\right]_{x_{1}=x_{m}} = \frac{1}{\alpha^3} \tan \theta \quad (3)
\]

where \( h \) is the depth of the fluid at position \( x \), \( \zeta = \frac{m}{h} = \frac{h_0}{h_0} \) is the dimensionless depth, and \( \alpha \) is defined as \( \alpha = \frac{1}{U} \). Primes denote the differentiation operation (see APPENDIX A).

Nevertheless, for the opening of alveolar folds and pleats, it is a quite different picture. First and foremost, in this case, the entire flow domain includes only regions I and II; that is, the domain is finite rather than infinite due to boundary constraints from alveolar pleats. Second, compared with the pushing effects of the air bubble, the peeling effects of wall tension are the main contribution to the reopening of pleats, because the sides of pleats are not parallel to each other. Finally, alveolar pleats tend to open in a way of rotation motion that may cause large displacement of the alveolar wall in both the \( x \) and \( y \) directions and consequently, disturb flow stability, resulting in the occurrence of turbulent flow. Because a part of mechanical energy may be dissipated by deforming the structure, we therefore presume that the epithelial cells are possibly free from severe damage during the unfolding process of alveolar folds and pleats.

**Capillary number.** To estimate the alveolar opening angles during mechanical ventilation (MV), we first need to know the Ca that reflects the relative contributions of the viscous and capillary pressures to the alveolar opening. For a normal lung, we take the surface tension \( \gamma = 25 \, \text{dyn/cm} \) and the viscosity \( \mu = 0.01 \, \text{g} \cdot \text{s}^{-1} \cdot \text{cm}^{-1} \).

Next, we will speculate the possible ranges of alveolar opening velocity \( U \) from both the previous studies and the clinical practice of MV. Yap and colleagues (65) ventilated the freshly excised canine lung lobes with a constant flow of \( \sim 6 \, \text{ml/min} \) to investigate the influence of parenchymal tethering on the reopening of closed pulmonary airways. They found that as the magnitude of pleural pressure (Ppl) increased, the reopening time decreased from \( \sim 718 \, \text{ms} \) at Ppl = \(-3.5 \, \text{cmH}_2\text{O} \) to \( \sim 371 \, \text{ms} \) at Ppl = \(-5.0 \, \text{cmH}_2\text{O} \) and finally, to \( \sim 14 \, \text{ms} \) at Ppl = \(-9.0 \, \text{cmH}_2\text{O} \). For a 2-mm diameter airway studied, this flow corresponded approximately to a velocity of \( \sim 1.85 \) cm/s. Thus the corresponding collapsed length is 2.2868 cm at Ppl = \(-3.5 \, \text{cmH}_2\text{O} \), 1.0096 cm at Ppl = \(-5.0 \, \text{cmH}_2\text{O} \), and 0.0446 cm at Ppl = \(-9.0 \, \text{cmH}_2\text{O} \), respectively, in the case of
compliant collapse. Similarly, Gaver et al. (18) predicted the time required to open airways of generation 8–14 for a normal lung, which is approximately the order of magnitude of <50 ms, and if the viscosity of the lining increased by several orders of magnitude, then the opening time would increase dramatically to >200 ms.

If the alveolar opening time is so long that the alveolus remains closed for a considerable portion of inspiration, then hypoventilation may occur and lead to deterioration of arterial oxygenation; take an atelectatic alveolus with an average diameter of 200 μm, for example (59). With the assumption that the alveolar opening occurs throughout the time course of inspiration, we consider here the inspiratory time settings over a broad range of 1 s, 0.5 s, 0.1 s, 10 ms, and 5 ms, and the computed Ca is $8 \times 10^{-6}$, $1.6 \times 10^{-5}$, $8 \times 10^{-5}$, $8 \times 10^{-4}$, and $1.6 \times 10^{-3}$, respectively. If hypersecretion of mucus exists, due, for example, to pulmonary diseases, such as bronchitis, bronchial asthma, and cystic fibrosis (13), then the viscosity of the lining fluid may elevate by several orders of magnitude, for example, $\mu = 1 \text{ g} \cdot \text{s}^{-1} \cdot \text{cm}^{-1}$. In this case, Ca will increase correspondingly to $8 \times 10^{-4}$, $1.6 \times 10^{-3}$, $8 \times 10^{-3}$, 0.08, and 0.16.

For these low values of Ca, McEwan and Taylor (35) gave the following empirical relationship

$$m = \frac{\lambda h_0}{h_m} \approx 0.63 (\mu U / \gamma)^{0.5}$$

(4)

where $h_m$ refers to the width of the gap at the meniscus, and $\lambda$ is a constant that depends on the curvature of the sheet and the flow conditions upstream of the meniscus. For small peeling angles, take $\lambda = 1$, and if $h_m$ is substantially larger than $h_0$, then the meniscus has little effect on changing the value of $\lambda$. In Table 1, we summarized two sets of calculated m for different values of Ca. For a lung with normal viscosity $\mu = 0.01 \text{ g} \cdot \text{s}^{-1} \cdot \text{cm}^{-1}$, the speculative Ca varies between $8 \times 10^{-6}$ and $1.6 \times 10^{-3}$ over the ranges of velocities examined, which means surface tension dominates the alveolar opening. Referring to Fig. 2A, we speculate that the bubble will occupy a large fraction of channel width. Furthermore, we assume that in this case, the width of the gap in the vicinity of the meniscus is less than the average diameter of the alveolar entrance ring, $\sim 150 \mu \text{m}$ (1, 36).

For a diseased lung with elevated viscosity $\mu = 1 \text{ g} \cdot \text{s}^{-1} \cdot \text{cm}^{-1}$, the calculated Ca varies in the range of 0.0008–0.16, as shown in Table 1. In particular, as U increases to 2 or 4 cm/s, Ca correspondingly has reached 0.08 or 0.16, indicating that the contribution of viscous forces to the alveolar opening has become non-negligible. At this time, the alveolus will open at a relatively small angle, and the width of the gap near the meniscus can be estimated using Eq. 4.

Alveolar wall tension. In vitro airway reopening experiments by Gaver and colleagues (16) demonstrated that airway reopening pressures depended on the imposed axial wall tension. Specifically, the reopening pressure decreased as the wall tension increased. For a pair of juxtaposed alveoli a1–a3 or a2–a3, shown in Fig. 1, our prior study (8) showed that the wall-tension stress in rat lungs varied approximately in the range of 2.07 kPa $\leq \sigma \leq 5.12$ kPa during inflation, from 5 to near 15 cmH2O. With an average human alveolar septum thickness of 8 μm (37), we estimate the alveolar wall tension $T$ approximately in the range of 16.56 dyn/cm $\leq T \leq 40.96$ dyn/cm.

The interaction of alveolar wall tension with the airway opening angle is complicated, and to date, we have been unable to give an exact relation of the alveolar pressure to alveolar wall tension. However, in terms of airway reopening and closure being discussed, we are more interested in the maximal or minimal alveolar wall tension than the exact tension contour, because each is directly related to the “yield pressure” or critical alveolar reopening pressure, which has been a critical matter of lung recruitment. Hence, for the sake of simplicity, we take $T$ as constant and consider the small alveolar wall tension $T = 20$ dyn/cm and the large $T = 200$ dyn/cm due to higher plateau pressure than 15 cmH2O during MV.

**Thickness of intra-alveoli fluid.** In mammalian species, the alveolar surface is lined with a continuous thin, aqueous layer that includes surfactant and its aqueous subphase. This lining layer varies from a few nanometers to several micrometers in thickness, and in rat lungs, for example, it has an average thickness of 0.14 μm over relatively flat portions of the alveolar walls and 0.89 μm in alveolar corners, with an overall area-weighted average thickness of 0.2 μm (3, 21, 31, 66). Surfactant deficiency predisposes the alveolar walls to collapse, forming adhesive atelectasis.

Although evidently without cilia, the alveolar lining layer is confluent with small airway surface liquid (ASL), and the latter consists of at least two layers—a mucus layer and a periciliary liquid layer. The depth of the periciliary liquid layer appears to be equal to the length of the cilium (~6 μm). In most microscopic studies, the thickness of the mucus layer is $2 \sim 20 \mu \text{m}$ (24, 33, 60, 63). Chronic irritation or injury can induce mucous hypersecretion with a 10-fold increase in the thickness of the mucus layer (40). Importantly, impairment of mucociliary clearance can make the mucus migrate in a retrograde fashion into the peripheral airways and pool there, which is the most common cause of resorption atelectasis (62).

Morphometric results of Bachofen and associates (2) showed that the volume fraction of alveolar edema fluid is in the range of 10–50% in rabbit lungs. Besides, the distribution of alveolar edema is gravity dependent and inhomogeneous, even at the same lung height. We consider an alveolus at maximum volume with the radius of 100 μm. If the volume of a completely collapsed, fluid-filled alveolus is taken to be 20% of alveolar capacity, then the radius corresponding to that volume is 58 μm. A calculation of Staub (50) further indicated that the same amount of edema fluid would be distributed in a fluid layer, 7 and 12 μm thick at the alveolar pressure 30 and 10 cmH2O, respectively. These calculations are consistent with the recent experimental measurements of edematous alveoli by confocal microscopy (32, 42, 58).

As can be seen from the above discussion, intra-alveoli fluid is possibly a mixture of pulmonary surfactant, reverse-flow ASL, and edema fluid, depending on the types of pulmonary atelectasis. In the following calculation, we therefore take the initial thickness of intra-alveoli fluid in the range of 5–30 μm.

**RESULTS**

Alveolar opening angles. Figure 4 shows the relationship between Ca and alveolar opening angles for alveolar wall tension $T = 20$ dyn/cm and $T = 200$ dyn/cm. The first conspicuous feature is that alveolar opening angles remain at a constant angle of $\sim 65^\circ$ over the studied range $8\leq Ca \leq 16$ when the wall tension is small. Second, for the relatively large wall tension $T = 200$ dyn/cm, alveolar opening angles

Table 1. Calculated m for different capillary number Ca, with $\gamma = 25$ dyn/cm

<table>
<thead>
<tr>
<th>$\mu$, g · s⁻¹ · cm⁻¹</th>
<th>U, cm/s</th>
<th>Ca, μU/γ</th>
<th>m, h₀/hₘ₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0.02</td>
<td>$8 \times 10^{-6}$</td>
<td>0.0018</td>
</tr>
<tr>
<td>0.01</td>
<td>0.04</td>
<td>$1.6 \times 10^{-5}$</td>
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<tr>
<td>0.01</td>
<td>0.2</td>
<td>$8 \times 10^{-5}$</td>
<td>0.0056</td>
</tr>
<tr>
<td>0.01</td>
<td>2</td>
<td>$8 \times 10^{-4}$</td>
<td>0.018</td>
</tr>
<tr>
<td>0.01</td>
<td>4</td>
<td>$1.6 \times 10^{-3}$</td>
<td>0.025</td>
</tr>
<tr>
<td>1</td>
<td>0.02</td>
<td>$8 \times 10^{-4}$</td>
<td>0.018</td>
</tr>
<tr>
<td>1</td>
<td>0.04</td>
<td>$1.6 \times 10^{-3}$</td>
<td>0.025</td>
</tr>
<tr>
<td>1</td>
<td>0.2</td>
<td>$8 \times 10^{-3}$</td>
<td>0.056</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>0.08</td>
<td>0.18</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>0.16</td>
<td>0.25</td>
</tr>
</tbody>
</table>

m, ratio of the thickness of the layers of fluid adhering to the moving surface to the width of the gap at the meniscus; Ca, capillary number; $\gamma$, surface tension; $\mu$, viscosity; U, meniscus veloclty; h₀/hₘ₀, initial thickness/width of the gap at the meniscus.
are \( \sim 35.5^\circ \) and hold constant when \( 8e^{-6} \leq Ca \leq 8e^{-4} \), but when \( 0.0016 \leq Ca \leq 0.16 \), alveolar opening angles are increased with increasing \( Ca \). Third, the increased wall tension leads to a decrease in the alveolar opening angle, indicating that the wall tension can modulate the meniscus shape, which is presented further in Fig. 5. As wall tension increases from 20 to 200 dyn/cm, the corresponding alveolar opening angles decrease from 66\(^\circ\) to 35.8\(^\circ\) for \( Ca = 0.0008 \). The same is true for \( Ca = 0.08 \). Furthermore, it can be seen from Fig. 5 that alveolar opening angles at \( Ca = 0.08 \) are slightly larger than those at \( Ca = 0.0008 \) under the condition of the same wall tension. This result is qualitatively in agreement with the analysis of airway opening by Gaver et al. (16). A larger \( Ca \) means the larger viscous forces and pressure gradients are in the front of the meniscus and accordingly, larger inward deflection of alveolar walls and thus larger alveolar opening angles (Fig. 2, A–D).

We have noted that in Fig. 4, the peeling angles for \( T = 20 \) dyn/cm are \( >65^\circ \), but in deriving a differential equation of the system (see Eq. A6 in APPENDIX A), it is assumed that the angle is small, so that wall tension can be taken as a constant. In a physical sense, Eq. A6 signifies that a local wall curvature creates pressure gradients in the fluid. Inversely, if wall tension is too small, then a relatively large wall curvature is required to balance the pressure-gradient term on the right side of the equation. In addition, the influence of the wall elasticity is not considered in the current peeling model, which we think is another reason why the predicted angles are rather large for \( T = 20 \) dyn/cm.

Maximal wall shear stress. According to Eq. 1, the maximal wall shear stresses near the meniscus are reported in Figs. 6 and 7. The current model is unable to give an overall spatial distribution of shear stresses upstream, near, and downstream of the meniscus, but fortunately, as far as a single alveolar opening event is concerned, several studies have demonstrated that the maximal wall shear stress is a more decisive factor in causing atelectrauma compared with a whole wall shear profile (28, 45, 48). In Figs. 6 and 7, surface tension is taken to be constant as 25 dyn/cm. For a normal lung with viscosity \( \mu = 0.01 \, \text{g} \cdot \text{s}^{-1} \cdot \text{cm}^{-1} \), the calculated wall shear stress gradually increases as \( Ca \) varies from \( 8e^{-6} \) to \( 1.6e^{-3} \). In addition, at the same alveolar opening velocity, the increase in initial intra-alveoli fluid thickness \( h_0 \) will lead to a minor decrease in the wall shear stress. Take a close look at the case of \( h_0 = 20 \, \mu\text{m} \) (Fig. 6). Over the range of \( 8e^{-6} \leq Ca \leq 1.6e^{-3} \), the wall shear stress \( \tau_w \) increases from a minimum value of 0.069 dyn/cm\(^2\) to the maximum 13.867 dyn/cm\(^2\). Particularly, for the “fast” alveolar opening time of 0.1 s, 10 ms, and 5 ms, the wall shear stress is 0.693, 6.93, and 13.87 dyn/cm\(^2\), respectively. By fast,
we mean that the opening time is far smaller than a clinical, typical inspiratory time setting, for instance, 1 s, to ensure that the collapsed alveolus is opened completely and that hyperventilation never occurs. As described in the Introduction, if we take a “harmful” threshold of shear stress as 15 dyn/cm², then a single alveolar opening event, in this case, will not induce mechanical cellular injury.

However, with the presence of accumulation of hyperviscous mucus, due to lung diseases, the viscosity may increase sharply by orders of magnitude. As shown in Fig. 7, we take viscosity μ₁ as 1 g·s⁻¹·cm⁻¹. Accordingly, as viscosity increases dramatically, the calculated wall shear stress also increases by several orders of magnitude, even at the same alveolar opening velocity compared with Fig. 6. Besides, the wall shear stress is greatly influenced by the increase in the initial intra-alveoli fluid thickness h₀ and the larger that the alveolar opening velocity is, the stronger the influence of h₀ on τₘ is. We still consider the example of h₀ = 20 µm (Fig. 7). Over the range of 8e⁻⁴ ≤ Ca ≤ 0.16, the wall shear stress τₘ increases from the minimum 6.93 dyn/cm² to the maximum 2,262 dyn/cm². Similarly, for the fast alveolar opening time of 0.1 s, 10 ms, and 5 ms, the wall shear stress is 69, 879, and 2,262 dyn/cm², respectively, and with the consideration of a harmful threshold of shear stress as 15 dyn/cm², a single alveolar opening event in this case may cause severe mechanical cellular injury.

**Pressure gradient.** It can be seen from Figs. 8 and 9 that pressure gradients are increased with increasing dimensionless velocity Ca or viscosity μ₁. A number of recent studies (7, 31, 39) have demonstrated that the pressure gradient is the primary determinant of cell damage in the airway reopening. The experimental data from Kay et al. (31) indicated that significant cell-membrane damage occurred when the fore-aft pressure changes across a cell (ΔPₘₑₙ) were ~300 dyn/cm², which was reduced when ΔPₘₑₙ was ~120 dyn/cm², and little membrane disruption was observed for ΔPₘₑₙ ~80 dyn/cm². With the assumption that the initial thickness of intra-alveoli fluid h₀ is to be 20 µm (Figs. 8 and 9), we give a rough estimation of changes in pressure along the length of a 40-µm cell shown in Table 2.

Clearly, the magnitude of ΔP increases with increasing Ca, and this trend is seemingly inconsistent with results from Kay et al. (31). In fact, this discrepancy can be explained by the different definition or location pressure gradient (dP/dx) discussed. In the studies by Kay et al. (31), dP/dx is the pressure gradient across the perimeter of the meniscus, which shows multibranch behavior with Ca (5, 16, 30), whereas dP/dx, discussed in our study, represents the downstream viscous pressure gradient in the fluid, which
Table 2. Predicted pressure gradients and fore-aft pressure changes across a cell

<table>
<thead>
<tr>
<th>( \mu ), g \cdot s^{-1} \cdot cm^{-1}</th>
<th>U, cm/s</th>
<th>Ca</th>
<th>dP/dx, dyn \cdot cm^{-2} \cdot \mu m^{-1}</th>
<th>\Delta P, dyn/cm²</th>
</tr>
</thead>
<tbody>
<tr>
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<td>8e-5</td>
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<td>2.79</td>
</tr>
<tr>
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<td>2</td>
<td>8e-4</td>
<td>0.696</td>
<td>27.85</td>
</tr>
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<td>4</td>
<td>0.0016</td>
<td>1.393</td>
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</tr>
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<tr>
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<td>4</td>
<td>0.16</td>
<td>57.001</td>
<td>2280*</td>
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</table>

\( dP/dx \), pressure gradient; \( \Delta P \), change in pressure along the length of a 40-\( \mu m \) cell. The depth of intra-alveoli fluid \( h_0 \) is assumed to be 20 \( \mu m \), and \( \gamma = 25 \) dyn/cm. *Probable significant cell damage due to \( \Delta P \) scales \( \geq 300 \) dyn/cm².

according to Eq. 2, is proportional to velocity \( U \) or viscosity \( \mu \). Apparently, the maximum pressure gradient of the entire system occurs in the vicinity of the meniscus (region II); nevertheless, our calculations demonstrate further that even in the downstream region III, where \( \Delta P \) has a relatively lower magnitude than in region II, AECs may be subjected to severe damage due to \( \Delta P \) scales \( \geq 300 \) dyn/cm² in the case of elevated viscosity (see Table 2). Additionally, the work of Halpern and Gaver (25) has demonstrated that the change of the pressure gradient with \( Ca \) also relates to whether the wall is flexible or rigid.

So far, we have assumed that surface tension in alveoli is constant. Actually, surface tension is varied, as air-liquid interface expands during alveolar reopening. Furthermore, in patients with ALI or ARDS, alveolar surface tension is increased due to surfactant inactivation (27). The variation of surface tension can influence the domain shape. For small peeling angles, McEwan and Taylor (35) gave the following equation

\[ \tan^2 \theta = 4\gamma/T \]  

indicating that for the fixed \( \mu, T, \) and \( U \), the increase in \( \gamma \) results in an increase in \( \theta \). In addition, according to the analysis by Gaver et al. (16), increased \( \gamma \) decreased \( Ca \), which in turn, would result in a decrease in the magnitudes of both wall normal stress and shear stress.

Predictions of capillary pressure. As discussed above, the opening angle increased as the alveolar wall tension decreased for a fixed value of \( m \). Accordingly, the curvature radii of the meniscus increased due to the increased opening angles. Figure 10 plots the geometry of the alveolar reopening at the different wall tension of \( T_1 = 200 \) dyn/cm and \( T_2 = 20 \) dyn/cm. According to the observations made by McEwan and Taylor (35), Pitts and Greiller (43), and Taylor (53), since \( m \) represents the fraction of the thickness of the layers of fluid adhering to the moving surface to the gap width at the meniscus, there is a reason to believe that \( h_1 \) and \( h_2 \) (Fig. 10), thicknesses of lining fluid downstream the meniscus, are equal for a fixed value of \( m \). It is extremely difficult to deduce the profile and position of the meniscus from purely theoretical considerations. Instead, the experimental observations show that the meniscus appears as a parabolic profile at the large peeling angles, and especially, it is very likely to have a circular arc profile at the small peeling angles. Here, for simplicity, we assume the gap width \( A'F' \) in the vicinity of the meniscus \( M_1 \) is equal to the gap width \( AF \) near the meniscus \( M_2 \); i.e., \( h_{m1} = h_{m2} = h_m \), and both \( M_1 \) and \( M_2 \) take on a circular arc profile. From the geometric relationship shown in Fig. 10, it is not difficult to obtain the following equation

\[ h_m - (h_1 + R)^3 + R^2 = \left[ \frac{R - (h_1 + R)\sin \theta}{\cos \theta} \right]^2 + (h_1 + R)^2 \]  

where \( \theta \) is the peeling angle, and \( R \) refers to the radius of the meniscus (Appendix B). According to Eq. 6, we can roughly predict the capillary pressure or critical pressure associated with the alveolar opening as the alveolar wall tension or opening angle varies.

For a typical calculation, take \( Ca = 0.08 \), which corresponds to \( m = 0.18 \) and from Fig. 5, the peeling angle \( \theta_1 = 39.3° \) at wall tension \( T_1 = 200 \) dyn/cm. Then, for \( h_0 = 20 \) \( \mu m \), and \( h_1 = m \cdot h_0 = 3.6 \) \( \mu m \), according to Eq. 6, the calculated \( R_1 \) is 69.8 \( \mu m \). In the same way, we obtain the radius \( R_2 \) of the meniscus \( M_2 \) to be 81.5 \( \mu m \), as the wall tension decreases to \( T_2 = 20 \) dyn/cm. Once the radius of curvature is known, we can further predict the capillary pressure \( P \) using the Law of Laplace, \( P = 2\gamma/R \), where \( \gamma \) is the surface tension. Figure 11 shows the capillary pressure–alveolar wall-tension relationship for different initial thickness of intra-alveoli fluid \( h_0 \) with \( Ca = 0.08 \). The predicted capillary pressures range, from 5 to 30 cmH₂O, strongly depends on the initial thickness of intra-alveoli fluid \( h_0 \). This result may, in part, explain the clinical findings that the transmural pressure, required for opening a stickily atelectatic alveolus, may be as high as 30–35 cmH₂O (11, 41). A detailed description of this point will be represented in DISCUSSION.

It is also noteworthy that the wall tension bears a relatively small influence on the magnitude of capillary pressure at a given initial thickness of intra-alveoli fluid \( h_0 \), although it greatly influences the alveolar opening angles, as discussed previously. In fact, with the assumption of a circular arc contour of the meniscus, the calculated meniscus radii all varied \(<17% \) at various thicknesses of \( h_0 \) when the wall tension changed from 20 dyn/cm to 200 dyn/cm.
plasma membrane (PM)], Oeckler et al. (39) invoked the
skeleton), covered by a layer of an impermeable barrier [the
consideration that a cell is a fluid sponge (cytosol and cyto-
fracture or denudation of epithelial monolayers. With the
highly correlated with cellular mechanical damage, such as
injuries, and epithelial cracks appeared after stretch cessation but not after
stretch application and that cracks were independent of epithe-
lial tension. The observed crack size and sealing dynamics
were predicted successfully by poroelastic theory. Therefore,
they also came to a similar conclusion that epithelial cracks
during stretch cessation were caused by the buildup of solute
pressure in the hydrogel substrates.

Conrad and coworkers (10) studied the effect of respiratory
frequency on the development of ventilator-associated lung
injury in the isolated, perfused rat lung model. Lung prepara-
tions were assigned to one of four respiratory frequencies (10,
20, 40, or 80 breaths/min, beats/min) and one of two tidal
volumes (5 or 20 ml/kg). Their data revealed that for the group
of lungs ventilated at a tidal volume of 5 ml/kg, there was no
difference between capillary filtration coefficient (Kf,c), a sen-
sitive index of lung microvascular permeability and injury, at
baseline and at 30, 60, or 90 min, regardless of respiratory
frequency. For lungs exposed to 20 ml/kg tidal volume and a
frequency of 80 beats/min, the Kf,c increased significantly from
baseline at all times compared with lungs exposed to respira-
tory frequencies of 10, 20, or 40 beats/min. Ventilation at 40
beats/min resulted in an insignificant increase in Kf,c, and at 10
and 20 beats/min, Kf,c remained unchanged from baseline
values at any time.

Hotchkiss et al. (26) obtained similar findings in an isolated,
perfused rabbit model. Lungs ventilated at a rate of 20 beats/
min, and an inflation pressure of 30 cmH2O for 30 min showed
at least a 4.5-fold greater weight gain, a threefold greater mean
incidence of perivascular hemorrhage, and a greater decrease
in compliance compared with those ventilated at 3 beats/min
but at the identical ventilatory pattern.

Rich et al. (44) used a rat model of VILI to examine the
synergistic effect of ventilatory rate and large tidal volume on
pulmonary cytokine levels and lung injury. They found that
rats ventilated at 7 ml/kg did not differ from control in any
outcome, regardless of respiratory rate. In contrast, MV at 40
ml/kg with 40 beats/min produced significant elevations of
bronchoalveolar lavage cytokine concentration, protein con-
tent, and epithelial lining fluid volume compared with MV at
20 beats/min with the same tidal volumes.

Our findings are well consistent with above animal experi-
iments. Moreover, the current model theoretically supports the
hypothesis of stress failure by Hotchkiss et al. (26) and Conrad
et al. (10), that higher respiratory frequencies may induce lung
injury by both elevating the magnitude of shear stress from
more rapid inflations and more rapidly reaching the total
number of cycles required for failure. It is clear from Eq. 1 that
shear stress magnitudes are linear to the alveolar opening
velocity. Rapid inflations may well lead to a fast velocity of
alveolar opening and consequently, a high shear stress (see
Figs. 6 and 7). Of note, although for a normal lung, shear stress
in a single opening event is less than a harmful threshold of

Fig. 11. Capillary pressure vs. wall tension for the different initial thickness of
intra-alveoli fluid h0, with Ca = 0.08.

DISCUSSION

We have estimated in situ mechanical stress magnitudes
associated with alveolar opening in mechanically ventilated
patients with ALI or ARDS via a tape-peeling model. Our
results show that the magnitudes of mechanical stress depend
on physical properties of intra-alveoli fluid, alveolar opening
velocity, and alveolar wall tension exerted by the neighboring
alveoli. We have also predicted the apparent yield pressure for
the alveolar opening by conceiving of a geometric model. The
main findings of this study were the following: 1) for a lung
with the normal fluid viscosity and surface tension, the mag-
nitudes of shear stress are <15 dyn/cm² at all alveolar opening
velocities in the physiological range, but for a lung with
elevated viscosity of intra-alveoli fluid, shear stress may in-
crease by several orders of magnitude, enough to induce
epithelial cell injury; 2) similarly, in the case of elevated
viscosity, pressure drops across a cell may rise to scales ≥300
dyn/cm² and consequently, result in hydraulic epithelial
cracks; 3) the capillary pressure for alveolar opening ranges
from 5 to 30 cmH2O, strongly depending on the initial thick-
ness of intra-alveoli fluid, which may explain clinically high
opening pressure in sticky atelectasis; 4) assuming intra-alveoli
fluid to be a Newtonian flow, the magnitudes of shear stress are
proportional to the alveolar opening velocity, and therefore,
the reduction of inspiratory flow rate or respiratory frequency will
lead to a decrease in shear stress and a concomitant reduction
in atelectrauma on AECs; and 5) geometry of the alveolar
opening is determined by the Ca and wall tension applied by
the adjacent alveoli.

It is noteworthy that although it is shear stress force that
plays a key role in altering micromechanical properties of KIF
networks in AECs, as described before, a number of studies (5,
7, 30, 31, 39) have indicated that pressure gradients are more
highly correlated with cellular mechanical damage, such as
fracture or denudation of epithelial monolayers. With the
consideration that a cell is a fluid sponge (cytosol and cyto-
skeleton), covered by a layer of an impermeable barrier [the
plasma membrane (PM)], Oeckler et al. (39) invoked the
theory of poroelasticity to explain the dynamics of observa-
tional PM wounding. Deforming stress accumulated pressure
gradients in the cytosol, which once exceeded the adhesive
energy between the PM and lipid-CSK protein, a phase sepa-
ration occurred, and a bleb formed. Investigators demonstrated
that interventions, such as hypertonic cell conditioning, which
increased PM-CSK adhesive interactions, prevented bleb for-
mation and were cytoprotective. Recent experiments by Casa-
res et al. (7) revealed that during stretch-unstretch maneuvers,
epithelial cracks appeared after stretch cessation but not after
stretch application and that cracks were independent of epithe-
lial tension. The observed crack size and sealing dynamics
were predicted successfully by poroelastic theory. Therefore,
they also came to a similar conclusion that epithelial cracks
during stretch cessation were caused by the buildup of solute
pressure in the hydrogel substrates.
shear stress of 15 dyn/cm², the increase of respiratory frequency clearly raised the total number of stress cycles and may ultimately cause lung injury according to theories of stress failure. Recently, the liquid-plug rupture experiments of Huh et al. (28) demonstrated the effect of an increased number of stress cycles on cellular injury. These investigators designed an in vitro, computerized, microfluidic device to investigate the effect of propagation and rupture of liquid plugs on primary human small airway epithelial cells. The extent of cellular injury increased proportionally with escalating doses of mechanical stresses exerted by 10, 50, and 100 events of plug progression and rupture over a period of 10 min, suggesting the important role of repetitive reopening events in eliciting and exacerbating mechanical cellular injury.

Protective ventilatory strategies have used low tidal volumes and the provision of PEEP to alleviate or avoid lung injury. However, a recent large, multicenter trial (6) demonstrated that clinical outcomes were similar whether lower or higher PEEP levels were used. Studies by Gattinoni et al. (15) and Grasso et al. (22) further suggested that the clinical and physiological effects of PEEP were strongly associated with the percentage of a potentially recruitable lung, which, however, varied widely among patients with ALI or ARDS, from a negligible proportion to >50% of the total lung weight. In addition, as PEEP was raised from 5 to 15 cmH₂O, lung recruitment increased progressively.

Hence, in this sense, whether PEEP produces beneficial or detrimental effects depends on ARDS etiology and the stage of the disease. Our data also support this argument in theory. Figure 11 shows that the predicted capillary pressure is closely associated with the initial thickness of intra-alveoli fluid h₀. It is widely believed that two kinds of atelectasis coexist in an ARDS lung: the adhesive atelectasis and the resorption atelectasis (41, 62). The adhesive atelectasis stems from surfactant deficiency. When there is a deficiency of surfactant, the pressure in the interstitial compartment around the alveoli becomes more negative and draws fluid from the capillary bed into the alveoli, causing the alveoli to collapse. As a quantity of fluid is filled in the alveoli, i.e., the initial thickness of intra-alveoli fluid h₀ is comparatively deep, the transmural pressure required for opening is relatively low, termed “loose” atelectasis.

The resorption atelectasis is due to resorption of alveolar air distal to the obstructed airways. It is the most common type of atelectasis. When obstruction of a large airway or peripheral small airway occurs, blood circulating begins to resorb air from it, resulting in a progressive decrease in the size of the alveoli. In particular, atelectasis can develop rapidly in patients receiving high concentrations of oxygen because of the fast diffusion rate of oxygen. As gas is resolved completely, the alveolar walls tend to adhere, and h₀ becomes very small; the transmural pressure required for opening may be unusually high, termed “sticky” atelectasis. Crotti et al. (11) studied five ALI/ARDS patients and found that in three patients, the maximal frequency of estimated threshold opening pressures was ~20 cmH₂O, and in two patients, this maximal frequency occurred at ~35 – 30 cmH₂O.

Over the past 40 years, great efforts have been made to use PEEP to improve arterial oxygenation and to reduce mechanical stresses produced by repetitive alveolar recruitment and derecruitment (34, 49, 51, 52). However, the question of how much PEEP is enough remains controversial. The present study suggests that when selecting an “optimum” level of PEEP in patients with ALI/ARDS, there are two crucial things that we should keep in mind. Firstly, PEEP may overdistend the already aerated lung units, as it opens the neighboring, collapsed lung units. Secondly, an “optimal” PEEP is usually not a constant level of PEEP; in contrast, the best PEEP varies greatly among patients. It depends on the underlying pulmonary condition. Even for a single patient in the different stages of the disease, PEEPs required to open an atelectatic alveolus may differ strikingly, ranging from several centimeters to dozens of centimeters of water.

**Limitations.** There exist several deviations between the present tape-peeling model and in situ alveolar reopening that might influence the validity of our results. First, in the peeling model of McEwan and Taylor (35), a Newtonian viscous fluid can be assumed at a small Reynolds number, provided that the peeling angle is small and that the layer remains intact in front of the meniscus. Although there is little ground to disbelieve that the latter condition is satisfied in vivo alveolar reopening, our calculation shows that the alveolar opening angles are comparatively large due to relatively small alveolar wall tension. Therefore, the predicted wall shear stress and pressure gradients could be much in error, especially at low inflation pressures. In addition, findings on electron microscopy revealed that a manifestation commonly seen in ALI and ARDS patients was hyaline membrane formation in air spaces, overlying the epithelial lining of the alveoli and alveolar ducts (47, 57). As such, there exists another probability that alveolar lining fluid experiences a phase transition from a fluid- to gel-like state rather than becoming more viscous in response to mechanical stress associated with the repeated closure and opening of alveolar units. Once hyaline membranes occur, the friction between them may cause underlying epithelia and basement membranes to undergo a large shear deformation. The present model, however, is limited to predict this shear deformation.

Another limitation of the current models is that they are unable to predict the viscous pressures $P_{vis}$. Because an exact shape of peeling regions was not considered in the peeling model, the resistance to reopening provided by shear stresses is unknown. Based on the experimental data from an in vitro model of airway reopening, Gaver et al. (18) obtained a regression formula describing the viscous pressure, i.e., $P_{vis} = 7.7 \ Ca^{0.82} (\gamma/R)$. With the use of this formula, we made a relatively rough estimation of $P_{vis}$ associated with alveolar opening under discussion. For a collapsed alveolus with $h_0 = 15 \mu m$ and meniscus radius $R = 52.3 \mu m$, the calculated $P_{vis}$ is ~4.73 cmH₂O when $Ca = 0.08$; by contrast, the calculated capillary pressure in this case is ~9.75 cmH₂O, and the sum of both (14.48 cmH₂O) is commensurate with clinically opening pressure (10 ~ 20 cmH₂O) for loose atelectasis. By means of lubrication analysis and the boundary element method, Gaver et al. (16) demonstrated further that the relationship between reopening pressures for small airways and the $Ca$ was not nonmonotonic but showed a multiple branch behavior, where the opening pressures were dominated by the coupling of surface tension and wall elasticity at low $Ca$, whereas high $Ca$ behavior was mainly governed by the balance between fluid viscous and axial wall-tension forces. In fact, the opening pressures for the collapsed alveoli still include hydrostatic pressures, however, which are neglected in the current models.
The third deviation from in vivo conditions arises because of the influence of cell topography and cell confluence. A couple of studies have demonstrated that the nonplanar topography of airway walls can magnify hydrodynamic stresses generated during airway reopening (12, 17, 29). For example, a computational study by Jacob and Gaver (29) indicated that the slope of the epithelial protuberances determined the magnification of hydrodynamic stresses. Even a small increase in the cell protrusion would elicit a marked increase in the values of stresses. Similarly, Gaver and Kute (17) predicted the magnification \( \beta \) of the maximum shear stress on an adherent cell due to flow within a narrow channel. They found that the maximum shear stress on the cell was dependent on cell aspect ratio \( R/H \), where \( R \) is cell height, and \( H \) is channel width. For small \( R/H \), \( \beta \) increases greatly and amounts to a maximum near \( R/H = 0.8 \).

Besides, in the acute phase of ARDS, the epithelial cell monolayer becomes less confluent due to a sloughing of AECs (57). Recently, in an in vitro cell-culture model of airway reopening, Yalcin et al. (64) observed a larger percentage of dead cells in the low confluence monolayers than in the high confluence monolayers at various opening velocities. The investigators concluded that microstructural differences between subconfluent and confluent cells and the presence of cell–cell contacts in the confluent monolayer might be responsible for the different injury levels.

**Possible clinical implications.** Overdistension of the alveoli and mechanical stresses generated by repetitive alveolar recruitment and derecruitment have been widely accepted as two primary mechanistic factors that may contribute to the evolution of VILI. To abate the volutrauma and atelectrauma, the ARDS Clinical Trials Network (54) has recommended the use of small tidal volume and PEEP ventilation. In this protective protocol, it is a common practice to increase the respiratory rate reflexively to maintain alveolar ventilation. However, the relative influence of respiration-rate increase in this setting has not been well characterized. In addition, how much PEEP is enough has been a matter of debate. In the present study, we developed a geometric model of alveolar opening, by which we are readily able to predict the yield pressures for alveolar opening and consequently, to prescribe an appropriate level of PEEP. Our results show that the levels of PEEP required to splint open a collapsed alveolus cover a wide range of pressures, from several centimeters to dozens of centimeters of water, supporting the recent clinical results (11, 41). Therefore, in the clinical practice, it is important to establish an adequate regional ventilation-to-perfusion ratio for holding the alveoli open and preventing them from reabsorption atelectasis. This, in turn, could effectively decrease the required PEEP levels and the risk of alveolar overdistension.

We also assessed the influence of respiration rate and pulmonary fluid properties (\( \gamma, \mu, \) and \( h_0 \)) on the magnitudes of mechanical stresses associated with alveolar reopening by using a tape-peeling model. Our calculations show that the increase of respiration rate or inflation rate leads to an escalation of the values of mechanical stresses. For a normal lung, the predicted mechanical stresses are within safety physiological limits at all respiratory rates or inflation rates, but for a diseased lung with elevated surface tension or fluid viscosity, mechanical stresses will increase dramatically, even at a slow inflation rate. Likewise, our data give credence to the results of several animal experiments regarding effects of respiratory rate on lung injury (10, 26, 44). In conclusion, the present study plus these animal experiments congruously suggest that a lung-protective ventilation strategy should not only include small tidal volume and plateau pressure limitations but also consider such cofactors as ventilation frequency and inflation rate.

**APPENDIX A**

By confining our attention to small peeling angles \( \theta \), the flow may be determined from the Reynolds approximation. The boundary conditions are taken as

\[ u(x, h) = U, \quad u(x, 0) = 0 \]  

(A1)

The Reynolds flow equation leads to

\[ u(x, y) = \frac{1}{2\mu} \left( \frac{dp}{dx} y^2 - \frac{1}{2} \frac{dp}{dx} vy + U \right) \]  

(A2)

\[ \frac{dp}{dx} = 12\mu U \frac{(h - h_0)}{h^3} \]  

(A3)

where \( U \) is the propagation velocity of the separation meniscus, and \( p \) is the pressure excess over the atmospheric pressure. With the combination of the derivative of Eqs. A2 and A3, we obtain the shear stress on the fluid

\[ \tau(x, y) = \frac{6U(h - h_0)}{h^3} \left( 2y - h \right) \]  

(A4)

If the strip possesses no flexural rigidity, then for small peeling angles, the pressure in the liquid phase and the local curvature of the strip satisfy

\[ T \frac{d^2 h}{dx^2} = -p \]  

(A5)

By taking the derivative with respect to \( x \) on both sides of Eq. A5 and then combining Eq. A3 yield

\[ \frac{d}{dx} \left( T \frac{d^2 h}{dx^2} \right) = -12\mu U \frac{(h - h_0)}{h^3} \]  

(A6)

![Fig. 12. \( \zeta \) and \( \zeta' \) vs. 1/\( \lambda \). \( \zeta, \zeta' \) denote the 1st and 2nd derivatives of \( \zeta \), respectively.](http://japl.physiology.org/DownloadedFrom/10.1152/japplphysiol.00112.2015)
Since for the cases of practical interest, the slope is always small, the tension $T$ can be taken as constant, and by setting new variables, substitution into Eq. A6 gives

$$\frac{d^2 \xi}{d \xi^2} = 1 - \frac{\xi}{\xi^3} \quad (A7)$$

Equation A7 describes the gap width $h$ as a function of position $x$, and no general closed-form solution for $h(x)$ has been found. It was solved by numerical integration using MATLAB R2011b (MathWorks, Natick, MA). A Runge-Kutta method was adopted, and integration was commenced from $\xi = 1$, with initial values of $\xi$ and $\xi'$ chosen, according to McEwan and Taylor (35), to cover adequately the resultant range of variables. Figure 12 plots $\xi'$ and $\xi''$ as a function of $\xi$ for parts of the curves of $\xi$ vs. $\xi$, which shows positive values for these derivatives. Furthermore, for a practical interest, McEwan and Taylor (35) deduced Eqs. A8 and A9, which enable the solution of Eq. A7 to be related to the externally measurable quantities in a peeling experiment, namely, $\mu U / \gamma$, $\alpha$, and $\theta$.

$$\left[\frac{\xi'}{1 - m}\right]_{1-m} = \alpha^2 \frac{1}{\theta} \quad (A8)$$

$$\xi'' = \frac{m(\mu U / \gamma)}{\gamma / 6 \alpha^3 \mu U} \quad (A9)$$

APPENDIX B

From the geometric relationship shown in Fig. 10, it is not difficult to obtain the following equation

$$(O' E')^2 + (E' F')^2 = (O' G')^2 + (F' G')^2$$

Since point O is on the angle bisector of angle $\theta_1$, then we have $O' G' = O' C'$ due to symmetry. If $O' E' = R$, $G' H' = h_1$, $h_1 = \theta$, and $A' F' = h_{m}$, then with the substitution of these symbols into the above equation and the use of simple trigonometric functions, we can immediately obtain Eq. 6 as below

$$[h_m - (h_1 + R)]^2 + R^2 = \left[ \frac{R - (h_1 + R) \sin \theta}{\cos \theta} \right]^2 + (h_1 + R)^2$$

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: Z-l.C. conception and design of research; Z-l.C. and S.Z. edited and revised manuscript; S.Z. and Y-z.C. contributed substantially to the data analysis of the study. Z-l.C. wrote the first draft of the manuscript.

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