Pulmonary Surfactant in Health and Disease*

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INTRODUCTION

Surface tension is a force which tends to reduce surface area and generally tends to reduce volume. A soap bubble blown on the end of a child’s pipe tends to retract into the pipe unless a distending pressure is maintained. In a similar fashion, an alveolus is blown on the alveolar duct or airway and would retract towards the airway unless a distending pressure were maintained to overcome the surface forces. It is remarkable, however, that the distending pressure necessary to maintain the inflation of an alveolus is extremely low, apparently because the lung contains an extremely surface-active substance. This surface-active substance, or pulmonary surfactant, can lower the surface tension almost to zero and reduce the distending pressure required. It cannot, however, maintain very low surface tensions for prolonged periods of time without a change of surface area.

During this presentation, I will discuss the following aspects of surface phenomena within the lung:

1. Current evidence of the nature of the pulmonary surfactant.
2. Current concepts of the role of the pulmonary surfactant in maintaining alveolar stability.
3. The changing compliance and eventual atelectasis that occurs with shallow breathing, which may be related to the time-dependent characteristics of the pulmonary surfactant.

Clements and associates1 obtained pulmonary surfactant by rinsing saline through the lung airways and by extracting it from minced lung with saline solution. They found that surface tensions less than 10 dynes/cm. could be obtained in extracts from normal lungs. However, these methods are not quantitative and the presence of inhibitors in the extract may prevent the development of very low surface tension.

Lung extracts can be inactivated so that surface tensions are always more than 20 dynes/cm.2 A lung extract can be inactivated by the following means:

1. Addition of oleic acid or cholesterol to the surface.
2. Preparing the extract with distilled water instead of saline solution (presumably the cells are damaged and release inhibiting substances).
3. Heating above 40° to 42°C.

The degree to which inactivation of the surfactant occurs in vivo has not been adequately determined, although elevated temperature can apparently inactivate the surfactant reversibly in excised rat lungs.3

These studies indicated that if a low surface tension developed one could conclude that a highly surface active substance was present in the extract, but if low surface tension did not develop, a deficiency of surfactant could not be assured.

It now appears that specific phospholipids must be present in lung extracts if surface tensions less than 10 dynes/cm. are to develop.4 These phospholipids include the saturated lecithins and possibly sphingomyelin. Unsaturated fatty acids in the lecithin molecule greatly alter the surface tension characteristics so that at 20°C surface tensions below 20 dynes/cm. do not develop.5 In addition we have found6 that phospholipase C, which attacks phospholipids such as lecithin, will inactivate a lung extract. Large quantities of the surface-active phospholipids are present in the

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lung and they appear to be important components of the pulmonary surfactant.

Since this surfactant can be inactivated by other substances within the lung, methods to measure quantitatively the surface-active phospholipids are under development.

The Role of Pulmonary Surfactant in Maintaining Alveolar Stability

Two considerations underlie the concepts of alveolar stability which have been developed by Clements. The considerations are:

1. Pressure, tension, and radius of curvature are interrelated, according to the Laplace equation. For a sphere this equation is: pressure = \( \frac{2T}{r} \)

2. The surface tension of the pulmonary surfactant is reduced if the surface area is reduced.

The Laplace equation can be used to calculate the distending pressure necessary to keep a bubble inflated in a liquid. The surface tension of plasma and of extracts of most organs is relatively constant even when the surface area is reduced. The distending pressure necessary to keep a bubble inflated in plasma is 10 cm. H_2O if the surface tension of plasma is 40 dynes/cm. and the bubble radius is 80 microns, the size of a human alveolus. However, the distending pressure within a lung at the end of expiration may be only 1 to 5 cm. H_2O. In other words, the total distending pressure within the lung, the transpulmonary pressure, may be considerably less than the pressure in a plasma bubble. The distending force in the lung is opposed by the sum of surface plus tissue forces, whereas the bubble has only surface forces. Furthermore, the pressure-volume relationships of an excised rat lung are greatly altered if we rinse dilute serum through the airway and into the lung. It, therefore, is unlikely that the normal lung surface is a simple transudate of serum.

Since airspaces with radii less than 40 microns are open in animal lungs at distending pressures of 3 to 5 cm. H_2O, the Laplace equation indicates that the surface tension must be considerably less than 40 dynes/cm. The studies of Clements and co-workers have shown that the surface tension of pulmonary surfactant on saline may vary between 0 and 40 dynes/cm. depending on surface area.

At the end of an expiration, the distending pressure in adjacent alveoli can be assumed to be the same. The Laplace equation states that the ratio of tension/radius must be equal wherever the pressure is equal. Therefore, two different sized alveoli must have the same ratio of tension/radius although the radii are different. We conclude that the tensions must be higher in the larger alveolus than in the smaller one. This variability of the surface tension stabilizes alveoli and prevents their collapse when the distending pressure is low. To

![Diagram of alveoli with varying surface tensions and pressures](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21415/)
some extent tissue forces may stabilize the lungs at the end of expiration by determining airspace configuration. However, it is also likely that tissue forces stabilize the lung at end inspiration when the tissues are stretched rather than collapsed.

The tissues, therefore, probably stabilize the lung by preventing over-expansion of units; the surface tension is a significant factor in the recoil of the lung; and the surfactant prevents collapse by lowering the surface tension when the volume is suddenly reduced.

The significance of a changing surface tension as implied by application of the Laplace equation and as found in lung extracts can be seen in Fig. 1. This figure shows two bubbles which are being deflated, from A to B. The top bubble has the surface tension characteristics of a lung extract, but the lower bubble has a constant surface tension of approximately 40 dynes/cm. as might be found in some detergents or plasma. We will use the Laplace equation to calculate the change in pressure as the two bubbles are deflated.

At 'A,' both bubbles have the same initial pressure, surface tension and radius. 'B' illustrates deflation to three-fourths of the initial radius. In the top bubble the surface tension decreases more than the radius decreases. The pressure, therefore, decreases. However, the pressure in the lower bubble increases because the surface tension did not change. As the bubbles are further deflated the pressure in the top bubble falls even more while the pressure in the lower bubble continues to increase. Therefore, a bubble with the surface tension characteristics of a lung extract will have decreasing pressures during deflation. Since the lung has decreasing pressures during deflation, the lower bubble, with decreasing radius but constant surface tension, is not consistent with the observed pressure-volume characteristics of the lung. The top bubble, however, is consistent with the deflation characteristics of the lung and with different surface tensions in alveoli of different sizes.

The following generalizations can be made from these concepts:

1. Atelectasis which is related to surface forces is likely to be spotty or focal and most likely to occur where the surface is abnormal, distending pressures are low, or the air units are small. This distribution is in contrast to that caused by airway obstruction where atelectasis tends to follow anatomic segmentation and may be cone-shaped.

2. A constant high surface tension should empty alveoli at the end of expiration, and only the alveolar ducts, with large radii, may be open.

3. If the alveoli are empty and do not fill with each tidal breath, the compliance would be expected to be decreased in these lungs.

Time Dependent Characteristics of the Pulmonary Surfactant and Lung Mechanics

To measure the surface tension of a lung extract, we use a long shallow trough. The surface tension is measured by weighing the water meniscus which is clinging to a thin platinum plate suspended from a force transducer. The weight of the water meniscus is proportional to the surface tension. We move a barrier along the trough to reduce the surface area and this causes the surface tension of a lung extract to decrease.

Although the surface tension of a lung extract can fall nearly to zero after reduction of surface area, surface tensions which are less than 24 dynes/cm. are not stable. The surface area must be reduced continually to maintain surface tensions less than 24 dynes/cm. Fig. 2 illustrates the percentage reduction in surface area necessary to maintain the surface tension of a lung extract at either 11 to 13 dynes/cm. or 19 to 21 dynes/cm. The lower the surface tension, the faster the area must be reduced to maintain that low value. The rate of area change is very much faster when the surface tension is only slightly lower. If the lung were forced to maintain a low surface tension, we
would expect a rapid reduction of surface area.

If these changes of surface tension develop at a reduced area, then subsequent expansion of the extract surface will reverse the process so that the surface tension at maximum area may be unaffected. The surface, therefore, is replenished by expansion of the area. Since the surface area of the lung is increased during a deep breath, changes of lung mechanics associated with changes of the lung surface may be reversed by a deep breath.

Fig. 2 shows the results obtained from a lung extract which is a mixture of the pulmonary surfactant and many other substances. Pure saturated lecithin, such as dipalmitoyl lecithin, has a much slower change of surface tension, but the rate of change is still proportionately much faster when the surface tension is lower.

Fig. 3 illustrates that bubbles of equal size but different distending pressures must have different surface tensions. The distending pressures are 3 and 5 cmH2O. The Laplace equation states that the tension of such a bubble must equal: 

\[ \text{pressure} \times \frac{\text{radius}}{2} \]

The bubble at the lower distending pressure must have the lower surface tension.

The ratio of the surface tension of these bubbles is 3/5; the same ratio as seen in Fig. 2.

If we assume that these bubbles have the surface tension characteristics of lung extracts, then the bubble at the lower distending pressure and, therefore, the lower surface tension, must have the more rapid change of surface area in order to maintain that low surface tension. If we use the lung extract data from Fig. 2 to calculate the relative volume changes of the two bubbles, then the bubble at 3 cm. H2O distending pressure would be decreasing its volume ten times faster than the other bubble. This rate of change is far greater than might have been assumed by the relatively small differences in distending pressure.

If this concept is applied to lungs then the rate of change of surface area and the eventual collapse of parts of the lung should be very dependent upon the distending pressure. To test this proposal we studied the rate of compliance changes of excised rat lungs at different transpulmonary pressures. We assumed that the decrease of surface area should decrease the participation of airspaces, and therefore, decrease the compliance.

The excised rat lungs were made gas free by subjecting them to a vacuum for 10 to
ments made at 3 cm. $H_2O$ and five measurements at 5 cm. $H_2O$ distending pressure. The lungs at the lower distending pressure have a much more rapid change of compliance. These lungs should also have the lower surface tension for the same reasons that bubbles at low distending pressures have lower surface tensions.

These studies showed that, at least in excised rat lungs, there is a marked difference in the rate at which the compliance changes, and presumably the rate at which atelectasis occurs, when the transpulmonary pressure is changed by 2 cm. $H_2O$.

To test the possibility that this change of compliance was due to airway collapse, we froze lungs rapidly with liquid propane by the method of Staub and Storey. At the time the lung was frozen, the compliance had decreased to one-half the value obtained immediately after deflation. Serial sections of one lung frozen 20 minutes after deflation from maximal volume showed the airways to be wide open. The compliance change of this lung was apparently not due to airway collapse.

We also compared the rate of change of compliance of lungs filled first with saline and then with an equal volume of air. The rate of change of compliance is

\[
\begin{align*}
T &= \frac{Pr}{2} \\
T &= 2.5r \\
T &= 1.5r
\end{align*}
\]

**Figure 3:** Use of the Laplace equation to demonstrate that bubbles of equal size, but different distending pressures have different surface tensions.

20 seconds. They were inflated with air to a maximal volume at 25 to 30 cm. $H_2O$ pressure and then deflated to either 5 or 3 cm. $H_2O$ distending pressure. We measured the compliance by injecting 1 ml. of air which was about 8 per cent of the maximal volume. All studies were done at 37° C.

Fig. 4 shows the rate of change of compliance of excised rat lungs at 3 and 5 cm. $H_2O$ distending pressure. The points represent the mean plus or minus the standard error of the mean for 11 measurements made at 3 cm. $H_2O$ and five measurements at 5 cm. $H_2O$ distending pressure.
much greater for the air-filled lung than for the saline-filled lung. A saline-solution-filled lung should have recoil due only to tissue forces since there is no air-to-liquid surface in the liquid-filled lung. However, an air-filled lung should have recoil due to tissue plus surface forces. This study, therefore, suggests that changing tissue recoil is not likely to be responsible for the changed compliance of the air-filled lung.

We conclude from these studies that the excised rat lung, when maintained at low distending pressure, has a rapidly changing compliance which is not due to airflow collapse and is consistent with a change of surface forces in the lung.

These studies may be related to the mechanism of changing compliance and atelectasis found with prolonged shallow breathing. Recumbency during anesthesia is associated with a low distending pressure and small tidal volume. During anesthesia, there is a gradual fall of lung compliance and eventually atelectasis occurs. Accumulation of fluid in the airway and aspiration of mucus may be responsible for some cases of postoperative atelectasis. However, it is possible that other cases are due to gradual collapse of the lung in areas where the distending force is insufficient to oppose the surface forces.

Many cases with radiological evidence of linear atelectasis in the lung are associated with restricted ventilation or shallow breathing when the distending pressure of the lung can be assumed to be reduced. This type of atelectasis is frequently seen with broken ribs or coma. Collapse of the lung in areas with decreased distending force would not need to follow the triangular or cone-shaped distribution of a bronchus. Instead, the decreased distending pressure may overlap the distribution of several bronchi and produce the plate-like atelectasis seen in these conditions.

Another interesting aspect of this type of atelectasis is that the distribution may be similar to that of bronchopneumonia. Atelectasis is commonly believed to predispose the lung to infection. It is possible, therefore, that some cases of bronchopneumonia begin as spotty atelectasis due to surface forces and the infection is secondary to the atelectasis. Debilitated and comatose patients with shallow respiration might be especially likely to develop this type of spotty atelectasis.

In patients with emphysema, the transpulmonary pressure is very low and a rapidly changing compliance might be anticipated. However, many lung units are abnormally large and consequently, they do not require a very low surface tension even when the distending pressure is low. These large, but abnormal, units should have a relatively small change of surface area during shallow breathing. The normal sized alveoli, however, should be subject to the low distending pressure and they should have a rapidly decreasing surface area. The distribution of ventilation during tidal breathing might be shifted away from the smaller, more normal, airspaces for this reason.

**Summary**

The airspaces of the lung may be compared to several hundred million bubbles blown on airways, and the surface tension necessary to prevent alveolar emptying can be estimated. If the alveolar surface were made of a transudate of plasma, we would expect the alveoli to be empty at the end of expiration. Instead, current evidence indicates that the surface tension of the lung varies widely and alveoli do not collapse because the surface tension can be very low. However, if the surface tension is high due to an abnormal surface, or if the distending pressure is maintained low, we would expect focal atelectasis. Although a very low surface tension must be necessary in the lung at low distending pressures, the lung extracts and apparently the lung, cannot maintain a low surface tension for a prolonged period. Occasional increase of the surface area, as normally occurs with a deep breath, may replenish the surface, but during shallow breathing with a low distending pressure, the lung surface area
decreases with eventual atelectasis. This atelectasis is not due to airway collapse and does not need to follow the distribution of a bronchus.

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Resumen

Los espacios aéreos del pulmón pueden compararse con varios millones de burbujas insufladas en las vías respiratorias y la tensoión superficial es necesaria para evitar el vaciamiento alveolar y puede valorarse. Si la superficie alveolar estuviese formada por un trasudado de plasma era de esperarse que los alvéolos se vaciaran al final de la aspiración. En vez de eso la evidencia actual indica que la tensión superficial de los pulmones varía ampliamente y que los alvéolos no se colapan porque la tensión superficial sea muy baja. Sin embargo, si la tensión superficial es elevada debido a una anormalidad en la superficie podemos esperar que haya atelectasia focal. Aunque una tensión superficial muy baja debe necesitarse en el pulmón a bajas presiones en la distención, el pulmón no puede mantener una baja tensión superficial por mucho tiempo.

El aumento ocasional del área de superficie como ocurre normalmente durante la inspiración profunda puede rellenar la superficie, pero durante la respiración superficial con una baja presión para la distención, la superficie pulmonar disminuye con posible atelectasia resultante.

Esta atelectasia no es debida a colapso de las vías aéreas y no necesita por eso ajustarse a la distribución bronquial.

Zusammenfassung

Die lufthaltigen Beiriche der Lunge kann man etwa vergleichen mit hundert Millionen an die Luftwege geknüpft Blasen. Und daraus mag die zur Verhütung der alveolären Entleerung notwendige Oberflächenspannung abgeschätzt werden. Wäre die alveoläre Oberfläche aus einem Plasmatransudat hergestellt, könnte man erwarten, daß die Alveolen am Ende der Expirationsphase entleert werden. Stattdessen zeigt aber die laufende Beobachtung, daß die Oberflächenspannung der Lunge erheblich schwankt und die Alveolen nicht kollabieren, weil die Oberflächenspannung sehr gering sein kann. Ist jedoch die Oberflächenspannung hoch infolge einer abnormen Oberfläche, oder bleibt der Dehnungsdruck gering, würde man eine herdförmige Atelektase erwarten. Wenn auch eine sehr geringe Oberflächenspannung in der Lunge bei niedrigem Dehnungsdruck notwendig sein muß, so dehnt sich die Lunge doch aus und vermag eine niedrige Oberflächenspannung für eine längere Zeitspanne nicht eufrecht zu erhalten. Gelegentlich kann eine Zunahme des Oberflächenbereichs, wie es normalerweise bei einem tiefen Atemzug der Fall ist, die Oberfläche wieder glätten, aber während einer oberflächlichen Atmung mit geringem Dehnungsdruck nimmt die Lungenoberfläche mit evtl. Atelektase ab. Diese Atelektase ist nicht die Folge eines Kollapses der Luftwege sich nicht notwendigerweise entlang der Verzweigungsrichtung eines Bronchus.

References