# Alveolar Mechanics in the Acutely Injured Lung: Role of Alveolar Instability in the Pathogenesis of Ventilator-Induced Lung Injury

Louis A Gatto PhD, Robert R Fluck Jr MSc RRT, and Gary F Nieman

**With patients who have acute lung injury, respiratory function is routinely evaluated and the treatment may entail choices from various ventilatory strategies. The ventilatory strategies that have been used over the years are being replaced by newer protocols that represent improvements in patient treatment. However, the rationales for the various ventilatory strategies are largely empirical, because the physiology and mechanics of lung inflation are poorly understood. Researchers have proposed competing and contradictory mechanisms of lung inflation at the alveolar level, based on assessments of lung function and discordant descriptions of histological changes during ventilation. We have researched alveolar histophysiology with animal experiments that combined a conventional histological approach with in vivo microscopy to assess alveolar dynamics during normal and disease-state ventilation. Our video and computer analyses document real-time changes of alveolar size and function, often in the same animal and in adjacent areas of the same lung. Our research indicates that, instead of supporting one theory of alveolar mechanics or another, the various behaviors reportedly exhibited by alveoli may be consistent and represent a continuum between normal alveolar function and the alveolar mechanics of acute lung injury.** *Key words: respiratory, pulmonary, alveoli, microscopy, ventilation, lung injury, respiratory distress syndrome.*
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## Introduction

Lung ventilation is marked by conspicuous volume changes that amount to approximately 10% of the total lung capacity during tidal ventilation and as much as 50% during exercise. Studies have failed to elucidate the internal rearrangement of the lung during lung expansion and contraction, and it is not known how much airways and alveoli expand and contract during ventilation. It is also not clear how airway pathology or alveolar function pathology relate to lung injury. It is known that improper use of mechanical ventilation can cause ventilator-induced lung injury (VILI). A great deal of research is underway regarding the mechanism of VILI. However, without knowledge of normal and pathologic alveolar mechanics, it is very difficult to establish the mechanism. This review describes current knowledge of and theories about alveolar mechanics, understanding of which will help clinicians to prevent VILI.

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## Volume Changes in the Lung

The mechanism by which the lung inflates and deflates at the alveolar level has not been thoroughly elucidated. Early studies of alveolar function focused on the role of pulmonary surfactant.[1,2] The basic model for surfactant's function has been of a soap bubble at the end of a capillary tube and kept from collapsing by steady pressure. The soap bubble represents the alveolus, thought to be maintained in a physiologically stable condition (at least in part) by pulmonary surfactant. Surfactant's ability to prevent alveolar collapse was shown in theoretical assessments that used the Laplace law.[1,2] A body of literature based on that model tacitly supports the assumption that alveoli behave like individual soap bubbles, isotropically

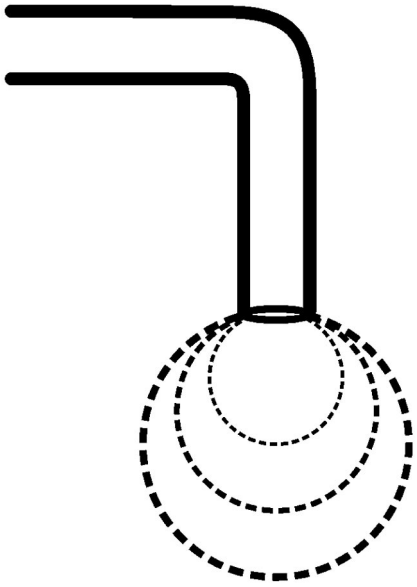

Fig. 1. Isometric volume changes in a bubble (dashed lines) at the tip of a probe (solid line). This is the traditional but anatomically incorrect model of the alveolus.

expanding and contracting (ie, in a balloon-like manner) with changes in airway pressure.

The concept of isotropic (balloon-like) alveolar expansion and contraction (Fig. 1) provides the most intuitive explanation for the internal events that accommodate lung volume changes. This simplistic (and incorrect) concept of alveolar mechanics appears in textbooks[3] as the accepted explanation of alveolar ventilatory function, with dynamic differences in alveolar size and shape being regarded as proof that isotropic alveolar inflation is the fundamental mechanism of ventilation.

The role of surfactant is more controversial. There is consensus that pulmonary surfactant is a key factor in alveolar mechanics, but the mechanism of surfactant function is subject to question. The debate over the role of surfactant involves diverse notions such as:

1. Surfactant lowers alveolar surface tension and thus prevents atelectasis.
2. Surfactant buttresses the alveoli with bubbles that support alveolar structure, like an inner tube inside a tire.
3. Surfactant acts as a "biological wax" that prevents the formation of a liquid layer over the alveolar surface.

Current theories on the physiologic role of surfactant are discussed below.

### Surface Tension Support of the Lung

The architecture of lung tissue is physically supported by a connective tissue framework. It is believed that pulmonary surfactant adds to the anatomical support of pulmonary structure by lowering surface tension at the air-liquid interface on the alveolar surface. Surface forces exert a molding effect on alveolar tissue, such that changes in surface tension alter lung recoil pressure and thus change tissue tension.[4] Bachofen and Schürch offered a model of lung parenchyma structure that includes both connective tissue and surface forces.[4] Wilson and Bachofen[5] compared the alveolar morphometrics of lungs with zero surface tension (saline-filled lungs), normal surface tension (air-filled lungs), and very high surface tension (detergent-rinsed, air-filled lungs) and found that alveolar septa with zero surface tension were not homogeneously expanded, the alveolar ducts were very narrow, and capillaries bulged into the alveolar lumen, which indicates a structural redundancy. Normal surface tension reduced capillary bulging, resulting in a smooth alveolar wall surface as alveolar ducts widen.[5] High surface tension results in substantial septal "pleating" and widened alveolar ducts. Thus, with low surface tension the alveolar ducts are narrow and the alveoli form deep "cups," whereas with high surface tension the ducts are wider and the alveoli form shallower "cups" (Fig. 2). Thus, increasing the surface tension decreases the alveolar surface area, "indicating that the dimension of the alveolar surface is governed by the equilibrium between surface and tissue forces."[4]

Scarpelli developed a different model of lung parenchyma structure, in which surfactant bubbles constitute a "foam" that imparts structural stability by filling the alveolar lumen.[6] Scarpelli hypothesized that the alveolar surface network consists of gas bubbles that amount to a foam that mechanically supports the alveolar infrastructure, in the respiratory bronchioles and the alveolar sacs (Fig. 3). In Scarpelli's model each aerated alveolus is supported by a single bubble, and the alveolar duct is supported by a larger bubble. The central notion is that the alveolus derives structural support from the inflated bubble within its lumen. In Scarpelli's model, "the unit bubble is the essential infrastructure of the alveolus and the alveolar duct. . . [and] if [the foam bubble is] removed the parent unit [al-

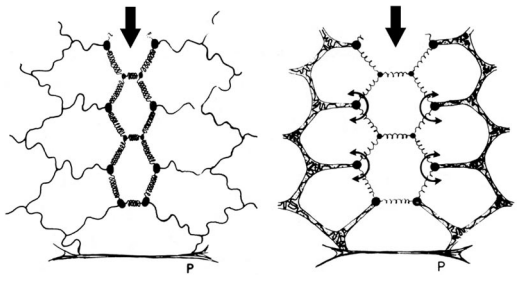


Fig. 2. Left: Low surface tension in saline-filled lung. Alveolar entrance rings (dark) make up the wall of the alveolar duct (arrow). Right: High surface tension in air-filled lung, showing expansion of entrance rings and alveolar duct. (From Reference 5, with permission.)

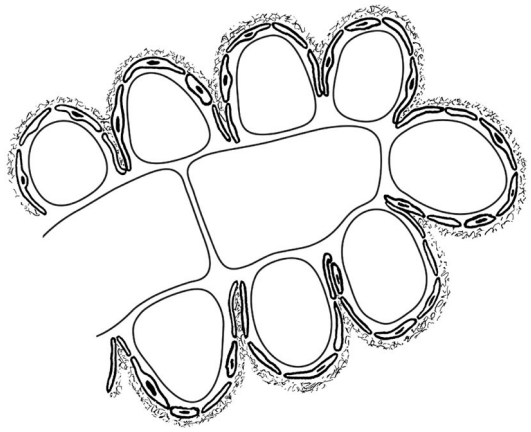

Fig. 3. Scarpelli's model of surfactant's function in the alveoli and alveolar ducts. Each aerated alveolus is supported by a surfactant bubble. The alveolar duct is supported by larger bubbles. (From Reference 6, with permission.)

veolus] becomes airless unless an adjoining bubble moves into the space."[6]

Hills et al[7–9] disagreed with the foam bubble hypothesis and instead propose that surfactant coats the alveolar epithelium as a "biological wax" (Fig. 4) that prevents the formation of a hypophase (continuous liquid layer). This is not consistent with the classic description of surfactant function, which depicts a liquid hypophase lining the entire inside of the alveolus and surfactant molecules coating the hypophase layer. The surface tension of the hypophase without surfactant is approximately 72 dyn/cm and does not change as the alveolus decreases in size during exhalation. The surfactant molecules lower the surface tension to approximately 40 dyn/cm when the alveolus is fully inflated; more importantly, the surfactant substantially reduces surface tension, to as low as zero dyn/cm as the alveolus decreases in size during exhalation. Surfactant's ability to change surface tension is believed to play a critical role in maintaining alveolar stability and preventing atelectasis.

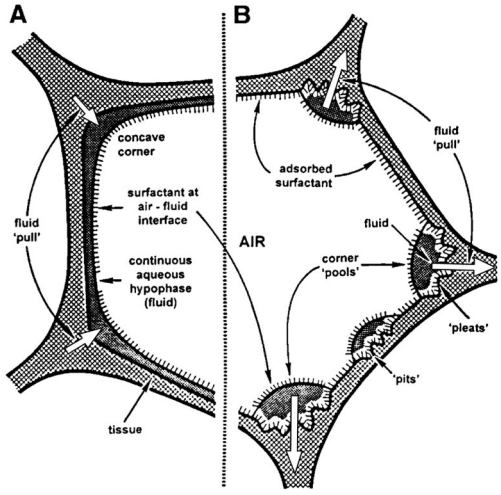


Fig. 4. Two models of the alveolus. A: Classic theory, in which surfactant is separated from the alveolar wall by a concave liquid hypophase that would pull fluids into the alveolar lumen (white arrows). B: "Hydrophobic" model, in which surfactant is adsorbed to the alveolar wall so fluids must bulge into the lumen and thus be subject to surface forces that would pull them toward the interstitium (white arrows). (From Reference 7, with permission.)

In Hills's theory, surfactant's function is not to lower the surface tension of the hypophase but to prevent the hypophase from forming.[7–9] Without an air-liquid interface, surface tension forces disappear, as would the tendency for the alveolus to collapse due to surface tension. Instead, surfactant acts as a biological wax directly attached to the alveolar epithelium. The surfactant causes liquid in the alveolus to bead up, thus preventing the formation of a hypophase. Thus, in Hills's model, the structural support of the lungs is derived solely from the tensile forces of the connective tissue framework.

In summary, the physiologic function of pulmonary surfactant remains in question, and there are currently 3 mutually exclusive theories:

1. The classic theory holds that surfactant reduces surface tension at the air-liquid interface.
2. Scarpelli's theory holds that surfactant foam bubbles act as "inner tubes" within the alveoli and alveolar ducts, and the bubbles are the major structural support of the pulmonary parenchyma.
3. Hills's hypothesis is that surfactant is attached to the alveolar epithelium and prevents the formation of a continuous hypophase, thus eliminating the role of surface tension.

Regardless of which theory prevails, it is widely accepted that surfactant is critical to normal alveolar function. Without surfactant the lung becomes noncompliant and atelectatic. Because we do not fully understand surfactant's function or the exact 3-dimensional structure of the alveolus and alveolar ducts, we remain somewhat uncertain in assessing alveolar mechanics.

### Connective Tissue Support of the Lung

Alveoli should not be depicted as individual balloons, since they have shared walls through which connective tissue binds adjacent alveoli together. Based on that anatomical fact, Mead et al[10] found that the structure of the pulmonary parenchyma involves functional interdependence among neighboring alveoli, which is important in stabilizing the alveolus and preventing alveolar collapse at low lung volumes. Mead et al suggested that if alveoli were independent, like single, non-interconnected balloons, they would nearly collapse at pressures lower than atmospheric, whereas mechanically interdependent alveoli (ie,

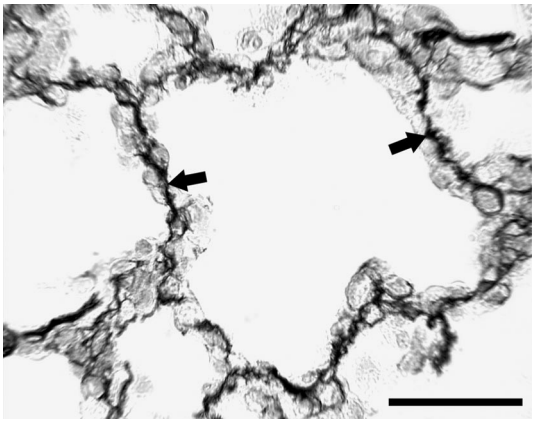

Fig. 5. Pig alveoli stained for reticulin. Fibers (arrows) support the shared (interdependent) walls of the alveoli. The black bar at the lower right represents 50 $\mu$m.

anatomically accurate alveoli with shared walls and connecting tissue) would maintain more than half of their initial volume under those conditions. Furthermore, when airway pressure was increased to atmospheric, independent alveoli would remain collapsed whereas interdependent alveoli would expand substantially. Thus, the interdependence of alveoli affects their distensibility, reducing their tendency to collapse or hyperexpand. Further research on those original concepts led to the development of sophisticated geometric models of the structure of alveoli and alveolar ducts.[11] Morphometric analysis of the lung parenchyma connective tissue has demonstrated that elastin and collagen are present and in the locations necessary to support the proposed geometric structure of the parenchyma.[12]

An alveolus can be envisioned as a deployed parachute: the elastin and collagen fibers are analogous to the tensed cords, and the alveolar walls are analogous to the delicate and flaccid parachute cloth (Fig. 5).[11] The lung must maintain the integrity of this "cord-and-cloth" internal structure during ventilation (Fig. 6). It is believed that this is accomplished by a sustained state of tension involving the connective tissue framework and surfactant-modification of alveolar surface tension. Various structures are believed to contribute to the tensile support of the lung. It has been estimated that about 2 percent of total lung recoil comes from the axial tension from the airways and vasculature[14] and 20% from the visceral pleura.[15] That suggests that the alveolar parenchyma must account for about 80% of the lung's tensile forces.[16]

The alveolar mouths are the main structural framework of the alveolar duct.[11] However, throughout the lung there is also a very complex network of collagen, which gives stiffness, and elastin, which gives extensibility.[16,17] Butler et al[12] undertook a stereological and topological study of alveolar mechanics (Fig. 7). They defined alveolar septa according to the septal borders and septal junctions. The principal borders and junctions were defined as (1) a border along which 1 septum joins 2 other septa (J for septal junction), (2) the border along which 1 septum joins 1 other septum at a distinct angle (B for septal bend), and (3)

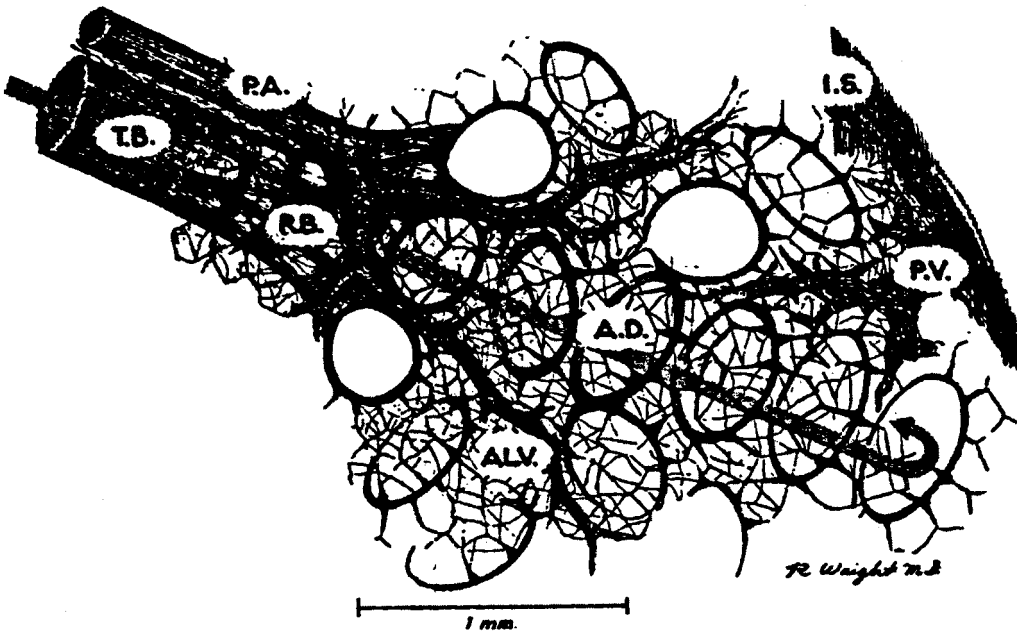


Fig. 6. Elastic tissue in the lung lobule, showing a continuum of elastic fibers between alveoli and airways. AD = alveolar duct. ALV = alveoli. IS = interlobular septum. PA = pulmonary artery. PV = pulmonary vein. RB = respiratory bronchiole. TB = terminal bronchiole. (From Reference 13, with permission.)

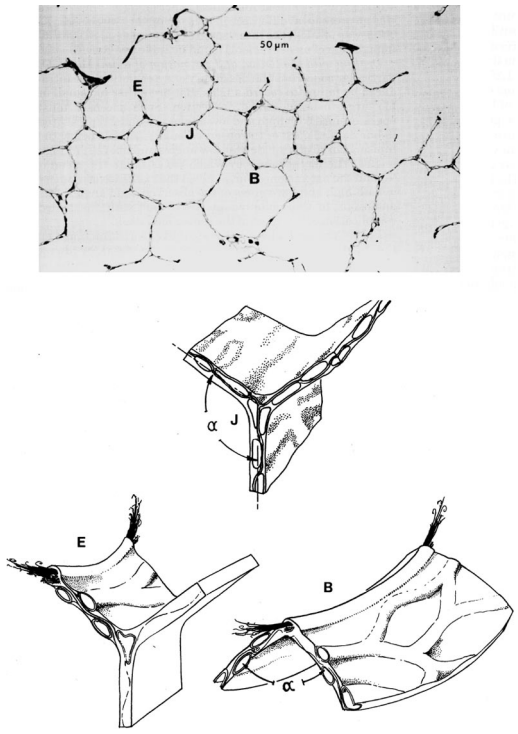


Fig. 7. Alveolar walls (septa) described in terms of the septal edges, junctions, and borders. E = free edge. J = septal junction. B = septal border. (From Reference 12, with permission.)

places where a septum joins no other structure (E for free edge). They noted that only JJJJ and EEEJ junctions would be found if the parenchyma were constructed only from freestanding entrance rings and septal junctions. However, the discovery of numerous other junction types, such as EBJ, EBE, and BBJJ, underscores the complexity of alveolar parenchymal mechanics. Indeed, alveoli can have wide or narrow mouths, can be very deep or very shallow, and can appear bulb-like or tapered.[18,19] Even with the diversity of alveolar shapes and septal junctions, Oldmixon et al[16] found that the interseptal angles were almost always 120°, thus equalizing the local tension.

### Alveolar Structural Anatomy

Current medical textbooks depict alveoli as individual balloon-like structures bunched together like a cluster of grapes.[3] That model is not supported by the anatomical evidence, which shows that alveoli are not physically independent structures but instead are interconnected by shared walls that contain elastin and collagen fibers. Although it is clear that alveoli are interdependent, that fact is commonly ignored in the current literature.

Histological studies have contributed substantially to our understanding of alveolar ducts and alveoli, but their focus is 2-dimensional and thus the 3-dimensional arrangement of these structures has remained poorly understood. This is a timely concern, since understanding the 3-dimensional interactions is essential to understanding normal alveolar mechanics and to the assessment of morphological alterations that may lead to VILI. Elucidating the 3-dimensional anatomy and mechanics of the air sac is critical to understanding the pathogenesis of VILI.

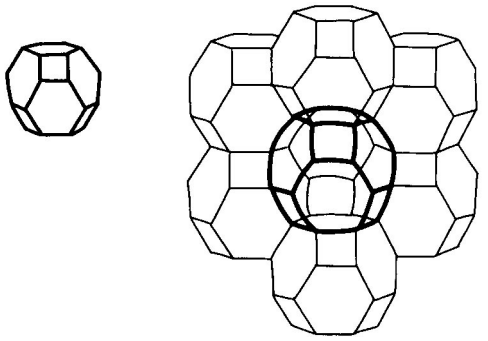

Fig. 8. Fung's model of the alveolus. Each alveolus is in the shape of a tetrakaidecahedron, which is a 14-sided polyhedron (left). In a group of adjacent alveoli (right) the tetrakaidecahedron in the center is left void (dark) and serves as the alveolar duct, without affecting structural stability. (From Reference 11, with permission.)

Fung[11] developed a mathematical model of the 3-dimensional structure of alveoli, based on 3 assumptions:

> 1. All alveoli are equal and space-filling before they are ventilated. 2. Alveoli are ventilated by ducts as uniformly as possible. 3. The alveoli are reinforced at the edges of the ventilation holes (mouths) for structural integrity and distorted by lung weight and inflation according to the theory of elasticity.[11]

Three-dimensional polyhedra that might represent the shape of an alveolus include the tetrahedron, the cube, and the regular octahedron. However, Fung noted histologic evidence that alveoli are not predominantly triangular, square, hexagonal, or rectangular. Fung suggests that an alveolus is in the shape of a tetrakaidecahedron (Fig. 8), which is a 14-sided polyhedron (3-dimensional, fulfilling Fung's first assumption). Fung posits that one tetrakaidecahedron is surrounded by 14 other tetrakaidecahedrons. The tetrakaidecahedron in the center of the cluster is referred to as the "Order-1" unit and the cluster of 14 tetrakaidecahedron is the "Order-2" unit. The spatial arrangement of the Order-2 unit allows uniform ventilation to all alveolar units, which fulfills Fung's second assumption. Each side of the tetrakaidecahedron in the center of the Order-2 cluster is attached to one of the 14 sides of the surrounding tetrakaidecahedrons. The tetrakaidecahedron in the center of the cluster serves as the alveolar duct, and the surrounding 14 tetrakaidecahedrons are alveoli. That arrangement places each of the 14 alveoli in direct contact

with the alveolar duct, ensuring uniform ventilation. On each Order-2 tetrakaidecahedron the side facing the central tetrakaidecahedron forms the alveolar mouth that connects the alveolus to the alveolar duct, and peripheral wall is removed to connect it with other Order-2 polyhedra or a bronchiole. To stabilize the model, the alveolar mouths (conceptualized as the side of the tetrakaidecahedron that has its wall removed) have to be curved and reinforced, which is consistent with histologic evidence that the alveolar mouths are indeed reinforced with connective tissue, thus satisfying Fung's final assumption.

Fung's model fulfills the necessary assumptions and is thus consistent with normal lung function. Its complexity elevates our understanding of alveolar function beyond the soap-bubble model, to a level where morphological observations can be interpreted as the structural basis of ventilatory function and pathology.

### The Mechanics of Lung Volume Changes

Understanding alveolar mechanics required unveiling the 3-dimensional anatomical structure of the alveoli and alveolar ducts and determining the role of surface tension and connective tissue in maintaining alveolar structural integrity. However, since the lung is a dynamic organ that changes shape with each breath, we must understand how its internal components adjust their size to accommodate changing lung volumes.

Various experimental approaches based on different techniques have been followed in the study of alveolar mechanics; accordingly, convincing results have been elusive and there is no consensus as to how the lung changes volume at the alveolar level.[20–44] Proposed models include (1) isotropic expansion and contraction of alveoli, (2) expansion and contraction of the alveolar ducts with little change in alveolar volume, (3) successive alveolar recruitment/derecruitment, (4) alveolar crumpling and uncrumpling (like a paper bag), and (5) pleating and unpleating of alveolar corners.

### Alveolar Dynamics During Ventilation

A growing body of morphological evidence and theoretical models suggests that alveoli and alveolar ducts are supported and structurally stabilized by tensile forces from connective tissue and surface tension, and that such support may set the boundaries for dynamic change in alveolar size and shape during ventilation. General questions regarding this structural framework include (1) how do tensile forces change in response to lung inflation and deflation? and (2) which structures (eg, alveoli, alveolar ducts, and/or respiratory bronchioles) change size during changes in lung volume? More specific questions concern the alveolus and its potential for isotropic volume changes, alveolar recruitment/derecruitment, pleating of alveolar corners, and paper-bag-like crumpling. Investigators have developed various techniques to assess alveolar mechanics during lung-volume changes.

Alveolar mechanics during positive-pressure ventilation have been studied, but the events related to changes in alveolar volume remain elusive. Elegant morphometric studies[28,30,31] suggested that lung-volume change is complex and involves alveolar recruitment/derecruitment, and isotropic and anisotropic (unequal expansion or contraction in one or more directions) alveolar size and shape change. The literature further suggests that the 2 predominant mechanisms are isotropic alveolar volume change and recruitment/derecruitment, but the relative contribution of those 2 mechanisms at various levels of inflation remains undetermined.

Early reports indicated that uniform, isotropic alveolar expansion and contraction are responsible for the majority of lung-volume change.[20–27] Studies of rapid freezing of fresh lung tissue at various levels of inflation and deflation[20,24–27] indicated that alveolar shape remains relatively unchanged with changes in lung volume, which suggests that alveoli expand and contract isotropically. Further support for that interpretation came from Dunnill's comparison of the regression line of alveolar-surface-area/alveolar-volume to the regression line of alveolar-surface-area/lung-volume, as it was noted that the lines were parallel and straight as alveolar surface area changed to the 2/3 power of lung volume, mathematically confirming uniform, isotropic alveolar expansion.[22] However, Forrest[24] later found that alveoli expand directly with lung volume and that recalculating Dunnill's data could yield either alveolar volume change directly with or to the 2/3 power of alveolar surface area. Thus, Dunnill's observations do not allow definite determination of whether the most important event in lung inflation is recruitment/derecruitment or isotropic alveolar volume change. Nonetheless, other investigators visualized subpleural alveoli directly and had results consistent with the morphometric evidence, which seemed to establish isotropic expansion as the primary mechanism of lung inflation.[21,23]

In 1950 Macklin demonstrated histologically that there was little change in alveolar size with lung volume change, which suggested that alveolar ducts and sacs may be the structures that enlarge.[32] The notion of constant alveolar size during ventilation was initially supported by Radford, who by directly visualizing subpleural alveoli, found that alveolar diameter either increased minimally or decreased with lung inflation, and decreased only slightly with deflation.[33] Unlike Macklin, Radford observed subpleural alveoli without fixation and concluded that lung volume change results from recruitment/derecruitment. Research by Nieman et al[29,34,41–45] support Radford's conclusions:

they found little change in alveolar volume during tidal ventilation.

Inconsistencies among the reports of early investigations may be explained by differences in experimental preparations and the relative insensitivity of morphometric techniques.[24] Lung tissue was fixed for morphometric study by vascular perfusion,[27,30,31] formalin vapor,[22] rapid freezing,[25,26,35] or by instillation of fixative.[37] However, tissue fixation allows analysis at only one lung volume per animal, which makes large animal studies difficult and expensive. Fixation is also associated with artifacts caused by tissue shrinkage and distortion.[37,38] Another problem with morphometric assessment is the possibility of operator-related variability, particularly in challenging tasks such as discerning alveolar ducts from alveolar sacs. Direct visualization is free from such difficulties but it is limited to observing only peripheral alveoli.

To avoid the problems associated with fixation and the limitation to only subpleural alveoli, Smaldone et al[39] injected a monodispersed aerosol into excised dog lung and observed the aerosol's gravitational deposition at zero airflow during fixed breath-hold. The fraction of deposited aerosol reflects the cross-sectional geometry of the air spaces. With that technique, particle deposition in the absence of flow is inversely proportional to the mean linear intercept. Repeat measurements of the mean linear intercept indicated that the lung inflates by progressive recruitment of alveoli and deflates by alveolar derecruitment. To avoid the difficulty in distinguishing alveolar ducts from alveoli, Lum et al[40] used cord length-frequency distribution analysis of freeze-dried lung sections. Their findings also support the notion that lung inflation is the result of alveolar recruitment.

We use in vivo microscopy to investigate alveolar mechanics in normal and acutely injured lung.[29,34,41–47] In vivo microscopy is the only technique that allows breath-to-breath analysis of alveolar mechanics in the living animal. We have found that normal subpleural alveoli change in size minimally during ventilation, even at high airway pressure, whereas alveoli with altered surfactant function develop a continuum of abnormal, unstable alveolar mechanics, which we have termed *repetitive alveolar collapse and expansion* (RACE).[41–43,45] Our results support the hypothesis that normal lung-volume change is not from simple isotropic expansion and contraction of alveoli. The following 2 sections review our in vivo microscopy techniques, findings, and the pathology ramifications of altered alveolar mechanics.

### Abnormal Ventilatory Mechanics

Acute respiratory distress syndrome involves high-permeability edema, leading to alveolar flooding and surfactant deactivation, which necessitates mechanical ventilation. It is believed that loss of surfactant function may alter alveolar mechanics and cause RACE. It is hypothesized that alveolar shear stress, secondary to RACE, is a major mechanism of VILI.[48–51] However, the evidence supporting that hypothesis is inferential and based on indirect measurements such as whole-lung pressure-volume tracings and tomograms.[48–51] Direct observations of alveolar recruitment/derecruitment had not been reported prior to our research. Using in vivo video microscopy we directly observed and quantified the dynamic changes in alveolar size during tidal ventilation in both the normal and the acutely injured lung. Those studies demonstrated that normal alveoli, once recruited, do not change volume appreciably during tidal ventilation.[21] However, following surfactant deactivation, which is a hallmark of acute respiratory distress syndrome, we observed markedly abnormal alveolar mechanics, which we described as RACE.[41]

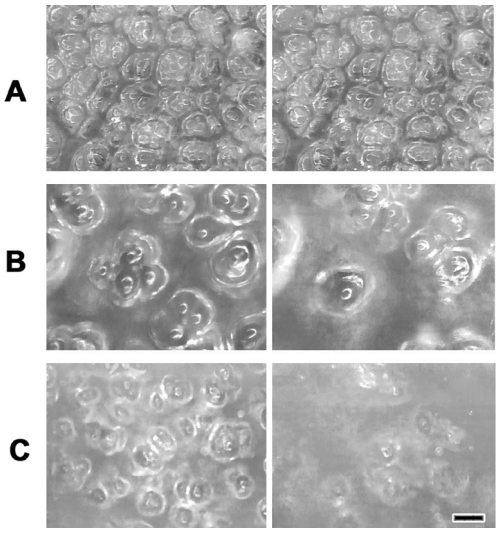


Fig. 9. In vivo views of subpleural alveoli in rat lung. The photographs on the left show alveoli at peak inspiration. The photographs on the right show the same alveoli at end-expiration. A: Normal alveoli exhibit no obvious size-change with ventilation. B and C: Alveoli subjected to injurious mechanical ventilation. Type II alveoli (B) change in size but do not totally collapse. Type III alveoli (C) cycle between open and total collapse. The black bar at the lower right represents 150 $\mu$m.

RACE is an alveolar pathology that is distinct from and more complex than simple recruitment/derecruitment (Fig. 9). Over the course of several studies[41–43] we found that alveolar behavior during RACE exhibits many of the characteristics proposed or described in previous reports. These behaviors may be concurrent; they include (1) seemingly normal alveoli that do not undergo perceptible volume changes during ventilation (we call these "Type I" alveoli), (2) alveoli that undergo substantial volume-change during ventilation but do not collapse at end-expiration ("Type II" alveoli), and (3) alveoli that collapse completely and subsequently re-inflate with each breath ("Type

III" alveoli) (see Fig. 9). Our findings show consistent evidence that acute insult to the lung results in a continuum of abnormal alveolar mechanics that cause shear stress within the lung parenchyma and thus play a key role in the development of VILI.

### Pathophysiology of Abnormal Alveolar Mechanics

If abnormal alveolar mechanics are indeed pathogenic, the mechanism of injury must be determined. There is no doubt that abnormal alveolar mechanics negatively impact oxygenation, but it is less clear whether the altered alveolar inflation patterns injure the alveolus and the surrounding microvasculature. Abnormal alveolar mechanics could cause direct mechanical injury to the alveolus, or indirectly trigger a secondary inflammatory injury, or both. Our first approach to the study of abnormal alveolar mechanics was to quantify the decrease in alveolar stability, as evidenced by RACE, and the change in alveolar size at peak inspiration.

Although much research remains to be done, we believe that in order to thoroughly understand the dynamics of altered alveolar mechanics, we must answer the following questions:

1. Do abnormal alveoli inflate and deflate in a linear fashion throughout tidal ventilation, or is there a rapid change in size at a specific airway pressure, which would be indicative of a critical opening-and-closing pressure?
2. At what point on the whole-lung inflation-deflation curve does change in alveolar size take place?
3. Of the total population of alveoli, what is the fraction of each alveolar type and how does this proportion change with the severity of lung injury?
4. Is the change in alveolar size during ventilation uniform in all directions?
5. Do abnormal alveolar mechanics change with the severity or mode of lung injury (eg, tween, endotoxin, oleic acid)?
6. Are abnormal alveolar mechanics observed in dependent lung regions, and does alveolar flooding of dependent alveoli influence those mechanics?

The mechanics of altered alveolar function remain largely unknown. Qualitative observations made in our laboratory suggest that there is a critical opening-and-closing pressure at which the injured alveolus "pops" open or closed. RACE describes all abnormal alveolar mechanics, regardless of whether the alveoli substantially change size during ventilation without collapsing at end-expiration (Type II), or collapse totally at end-expiration (Type III). The components of RACE mechanics in the injured alveolus seem to include (1) a large change in alveolar size between inspiration and expiration and (2) a rapid change in alveolar size over a small portion of the total inspiratory or expiratory cycle.[29] We recently demonstrated that RACE causes VILI.[52]

Anatomically, alveoli are not independent units, but rather they are interconnected, with shared alveolar walls that attach in a cluster around a terminal bronchiole, forming a functional unit called an acinus. Collectively, the air sac benefits from mutual structural support from this anatomical arrangement, similar to the structural integrity of a honeycomb.[10] Such mutual structural support, often termed interdependence, combines with surfactant's surface-tension-lowering properties to provide physical stability to the alveoli, in an arrangement that results in little change in alveolar volume during ventilation.[5,10] It must be noted, however, that the air sac is structurally sound only while all its alveoli are patent, since collapse of just one alveolus within the acinus causes shear stress not only on the walls of the collapsing alveolus, but also on the walls of all the adjacent alveoli (Fig. 10).[10] Shear forces developed during surfactant deactivation are generated as the individual alveolus collapses and reopens, and Mead et al calculated that the shear stress can be $> 140$ cm $H_2O$.[10] Thus, following surfactant deactivation the structural interdependence of the air sac is destroyed, and alveoli subsequently behave as individual "balloons" subject to substantial volume changes during tidal ventilation.[29,41] We hypothesize that such dramatic alteration in alveolar mechanics inflicts severe shear stress on the alveolar wall and this results in lung injury.

### In Vivo Observations of Alveolar Mechanics

The focus of our experimental research has been the study of alveolar mechanics in normal and acutely injured animal lung, using in vivo video microscopy under epi-illumination (see Fig. 10). The direct study of alveolar

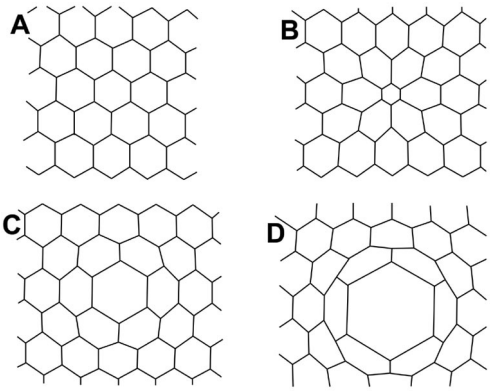


Fig. 10. Model of alveolar interdependence. A: Adjoining alveoli equally inflated. B: Alveolus in center collapses and distorts adjacent alveoli. C: Alveolus in center expands and distorts adjacent alveoli. D. Alveolus in center dramatically expands and greatly distorts adjacent alveoli. (From Reference 10, with permission.)

mechanics as such has received little attention, compared to parallel research by others on pulmonary microcirculation. Wagner was the first to undertake morphometric analysis of in vivo alveoli.[53] McNary et al used a metallurgy microscope with an epi-objective lens under dark-field illumination to make an in vivo video recording of alveoli and alveolar sacs during ventilation.[54] They noted that alveoli and alveolar sacs could be easily observed throughout the respiratory cycle, whereas capillaries could be distinguished only by the flow of blood through their lumens. They also noted that the addition of positive end-expiratory pressure (PEEP) rendered alveoli and alveolar sacs "more patent" and decreased alveolar wall motion. Daly et al also used in vivo microscopy to study the effect of PEEP on alveolar mechanics; they found that alveolar sac volume at peak-inspiration, alveolar sac volume at end-expiration, and alveolar sac tidal volume increase linearly with PEEP but plateau at PEEP of 10–15 cm $H_2O$.[55] In a subsequent report, Daly et al demonstrated that the elastic tissue within the alveolar wall, and forces due to interdependence from adjacent alveoli, are important determinants of alveolar wall motion and mechanics.[21]

Our research has consistently demonstrated little change in alveolar diameter in the normal lung, regardless of peak inspiratory pressure or PEEP.[29,34,41–44,46,47] Those data lead to the conclusion that the lung does not change volume primarily by isotropic expansion and contraction of alveoli. The exact mechanism of lung volume change at the alveolar level is unknown but seems to be a combination of normal alveolar recruitment/derecruitment, pleating and unpleating of the alveolar septa, simultaneous expansion of the alveolar duct and shortening of the alveolar wall connected to the duct, and isotropic expansion and contraction.[4,28,30,31] Regardless of the mechanism of lung-volume change at the alveolar level, it is clear that the mechanics of the normal alveolus during ventilation reflect physical stability. We have demonstrated that alveoli remain stable and do not change size appreciably with ventilation, even with peak airway pressures as high as 50 cm $H_2O$ and tidal volumes as large as 30 mL/kg.[45] The alveolus appears to be designed to resist change in diameter, which suggests that conditions associated with alveolar-diameter changes cause alveolar injury. Thus, alveoli that become unstable secondary to surfactant deactivation and develop RACE are very likely to suffer mechanical stress-induced injury.

### Critique of the Model

Numerous studies have used surrogate markers of alveolar function such as computed tomography,[49,50] whole-lung pressure-volume (P-V) curves,[50,51,56] and arterial blood gases[49,50] to infer the effects of mechanical ventilation on alveolar mechanics. Amato et al[56] inferred from whole-lung P-V curves that the lower inflection point represents alveolar recruitment and that the upper inflection point represents alveolar overdistention. Using only P-V curve inflection points, without direct evidence as to what those inflection points actually represent at the alveolar level, Amato et al[56] designed a ventilator protocol to reduce VILI in patients with acute respiratory distress syndrome, and they found that a lower driving pressure was independently associated with lower mortality. In direct opposition to Amato's interpretation of the P-V curve, Hickling found by way of mathematical analysis that the lower inflection point does not necessarily represent alveolar recruitment, nor does the upper inflection point represent alveolar overdistention.[57] Indeed, the animal studies discussed above[49–51] relied on alveolar recruitment/derecruitment to explain the changes in the variables they measured, without direct confirmation of recruitment/derecruitment. Without direct observation of normal and pathologic alveolar mechanics and knowledge of how various ventilator modes affect alveolar mechanics, lung-protective ventilator strategies remain empirical.

Though in vivo microscopy suffers limitations in the study of the whole lung, it is the only technique available to directly visualize and measure individual alveoli throughout tidal ventilation. The 2 major disadvantages of in vivo microscopy are that (1) observations are restricted to subpleural alveoli and (2) volume quantifications are limited to 2-dimensional measurements of alveolar profile. Although alveoli are morphologically distinct from the visceral pleura, there is a concern that subpleural alveoli may be subject to secondary pleural influence and that their mechanics may differ from those of more proximal alveoli.

We found that over a wide range of lung volumes there is a large change in pleural surface area with minimal change in alveolar size.[44] If subpleural alveoli were tethered to the pleura, alveolar size change would be exaggerated with lung inflation, but that is not the case. Moreover, alveoli demonstrate RACE mechanics following surfactant deactivation, with alveoli inflating and deflating at various rates and at different time points on the P-V curve, which suggests that alveoli are structurally independent of the visceral pleura rather than tethered to it.[29]

Subpleural alveoli are structurally dissimilar to interior alveoli, because they are not completely surrounded by adjacent alveoli, as one wall of the subpleural alveolus is adjacent to the pleura rather than shared with another alveolus. That structural arrangement may reduce mechanical support from alveolar interdependence, causing subpleural alveoli to collapse before their counterparts in the lung interior. However, in Mead's classic report[10] that described the importance of alveolar interdependence in alveolar mechanics, his model consisted of "alveoli" in a single plane, which is analogous to the condition of subpleural alveoli in vivo. Mead demonstrated that, even in a

single plane, loss of alveolar interdependence would yield shear stress in excess of 140 cm $H_2O$.[10] We therefore believe that alveolar interdependence is an important structural feature in both subpleural and centrally located alveoli (see Fig. 10).

Our technique allows only 2-dimensional measurement of alveolar size during ventilation, in the form of profile surface areas. Alveolar changes along the third dimension cannot be measured accurately because of depth-of-field limitations inherent to the microscopy system. Nevertheless, we have shown that alveolar mechanics are dramatically altered in 2 dimensions following surfactant deactivation. Although there may also be concurrent changes in depth that we miss with our technique, our 2-dimensional observations have been consistent and the image analysis is precise, which we believe assures that we have reliably defined and accurately quantified normal and abnormal alveolar function during ventilation.

We have developed a good working knowledge of this in vivo microscopic technique for analyzing alveolar mechanics,[29,34,41–46] having shown in preliminary studies that the subpleural structures we observe are indeed alveoli, and that a modest suction applied to the pleural surface to stabilize the lung during microscopy does not significantly alter the observed alveolar function.[29,34,41–46] A great deal of additional research is necessary to accurately define all of the complexities inherent in abnormal alveolar mechanics. Future studies will investigate alveolar opening and closing pressures, the rate at which alveoli change size, the percentages of the 3 alveolar types in injured lung, and whether abnormal alveolar mechanics change with the severity of lung injury.

## Summary

The current understanding of lung ventilation in health and disease is beset by unknowns that fuel controversy in clinically important issues such as the role of surfactant and judgment calls regarding ventilatory strategy. A great deal remains to be learned about ventilatory function, particularly about volume change at the alveolar level. Complex issues such as the 3-dimensional structure of the air sac, the arrangement of connective tissue, and the function of pulmonary surfactant must all be addressed. The structure and function of the pulmonary parenchyma must be studied together in a dynamic fashion as the air sac changes size and shape during ventilation. Understanding the dynamic change in the air sac during ventilation is essential to understanding the mechanism of VILI. The unveiling of normal alveolar mechanics will lead to knowledge about abnormal alveolar mechanics, which will help the practitioner to adjust mechanical ventilation to convert abnormal mechanics in the acutely injured lung into normal mechanics and thus reduce VILI.

Our preliminary research with the in vivo microscope has demonstrated that normal alveoli do not significantly change diameter during ventilation, even with very high tidal volumes. Volume change in normal subpleural alveoli could be explained, instead, by a combination of mechanisms, including changes in the size of the alveolar duct, alveolar shape changing from a deep cup to a shallow cup without a change in diameter, normal recruitment/derecruitment, and alveolar crumpling and uncrumpling. Regardless of how the normal lung changes volume at the alveolar level, it is clear that normal alveoli do not change in diameter, and that acutely injured alveoli collapse and expand like balloons with each breath. Our research has also demonstrated that that abnormal isotropic alveolar expansion and contraction injures the pulmonary parenchyma, whereas converting the balloon-like mechanics to normal, stable alveolar mechanics with PEEP reduces alveolar injury.

It will probably take a multidisciplinary approach to fully elucidate alveolar mechanics so that we can eliminate the theoretical and practical controversies regarding alveolar function, in both the normal and acutely injured lung. In the meantime, increased awareness of basic alveolar mechanics may help the practitioner to choose mechanical ventilation settings that will help prevent VILI.

## REFERENCES


1. Comroe JH. Physiology of respiration, 2nd ed. Chicago: Year Book Medical Publishers; 1975:106–111.
2. Clements JA, Hustead RF, Johnson RP, Gribetz I. Pulmonary surface tension and alveolar stability. J Appl Physiol 1961 May;16:444–450.
3. West JB. Respiratory physiology—the essentials, 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2000:83.
4. Bachofen H, Schürch S. Alveolar surface forces and lung architecture. Comp Biochem Physiol A Mol Integr Physiol 2001;129(1):183–193.
5. Wilson TA, Bachofen H. A model for mechanical structure of the alveolar duct. J Appl Physiol 1982;52(4):1064–1070.
6. Scarpelli EM. The alveolar surface network: a new anatomy and its physiological significance. Anat Rec 1998;251(4):491–527.
7. Hills BA. An alternative view of the role(s) of surfactant and the alveolar model. J Appl Physiol 1999;87(5):1567–1583.
8. Scarpelli EM, Hills BA. Opposing views on the alveolar surface, alveolar models, and the role of surfactant (comment). J Appl Physiol 2000;89(2):408–412.
9. Hills BA, Bryan-Brown CW. Role of surfactant in the lung and other organs. Crit Care Med 1983;11(12):951–956.
10. Mead J, Takishima T, Leith D. Stress distribution in lungs: a model of pulmonary elasticity. J Appl Physiol 1970;28(5):596–608.
11. Fung YC. A model of the lung structure and its validation. J Appl Physiol 1988;64(5):2132–2141.
12. Butler JP, Oldmixon EH, Hoppin FG Jr. Dihedral angles of septal "bend" structures in lung parenchyma. J Appl Physiol 1996;81(4): 1800–1806.
13. Wright RR. Elastic tissue of normal and emphysematous lungs: a tridimensional histologic study. Am J Pathol 1961 Sep;39:355–367.
14. Smith JC, Butler JP, Hoppin FG Jr. Contribution of tree structures in the lung to lung elastic recoil. J Appl Physiol 1984;57(5):1422–1429.

15. Oldmixon EH, Hoppin FG Jr. Comparison of amounts of collagen and elastin in pleural and parenchyma of the dog lung. J Appl Physiol 1984;56(5):1383–1388.
16. Oldmixon EH, Butler JP, Hoppin FG Jr. Lengths and topology of alveolar septal borders. J Appl Physiol 1989;67(5):1930–1940.
17. Oldmixon EH, Hoppin FG Jr. Distribution of elastin and collagen in canine lung alveolar parenchyma. J Appl Physiol 1989;67(5):1941–1949.
18. Hansen JE, Ampaya EP. Human air space shapes, sizes, areas, and volumes. J Appl Physiol 1975;38(6):990–995.
19. Mercer RR, Laco JM, Crapo JD. Three-dimensional reconstruction of alveoli in the rat lung for pressure-volume relationships. J Appl Physiol 1987;62(4):1480–1487.
20. D'Angelo E. Local alveolar size and transpulmonary pressure in situ and in isolated lungs. Respir Physiol 1972;14(3):251–266.
21. Daly BDT, Parks GE, Edmonds CH, Hibbs CW, Norman JC. Dynamic alveolar mechanics as studied by videomicroscopy. Respir Physiol 1975;24(2):217–232.
22. Dunnill MS. Effect of lung inflation on alveolar surface area in the dog. Nature 1967;214(92):1013–1014.
23. Flicker E, Lee JS. Equilibrium of force of subpleural alveoli: implications to lung mechanics. J Appl Physiol 1974;36(3):366–374.
24. Forrest JB. The effect of changes in lung volume on the size and shape of alveoli. J Physiol 1970;210(3):533–547.
25. Klingele TG, Staub NC. Alveolar shape changes with volume in isolated, air-filled lobes of cat lung. J Appl Physiol 1970;28(4):411–414.
26. Kuno K, Staub NC. Acute mechanical effects of lung volume changes on artificial microholes in alveolar walls. J Appl Physiol 1968;24(1):83–92.
27. Storey WF, Staub NC. Ventilation of terminal air units. J Appl Physiol 1962 May;17:391–397.
28. Gil J, Bachofen H, Gehr P, Weibel ER. Alveolar volume-surface area relation in air and saline-filled lungs fixed by vascular perfusion. J Appl Physiol 1979;47(5):990–1001.
29. Nieman GF, Bredenberg CE, Clark WR, West NR. Alveolar function following surfactant deactivation. J Appl Physiol 1981;51(4):895–904.
30. Gil J, Weibel ER. Morphological study of pressure-volume hysteresis in rat lungs fixed by vascular perfusion. Respir Physiol 1972; 15(2):190–213.
31. Bachofen H, Gehr P, Weibel ER. Alterations of mechanical properties and morphology in excised rabbit lungs rinsed with a detergent. J Appl Physiol 1979;47(5):1002–1010.
32. Macklin CC. Alveoli of mammalian lung: anatomical study with clinical correlation. Proc Inst Med Chic 1950;18:78.
33. Radford EP. Influence on physiochemical properties of the pulmonary surface on stability of alveolar air spaces and on static hysteresis of lungs. Proc Int Congress Physiol Sci 22nd Leiden 1962;1: 275–280.
34. Nieman GF, Bredenberg CE. High surface tension pulmonary edema induced by detergent aerosol. J Appl Physiol 1985;58(1):129–136.
35. Staub NC, Storey WF. Relation between morphological and physiological events in lung studied by rapid freezing. J Appl Physiol 1962 May;17:381–390.
36. Forrest JB. Lung tissue plasticity: morphometric analysis of anisotropic strain in liquid filled lungs. Respir Physiol 1976;27(2):223–239.
37. Forrest JB. Measurement of the volume shrinkage of lung tissue due to rapid freezing followed by freeze substitution. J Physiol 1969; 202(2):108P–109P.
38. Weibel ER, Limacher W, Bachofen H. Electron microscopy of rapidly frozen lungs: evaluation on the basis of standard criteria. J Appl Physiol 1982;53(2):516–527.
39. Smaldone GC, Mitzner W, Itoh H. Role of alveolar recruitment in lung inflation: influence on pressure-volume hysteresis. J Appl Physiol 1983;55(4):1321–1332.
40. Lum H, Huang I, Mitzner W. Morphological evidence for alveolar recruitment during inflation at high transpulmonary pressure. J Appl Physiol 1990;68(6):2280–2286.
41. Schiller HJ, McCann UG 2nd, Carney DE, Gatto LA, Steinberg JM, Nieman GF. Altered alveolar mechanics in the acutely injured lung. Crit Care Med 2001;29(5):1049–1055.
42. McCann UG 2nd, Schiller HJ, Gatto LA, Steinberg JM, Carney DE, Nieman GF. Alveolar mechanics alter hypoxic pulmonary vasoconstriction. Crit Care Med 2002;30(6):1315–1321.
43. Steinberg J, Schiller HJ, Halter JM, Gatto LA, Dasilva M, Amato M, et al. Tidal volume increases do not affect alveolar mechanics in normal lung but cause alveolar over-distension and exacerbate alveolar instability following surfactant deactivation. Crit Care Med 2002; 30:2675–2683.
44. Carney DE, Bredenberg CE, Schiller HJ, Picone AL, McCann UG, Gatto LA, et al. The mechanism of lung volume change during mechanical ventilation. Am J Respir Crit Care Med 1999;160(5): 1697–1702.
45. McCann UG 2nd, Schiller HJ, Carney DE, Gatto LA, Steinberg JM, Nieman GF. Visual validation of the mechanical stabilizing effects of positive end-expiratory pressure at the alveolar level. J Surg Res 2001;99(2):335–342.
46. Nieman GF, Hakim TS, Bredenberg CE. Effect of increased alveolar surface tension on segmental pulmonary vascular resistance. J Appl Physiol 1988;64(1):154–161.
47. Lutz CJ, Carney DE, Picone AL, Schiller HJ, Gatto LA, Snyder KP, et al. Videomicroscopy provides accurate in vivo assessment of pulmonary microvascular reactivity in rabbits. Shock 1999;11(5):367–371.
48. Neumann P, Berglund JE, Mondejar EF, Magnusson A, Hedenstierna G. Dynamics of lung collapse and recruitment during prolonged breathing in porcine lung injury. J Appl Physiol 1998;85(4):1533–1543.
49. Neumann P, Berglund JE, Mondejar EF, Magnusson A, Hedenstierna G. Effect of different pressure levels on the dynamics of lung collapse and recruitment in oleic-acid-induced lung injury. Am J Respir Crit Care Med 1998;158(5 Pt 1):1636–1643.
50. Taskar V, John J, Evander E, Robertson B, Jonson B. Surfactant dysfunction makes lungs vulnerable to repetitive collapse and reexpansion. Am J Respir Crit Care Med 1997;155(1):313–320.
51. Gattinoni L, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissoni A. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease: different syndromes? Am J Respir Crit Care Med 1998;158(1):3–11.
52. Steinberg JM, Schiller HJ, Halter JM, Gatto LA, Lee HM, Pavone LA, Nieman GF. Alveolar instability causes early ventilator-induced lung injury independent of neutrophils. Am J Respir Crit Care Med 2003;169(1):57–63.
53. Wagner WW Jr. Pulmonary microcirculatory observations in vivo under physiological conditions. J Appl Physiol 1969;26(3):375–377.
54. McNary WF Jr, Berman HJ, Daly B, Norman JC. The use of videotape to record and review data obtained by incident light dark-field microscopy of the living lung. Bibl Anat 1973;11:44–49.
55. Daly BDT, Huges DA, Norman JC. Alveolar morphometrics: effects of positive end-expiratory pressure. Surgery 1974;76(4):624–629.
56. Amato MB, Barbas CS, Medeiros DM, Schettino Gde P, Lorenzi Filho G, Kairalla RA, et al. Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome: a prospective randomized study on mechanical ventilation. Am J Respir Crit Care Med 1995;152(6 Pt 1):1835–1846.
57. Hickling KG. The pressure-volume curve is greatly modified by recruitment: a mathematical model of ARDS lungs. Am J Respir Crit Care Med 1998;158(1):194–202.