Physiology in Medicine: Understanding dynamic alveolar physiology to minimize ventilator-induced lung injury

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Submitted 9 February 2017; accepted in final form 3 April 2017

Nieman GF, Satalin J, Kollisch-Singule M, Andrews P, Aiash H, Habashi NM, Gatto LA. Physiology in Medicine: Understanding dynamic alveolar physiology to minimize ventilator-induced lung injury. J Appl Physiol 122: 1516–1522, 2017. First published April 6, 2017; doi:10.1152/japplphysiol.00123.2017.—Acute respiratory distress syndrome (ARDS) remains a serious clinical problem with the main treatment being supportive in the form of mechanical ventilation. However, mechanical ventilation can be a double-edged sword: if set improperly, it can exacerbate the tissue damage caused by ARDS; this is known as ventilator-induced lung injury (VILI). To minimize VILI, we must understand the pathophysiologic mechanisms of tissue damage at the alveolar level. In this Physiology in Medicine paper, the dynamic physiology of alveolar inflation and deflation during mechanical ventilation will be reviewed. In addition, the pathophysiologic mechanisms of VILI will be reviewed, and this knowledge will be used to suggest an optimal mechanical breath profile (MBP: all airway pressures, volumes, flows, rates, and the duration that they are applied at both inspiration and expiration) necessary to minimize VILI. Our review suggests that the current protective ventilation strategy, known as the “open lung strategy,” would be the optimal lung-protective approach. However, the viscoelastic behavior of dynamic alveolar inflation and deflation has not yet been incorporated into protective mechanical ventilation strategies. Using our knowledge of dynamic alveolar mechanics (i.e., the dynamic change in alveolar and alveolar duct size and shape during tidal ventilation) to modify the MBP so as to minimize VILI will reduce the morbidity and mortality associated with ARDS.

ventilator-induced lung injury; acute respiratory distress syndrome; acute lung injury; positive end-expiratory pressure; mechanical ventilation
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WHAT PHYSIOLOGIC PARAMETERS CAN DEFINE THE OPTIMALLY PROTECTIVE MECHANICAL BREATH?

The goal of the protective breath is not to optimize oxygen-
ation but rather to minimize damage to pulmonary epithelial
and vascular endothelial cells and their associated connective
tissues. To design the optimally protective breath, we must 1) consider the complex microanatomy of interconnected alveoli
with shared alveolar walls, 2) consider the physiologic mech-
anism of VILI in the microenvironment of the terminal air
space (the alveoli and alveolar ducts), 3) consider the dynamic
alveolar physiology (i.e., the dynamic change in alveolar size
and shape during tidal ventilation) and how changes in dy-
amic alveolar physiology cause tissue damage resulting in
VILI, and 4) apply this information to postulate an optimal
mechanical breath profile (MBP), necessary to a ventilation
protocol capable of blocking VILI. A mechanical breath com-
prises airway pressures, volumes, flows, rates, and the duration
over which they are applied throughout inspiration and expi-
ration. Critical consideration of VILI mechanisms and dynamic
alveolar physiology can unveil MBP parameter combinations
that are lung protective, thus enabling the practitioner to adjust
protocols and minimize or avert VILI. Our approach is to
identify an optimal combination of these physical parameters
over the course of the ventilator cycle that is adaptive in real
time to each individual breath.

Fig. 1. Interdependent alveoli with shared alveolar walls represented as hexagons. This homogeneous anatomical design assists in stabilizing alveoli
preventing collapse during expiration and overdistension during inspiration,
since there is no pressure (arrows) gradient between alveoli (opposing arrows
of equal force). Only ~2% change in alveolar area is measured between
inspiration (Supplemental Animation S1A) and expiration (Supplemental An-
imation S1B) using in vivo microscopy.

Fig. 2. Heterogeneous alveolar injury depicted as a cluster of collapsed alveoli in the center of the field (H) surrounded by open interdependent alveoli
(hexagons). Note the distortion and overdistension of the patent alveoli adjacent to the collapsed alveolar cluster (asterisks), with more overdistension
alveoli at expiration (B) compared with inspiration (A). The larger the change in size of these alveoli with each breath, the larger the dynamic strain-
induced tissue damage. These dynamic changes can be seen in Supplemental Animation S2.
derecruit (R/D) with tidal ventilation resulting in an increase in dynamic strain (Fig. 3, A and B, and Supplemental Animation S3; 1, 17).

Secondary VILI mechanisms are as follows: 1) ARDS causes a reduction in functional lung volume by a combination of partially and fully collapsed (i.e., atelectasis) alveoli. If lung volume loss is severe, even small tidal volumes can result in VILI caused by overdistension (OD; 24) of normal alveoli and alveolar ducts, in the remaining aerated lung regions (36). However, if the lung is fully recruited, even large tidal volumes set on the ventilator will not cause alveolar OD since this volume is shared by millions of alveoli, and thus alveolar Vt remains very small. 2) Stress/strain-induced injury secondary to the above mechanisms causes release of inflammatory mediators, which exacerbate the physical damage, termed “biotrauma” (54, 58).

Stress risers. Although even the normal lung is not homogeneous throughout, because of variation in gas distribution, conducting airway asymmetry, and anisotropic alveolar expansion, stress transmission is still relatively well distributed in most lung tissue (Fig. 1 and Supplemental Animation S1). However, alveolar collapse and edema result in a heterogeneous inflation pattern such that the stress during cyclic volume change becomes concentrated onto the open lung tissue adjacent to collapsed tissue (18, 49; Fig. 2, A and B, and Supplemental Animation S2). It has been shown that the homogeneous lung is stable but local atelectasis, causing stress risers, can occur if alveolar surface tension is high and insensitive to alveolar surface area (57).

Recruitment/derecruitment. Normal alveoli are stable and do not have marked changes in volume with each tidal breath (<4–6% change with each cycle; Fig. 1 and Supplemental Animation S1). Thus dynamic strain is minimal in normal alveoli (15, 16, 45). Loss of surfactant function with acute lung injury renders alveoli unstable, greatly reducing the alveolar collapse time constant, resulting in a rapid collapse of the alveolus with each expiration (58; Fig. 3, A and B, and Supplemental Animation S3). This leads to a large dynamic alveolar strain, which is known to be a primary VILI mechanism (1, 17). Pathologic changes in alveolar stability can be identified using a deep inflation (DI) and measuring the change in elastance (H) and hysteresivity (η). H and η not returning to normal following a DI correlates strongly with alveolar instability viewed directly using in vivo microscopy (4). Stabilizing alveoli and preventing derecruitment with adequate PEEP, measured directly by in vivo microscopy, significantly reduce acute lung injury (58).

Overdistension and biotrauma. In a homogeneous, stable lung, it is postulated that alveolar OD sufficient to cause VILI histopathology does not exist in the absence of S-R or R/D, unless extremely high airway pressures are delivered. We hypothesize that because of interdependence (Fig. 1), alveolar OD can only occur adjacent to collapsed or unstable alveoli (42, 55). Mead et al. demonstrated that the shared alveolar walls would be stretched in response to a single overdistended or collapsing alveolus (42). We have seen that loss of interdependence (i.e., collapse of 1 or more alveoli) can cause instability and OD of adjacent alveoli, using in vivo microscopy. Supplemental Animation S4 depicts how the collapse of a single “alveolus” results in instability and OD of adjacent alveoli, stressing the importance of maintaining a fully recruited lung. Biotrauma occurs secondary to alveolar S-R- and R/D-induced tissue trauma causing a release of inflammatory mediators. Thus VILI will be minimized if both S-R and R/D are blocked. OD of a fully inflated lung can cause airways to rupture (e.g., pneumothorax) if sufficiently elevated yet does not cause lung histopathology typical of VILI (56). Alveolar ducts, rather than alveolar sacs, may be the site of OD and the possible site of airway rupture in a heterogeneously ventilated lung (36). In summary, VILI is minimized in an open and stable lung, even with high lung volumes and pressures. In summary, VILI has most often been viewed as an alteration of the barrier between the alveolar space and capillary, which is closely associated with an increase in inflammation (biotrauma). However, physical failure of the load-bearing cells and tissues during ventilation is now understood to also play a major role in VILI (60).

Key Points
- VILI can occur when the normal, homogenous lung becomes heterogeneous.
- The heterogeneous lung is a combination of normal alveoli, alveoli flooded with edema, and unstable alveoli that collapse and reopen during tidal ventilation.
- The primary mechanism of VILI is an alteration of normal dynamic alveolar physiology resulting in excessive alveolar volume change (strain) with each breath.
- The secondary mechanism of VILI is alveolar overdistension and generation of inflammatory mediators caused by excessive alveolar strain.

DYNAMIC CHANGES IN ALVEOLAR VOLUME

Although a great deal of literature has been devoted to understanding the physiology of normal and abnormal alve-
Alveolar mechanics (i.e., the dynamic change in alveolar size and shape during tidal ventilation), there is still no consensus on alveolar size change in the normal lung with each breath (26). It is well accepted that alveolar microanatomy is complex, with alveoli sharing walls in a honeycomb fashion forming a structurally stable design (Fig. 1; 42). Because of this alveolar interdependence and the fact that alveolar walls are only one or two cells thick (a vascular endothelial cell and an alveolar epithelial cell), it is proposed that that alveolar volume change is not simply stretching and contracting, similar to a rubber balloon, although this has never been directly proven, with the more likely mechanism being folding and unfolding like a paper bag (62). The three most logical mechanisms by which alveoli and alveolar ducts can change size during ventilation are as follows: 1) an all-or-none alveolar opening and closing during each breath, such that there are more open alveoli at inspiration than at expiration; 2) fluctuations in alveolar size owing to crumpling and uncrumpling of alveolar walls, similar to how a paper bag would change volume; and 3) change in the size of the alveolar duct with minimal change in alveolar size (26, 50).

Alveolar volume change is often perceived to be elastic in nature such that for a given force causing stress [i.e., tidal volume (VT)], alveoli would be expected to change size (i.e., strain) immediately on both inspiration and expiration. However, alveoli do not behave as an elastic structure, but rather as a viscoelastic system. A viscoelastic system would not exhibit an immediate change in alveolar size during tidal ventilation (10, 19, 31, 40, 59). The delay in strain following the applied force-induced stress is represented graphically as a hysteresis in the stress (σ)-strain (ε) curve. Direct visualization of the whole lung and subpleural alveoli during lung inflation has demonstrated this lag between the time that the VT force delivers the stress until the time alveoli actually begin to expand or recruit (strain; Supplemental Movie S1; 3). Similar assessments of alveolar mechanics and stability have been previously published (61). Although in vivo microscopy is one of the few methods to measure the dynamic change in alveolar size during ventilation in real time, it must be remembered that subpleural alveoli are unique in that they are not totally surrounded by alveoli and thus they may inflate or deflate differently from the majority of alveoli that compose the lung. Also, measuring dynamic inflation and deflation of a single alveolus in an animal ARDS model demonstrated that there was no significant reduction in alveolar size until airway pressure fell from 13 to 6 mmHg (46). A second time lag would be generated by collapsed alveoli with different opening pressure/duration constants, such that for “stickier” alveoli, a higher pressure or longer duration at a pressure would be necessary for recruitment. This would generate a time lag from when the pressure was applied and when the alveolus was recruited. Thus time is a critical component in determining alveolar inflation and deflation during each mechanical breath.

**ALVEOLAR VISCOELASTICITY: THE SPRING AND DASHPOT**

The change in alveolar size with ventilation is complex and has been depicted as viscoelastic in nature. This viscoelasticity has been described on a molecular basis using a mathematical framework (20, 59). In this paper, we will use a very basic model to analyze viscoelastic behavior using a spring attached to a dash in a filled pot (Supplemental Animation S5). Using this model, the force, which in the case of the lung would be the pressure generated with the VT, is applied to the tissue represented by the spring and dashpot. Supplemental Animation S5 shows that in response to this stress, in such a viscoelastic system the spring would move rapidly whereas there would be a significant delay and a much slower movement of the dashpot. Conversely, when the stress is released (expiratory phase of lung ventilation), the spring compresses rapidly followed by a slow reverse strain of the dashpot (Supplemental Animation S4). Using this spring-and-dashpot model to describe dynamic alveolar inflation, we can postulate that the rate of dashpot movement on both inspiration and expiration could be altered by lung pathology. For example, with loss of surfactant function during ARDS, collapsed alveoli would be very sticky (25), and thus it would take a great deal of stress over time to recruit them. This would be depicted by a very slowly moving dashpot. Once these surfactant-depleted alveoli open, they would be unstable and derecruit very rapidly during expiration (28), and this would be represented by a fast collapsing dashpot.

Viscoelastic physiology implies that the time at inspiration and expiration is a key MBP parameter that has the potential to “open the lung and keep it open” (37). Unfortunately, time has been overlooked in most protective ventilation strategies (13). An extended duration at inspiration would apply the pressure to the alveolus for a longer period of time, gradually “nudging” open alveoli with each breath (Supplemental Animation S5 and Supplemental Movie S1). Minimal duration at expiration would quickly release the pressure, allowing for ventilation and CO₂ removal, but minimize alveolar collapse because the dashpot would not have time to move (Supplemental Animation S6). Using this physiologic knowledge, a mechanical breath that may better open and stabilize the lung can be constructed.

Considering viscoelasticity as a key component of dynamic alveolar mechanics is critical when undertaking the design of a mechanical breath that will minimize VILI. Since the two primary mechanisms of VILI are alveolar R/D and S-R, a protective breath must be designed to prevent or treat both of these pathologies. Considering that alveoli are viscoelastic, we postulate that a mechanical breath with an extended inspiratory and short expiratory duration would recruit alveoli with each breath (Supplemental Animation S5), as well as prevent alveolar collapse during expiration (Supplemental Animation S6). This would minimize VILI by reducing both S-R and alveolar R/D (Figs. 2 and 3 and Supplemental Animations S2 and S3). Thus our protective mechanical breath strategy uses the component of time, in addition to the airway pressures, volumes, and flows being delivered with each breath, to block VILI. If lung volume increase were slow, the corresponding pressure would be near the elastic limit of the tissue. Higher ventilation rates would generate higher stresses exacerbating tissue injury,
and if this were true, it would offer a second benefit of the extended inspiratory duration.

**Key Points**
- Alveoli do not inflate and deflate in an ideal elastic spring-like fashion (elastic), but rather are a viscoelastic system.
- In a viscoelastic system there is a time lag between the time the force (Vt) is applied or removed and when the alveolus opens or collapses.
- This knowledge of dynamic alveolar physiology suggests that an extended time at inspiration would recruit alveoli and a minimal time at expiration would prevent alveolar collapse.
- Recruiting alveoli and preventing their collapse would convert the heterogeneous lung to homogeneous ventilation and reduce VILI.

### TRANSLATING DYNAMIC ALVEOLAR PHYSIOLOGY TO THE BEDSIDE

The current standard-of-care protective mechanical ventilation in patients with established ARDS uses low Vt and a sliding scale of PEEP based on oxygenation (13). This strategy is based on the knowledge that a significant volume of lung is either collapsed or edema filled and thus if a normal Vt were forced into this lung, the remaining normal lung tissue would be injured by overdistension. We showed evidence earlier that OD does not occur in the homogeneously ventilated lung, and thus it seems that a better strategy would be initially opening the lung, which would eliminate heterogeneous ventilation and stress risers (33, 43). PEEP would then be applied to keep the newly recruited alveoli open, eliminating the final mechanical mechanism of VILI, that of alveolar R/D. Indeed, this strategy of initially recruiting the ARDS lung has been shown to improve oxygenation and driving pressure without detrimental effects on mortality, ventilator-free days, or mortality in a pilot study (32). In that study a decremental PEEP trial was conducted as the pressure in the recruited lung was decreased in 2-cmH2O increments with the optimal PEEP identified by the best dynamic lung compliance (32). A meta-analysis has recently shown that this open lung approach significantly reduces the mortality in ARDS patients (38).

The open lung approach makes sound physiologic sense as a method to minimize the mechanisms of VILI at the alveolar level. Indeed, a link has been shown between optimal compliance/elastance and alveolar overdistension and instability in an animal model (6) and the role of driving pressure, which is calculated using compliance, as an indicator of mortality in ARDS patients (5). However, using compliance/elastance does not take advantage of the viscoelastic component of alveolar inflation and deflation. In theory, an extended time at inflation would progressively recruit alveoli, and a short time at expiration would prevent alveolar collapse. There are three US Food and Drug Administration-approved mechanical breath strategies that incorporate an extended inspiratory and minimal expiratory duration: 1) inverse inspiratory-to-expiratory ratio (I:E; 11, 43), 2) high-frequency oscillatory ventilation (HFOV; 22, 66), and 3) airway pressure release ventilation (APRV; 27, 30). Relatively little study has been directed at inverse I:E in ARDS, and the results have been mixed (11, 43). HFOV has been extensively studied; however, recent work has shown that HFOV may increase mortality in ARDS patients (22, 65), although the reasons for this failure may not be due to the impact of HFOV on alveolar mechanics (41). The failure of HFOV to reduce mortality may be due to a misdistribution of ventilation in the heterogeneously injured lung (29). A very specific strategy of personalized APRV (30) has been shown to be effective at stabilizing alveoli (35, 36) and protecting from the development of ARDS in a clinically applicable porcine model (34, 51, 52). In a meta-analysis this personalized APRV strategy significantly reduced ARDS incidence and mortality in a surgical intensive care unit (8), but it has not been tested in a prospective clinical trial. It is also possible that a novel method of multifrequency oscillatory ventilation that would better personalize the HFOV breath to the patient’s lung pathology would improve outcome (33).

**Key Point**
- Ventilation strategies that 1) greatly extend the inspiratory time, continually recruiting the alveoli with slow opening time constants; and 2) dramatically reduce expiratory duration to a time less than the alveolar collapse time constant would be lung protective on the basis of our knowledge that dynamic alveolar physiology is viscoelastic in nature.

### CONCLUSIONS

Although controversy still exists, there is strong evidence suggesting that the two primary mechanisms of VILI at the alveolar level are stress risers and repetitive alveolar opening and collapsing. If these primary injury mechanisms are left untreated, they will result in a secondary mechanical mechanism of injury, alveolar overdistension. All three mechanical injuries cause inflammation resulting in biotrauma, which is the fourth component of the VILI tetrad. Logic dictates that if a mechanical breath can be applied that eliminates both of these primary VILI mechanisms, lung tissue damage would be significantly reduced. Thus the goal for protective mechanical ventilation is to open the lung and keep it open (37) or, if applied early, “never let the lung collapse.”

The normal lung on mechanical ventilation inflates via increased pressure delivered by the ventilator and deflates passively because of elastic lung recoil. Alveolar inflation and deflation are viscoelastic, and thus there is a short but distinct time lag between the time that the force of airway pressure is delivered and the time that alveolar inflation occurs. Conversely, there is a distinct time lag between the point that stress is removed during lung deflation and when alveoli begin to collapse. In the acutely injured lung with loss of surfactant function, a longer time is required at inspiration to open alveoli and a much shorter time at expiration to prevent alveolar collapse.

Understanding that alveoli are viscoelastic structures suggests that a greatly extended inspiratory duration would open alveoli and a very short duration at expiration would keep alveoli open. By modifying the time of the applied breath during both inspiration and expiration in an attempt to maintain a homogeneously ventilated lung, the incidence of VILI may be reduced, which may significantly lower the morbidity and mortality associated with ARDS.
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