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Impact of mechanical ventilation on the pathophysiology of progressive acute lung injury

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Nieman GF, Gatto LA, Habashi NM. Impact of mechanical ventilation on the pathophysiology of progressive acute lung injury. *J Appl Physiol* 119: 1245–1261, 2015. First published October 15, 2015; doi:10.1152/japplphysiol.00659.2015.—The earliest description of what is now known as the acute respiratory distress syndrome (ARDS) was a highly lethal double pneumonia. Ashbaugh and colleagues (Ashbaugh DG, Bigelow DB, Petty TL, Levine BE *Lancet* 2: 319-323, 1967) correctly identified the disease as ARDS in 1967. Their initial study showing the positive effect of mechanical ventilation with positive end-expiratory pressure (PEEP) on ARDS mortality was dampened when it was discovered that improperly used mechanical ventilation can cause a secondary ventilator-induced lung injury (VILI), thereby greatly exacerbating ARDS mortality. This Synthesis Report will review the pathophysiology of ARDS and VILI from a mechanical stress-strain perspective. Although inflammation is also an important component of VILI pathology, it is secondary to the mechanical damage caused by excessive strain. The mechanical breath will be deconstructed to show that multiple parameters that comprise the breath—airway pressure, flows, volumes, and the duration during which they are applied to each breath—are critical to lung injury and protection. Specifically, the mechanisms by which a properly set mechanical breath can reduce the development of excessive fluid flux and pulmonary edema, which are a hallmark of ARDS pathology, are reviewed. Using our knowledge of how multiple parameters in the mechanical breath affect lung physiology, the optimal combination of pressures, volumes, flows, and durations that should offer maximum lung protection are postulated.

acute lung injury; lung; pathophysiology ventilator; VILI

THE POLIO EPIDEMIC OF 1916 inspired many treatment attempts including vitamin C therapy, hydrotherapy, and electrotherapy, but no effective therapy was found until Philip Drinker's group invented negative pressure mechanical ventilation—the iron lung. Their landmark paper, "The use of a new apparatus for the prolonged administration of artificial respiration: I. A fatal case of poliomyelitis," published in 1929, demonstrated the effective clinical use of this device (Fig. 1) (38). The concept of conversion from negative to positive pressure ventilation was based on technical advances that were made during World War II to deliver pressurized oxygen to high-altitude fighter and bomber pilots. Concomitant with these technologic advances in mechanical ventilation was the realization that what was originally thought to be a universally fatal form of double pneumonia was indeed a unique clinical entity that we now call the acute respiratory distress syndrome (ARDS). In a 1967 seminal paper published in *The Lancet*, Ashbaugh et al. (10) first identified and described ARDS as a collection of pathologic abnormalities that can be caused by many unrelated insults such as sepsis, hemorrhagic shock, pneumonia, and trauma to name a few. The disease and the ventilator technology came together when it was shown that application of positive pressure mechanical ventilation with the addition of an expiratory retard (positive end-expiratory pressure, or PEEP), dramatically improved survival in patients with ARDS (10).

The initial enthusiasm over the effectiveness of positive pressure ventilation for treating ARDS was significantly dampened when it was learned that the ventilator was a double-edged sword and, if used improperly, could cause ventilator-induced lung injury (VILI) (136), which could significantly increase mortality (8). Discovery that the ventilator can damage the lungs of patients with established ARDS resulted in hundreds of studies investigating the molecular, cellular, and mechanical mechanisms of VILI (128). These efforts culminated in an article published in 2000 by the *The New England Journal of Medicine* (8) demonstrating that reduced tidal volume (VT) and plateau airway pressure were positively correlated with a reduction of ARDS mortality in a phase III clinical trial. However, recent studies have shown that the ARDS net low VT strategy has not reduced mortality (105, 131, 134), and patients who survive ARDS have significant pulmonary (64)

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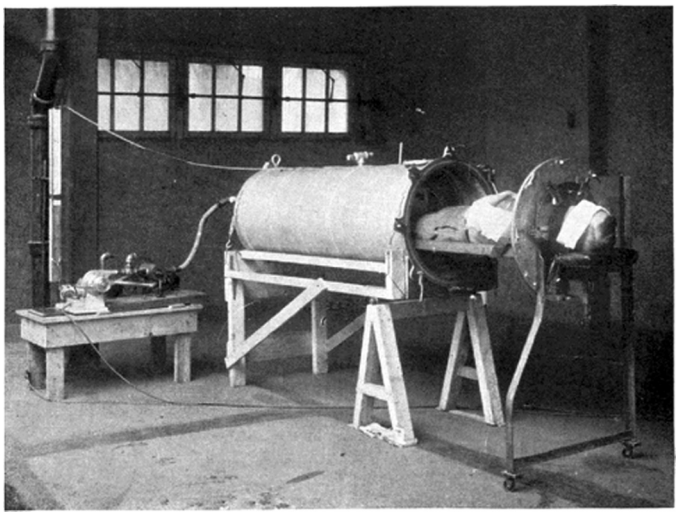

Fig. 1. The iron lung as it appeared in the initial paper by Drinker et al. (38) first describing the clinical use of negative pressure mechanical ventilation. Permissions to republish granted. [Published with permission (38)].

and cognitive (91) dysfunction. Thus the problem of VILI has not been solved.

MECHANICAL VENTILATION AND THE INCIDENCE OF ARDS

Not only does VILI increase the morbidity and mortality associated with ARDS (8), but improper ventilation of patients with normal lungs who are at high risk of developing acute lung injury (ALI) significantly increases the incidence of ARDS (Fig. 2) (35, 49, 52, 53, 66, 72, 119). However, if a protective mechanical breath is applied preemptively, during the early acute lung injury (EALI) period, progression of ALI may be halted and the incidence of ARDS may be significantly reduced (7, 50, 119, 120).

These studies illustrate four key concepts: *1*) mortality in patients with established ARDS remains unacceptably high even with low VT ventilation (105, 131, 134); *2*) improperly adjusted mechanical ventilation can exacerbate EALI in patients at high risk and thus increase ARDS incidence (73); *3*) preemptive application of a protective ventilation strategy in this same high-risk group of patients can significantly reduce ARDS incidence (7, 35, 49, 50, 52, 53, 58, 66, 72, 119); and *4*) the optimally protective breath necessary to block progressive ALI remains to be determined.

The inability to reduce the mortality of established ARDS indicates that attention needs to shift from treatment to prevention. However, the concept of preventing rather than treating ARDS is new, and the optimally protective mechanical breath remains illusive. Indeed, preemptive ventilation using low VT ventilation, the current standard of care in patients with established ARDS, has been shown to increase mortality in patients during major surgery and at high risk of developing ALI (72). This study suggests that ventilator strategies used to treat established ARDS (8) might not be optimal or might even be dangerous in patients with clinically normal lungs but with early progressive ALI (72).

TETRAD OF ARDS PATHOPHYSIOLOGY

Physiologists are in a unique position to make substantial contributions to the identification of the optimal mechanical breath necessary to prevent ARDS development. The key pathophysiological mechanisms that are the hallmarks of ARDS are already well known. That is, we know the critical components of ARDS pathology that make a patient sick are *1*) increased pulmonary capillary permeability (62), *2*) alveolar flooding with edema (86), *3*) surfactant deactivation (67), and *4*) altered alveolar mechanics (4) (i.e., the dynamic change is alveolar size and shape during ventilation) (Fig. 3). We also know that improper mechanical ventilation can exacerbate each component of this pathological tetrad (2, 23, 40, 47, 55, 124), which if unchecked, can drive progressive ALI into established ARDS. Because a mechanical ventilator can be adjusted in ways that can either exacerbate or minimize all of the tetrad pathologies (2, 23, 40, 47, 55, 124), physiologists must identify the mechanism by which the mechanical breath damages lung tissue and, once known, design a preemptive mechanical breath to prevent this damage.

EFFECT OF MECHANICAL VENTILATION ON TETRAD PATHOLOGY

Paradoxically, mechanical ventilation during the EALI period can have the opposite effect on lung pathology depending on ventilator settings; inappropriate settings can significantly increase the incidence of ARDS, whereas application of a protective breath can reduce ARDS incidence (7, 35, 49, 50, 52, 53, 66, 72, 119, 120). The challenge now is to determine how to precisely adjust the mechanical breath to prevent the development of one or all of the tetrad components and thereby reduce ARDS incidence. To accomplish this we need to first identify whether sufficient time exists following the initiating injury (e.g., trauma, sepsis, pneumonia, hemorrhagic shock) during which preemptive mechanical ventilation can be applied. In other words is ARDS a progressive disease that can be treated early or is it binary and the patient either has it or does not have it? If ARDS is a progressive disease we then need to identify how the parameters that comprise the mechanical breath profile (MB_P) (i.e., airway pressures, volumes, flows, rates, and the duration that these parameters are applied to the lung with each breath) can affect the pathophysiology of progressive ALI. Once we know the physiological effect of

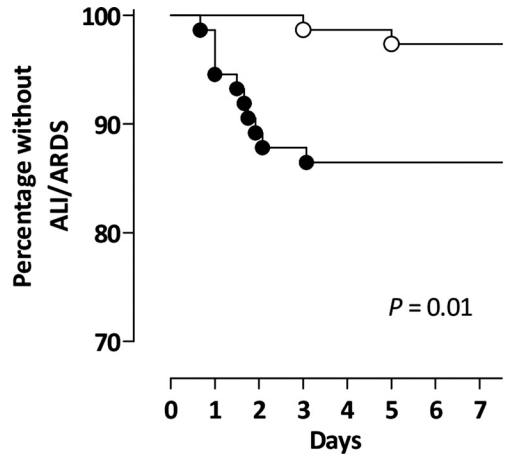

Fig. 2. Kaplan-Meier curve describing the incidence of acute lung injury in patients receiving mechanical ventilation before the development of acute lung injury with conventional tidal volume (solid circles) or lower tidal volume (open circles). [Published with open access permission (35)].

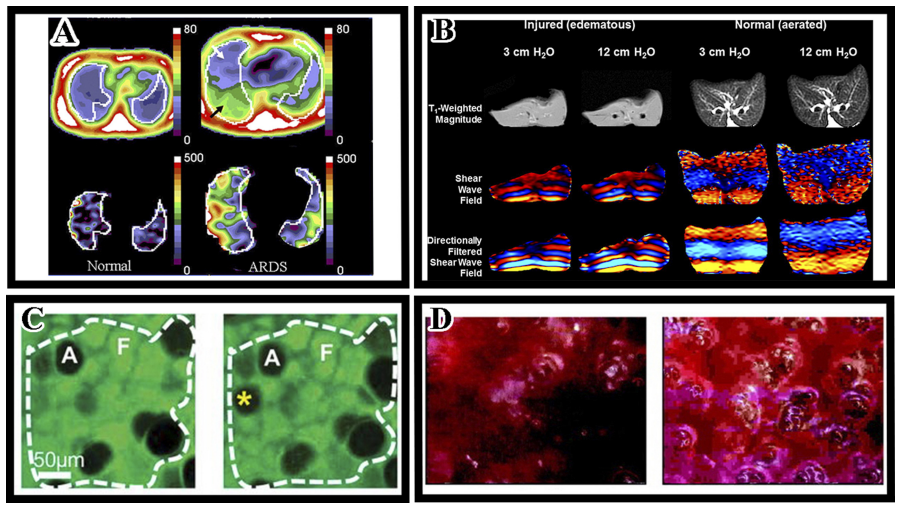

Fig. 3. Pathophysiology tetrad of acute respiratory distress syndrome (ARDS). *A*: increased pulmonary vascular permeability, *B*: pulmonary edema, *C*: surfactant deactivation, and *D*: altered alveolar mechanics (i.e., the dynamic size and shape change of the alveolus during tidal ventilation). *A*: increased pulmonary capillary permeability measured by positron emission tomography of two patients, one with ARDS. Structural injury is shown as an increase in extravascular density (EVD, *top* vertical scale 0–80) of the lung with ARDS with a ventral-dorsal gradient (white vs. black arrows). Change in vascular permeability is described as the pulmonary transcapillary escape rate (PTCER, *bottom* vertical scale 0–500) and is widespread in nature. PTCER suggests that a lung in a patient with ARDS is much more diffuse than suggested by the functional injury (EVD) and may explain why the ARDS lung is so vulnerable to ventilatory-induced lung injury (VILI) (62). *B*: injured (edematous) and normal (aerated) lungs with changes in mechanical properties caused by edema analyzed by magnetic resonance elastography (MRE). Lung volume was assessed using T_1-weighted spin echo. Shear wave propagation within an elastic or viscoelastic medium can quantify and spatially resolve the elastic properties of the lung. The shorter wavelengths in the injured lung suggest that the lung is more compliant due to edema and deactivation of surfactant function. This study demonstrates that both edema and surfactant deactivation play a key role in ARDS pathophysiology and that edema can be spatially located using MRE (86). *C*: not only is loss of surfactant function on the alveolar surface a key component in ARDS pathophysiology (2), but this study demonstrates the importance of the surface tension between the air-filled alveolar duct and the edema fluid in a flooded alveolus (67). Heterogeneous ventilation with air filled alveoli (A) adjacent to edema filled alveoli (F) create stress concentrators, which would result in a dynamic alveolar wall bowing into the edema-filled alveoli causing mechanical damage to the alveolar tissue. If a rhodamine dye that lowers the surface tension on the air-liquid interface the liquid flows out of the alveolus (*newly aerated alveolus) it will eliminate the stress concentrator, preventing damage to alveolar tissue. *D*: altered lung mechanics typical of ARDS have been ascribed to altered mechanics at the alveolar level. In this study, dynamic subpleural alveolar mechanics were measured using in vivo videomicroscopy. Alveolar mechanics (i.e., the dynamic change in alveolar size and shape during tidal ventilation) were correlated with lung mechanics as measured by elastance (*H*), impedance, and hysteresivity (η). It was concluded that simultaneous increase in both *H* and η are reflective of lung injury in the form of alveolar instability, whereas an increase in just *H* reflects merely derecruitment of alveoli. [Published with permission (4)].

each parameter comprising the mechanical breath on the pathological tetrad, we can generate hypotheses on the design of the optimally protective mechanical breath, which if applied preemptively, will block ALI pathogenesis and reduce ARDS incidence.

EALI PATHOGENESIS

ARDS Is a Disease that Progresses in Stages

The original concept of ARDS is that it was binary, either the lungs were sick and a patient had ARDS, or the patient did not have it, and thus lung protective strategies (i.e., low VT or proning) were implemented only after established ARDS had developed (8, 22, 59). It is logical to expect that there must be an EALI phase with identical pathological mechanisms at work, but because a relatively small percentage of the lung is damaged, combined with the ability of hypoxic pulmonary vasoconstriction (12) to match perfusion with patent alveoli, lung injury is not clinically apparent (Fig. 4, *stage 1*) (112).

It has been shown that EALI begins even before a patient begins receiving mechanical ventilation (48, 73). In addition, it has been found that patients being ventilated with room air who met the American-European consensus conference (AECC) definition of ARDS (13) no longer met ARDS criteria with the addition of PEEP and increased F_{IO_2} (46, 132). ARDS that disappeared with PEEP and increased F_{IO_2} was termed "transient ARDS" (Fig. 4, *stage 2*), whereas ARDS that did not disappear was termed "persistent" or "established ARDS" (Fig. 4, *stage 3*). Thus just because a patient meets the current criteria for established ARDS does not signify that all patients have the same stage of ARDS development.

This concept has been further supported by recent literature investigating the early development of ALI and the effect of the mechanical breath on disease progression (35, 49, 51–53, 63, 66, 119). These studies showed that patients who received mechanical ventilation for reasons other than respiratory failure developed more ALI/ARDS if they where ventilated with higher airway pressures and tidal volumes. Also, patients without ALI but on mechanical ventilation for >48 h have a 19% chance of developing ALI (66). It is well known that patients with truly healthy lungs, such as those who are paralyzed, can receive mechanical ventilation for years without developing ALI (28). This suggests that in patients receiving mechanical ventilation who eventually develop ALI/ARDS, the lungs are not "healthy" upon intubation; instead, the lungs are in the EALI stage and the injurious components of the mechanical breath act as a "second hit" to drive the progression of disease. For example, van Wessem et al. (129) showed in a rat hemorrhagic shock model that hemorrhagic shock alone did not produce significant pulmonary inflammation or lung injury unless it was combined with mechanical ventilation that precipitated ARDS (129).

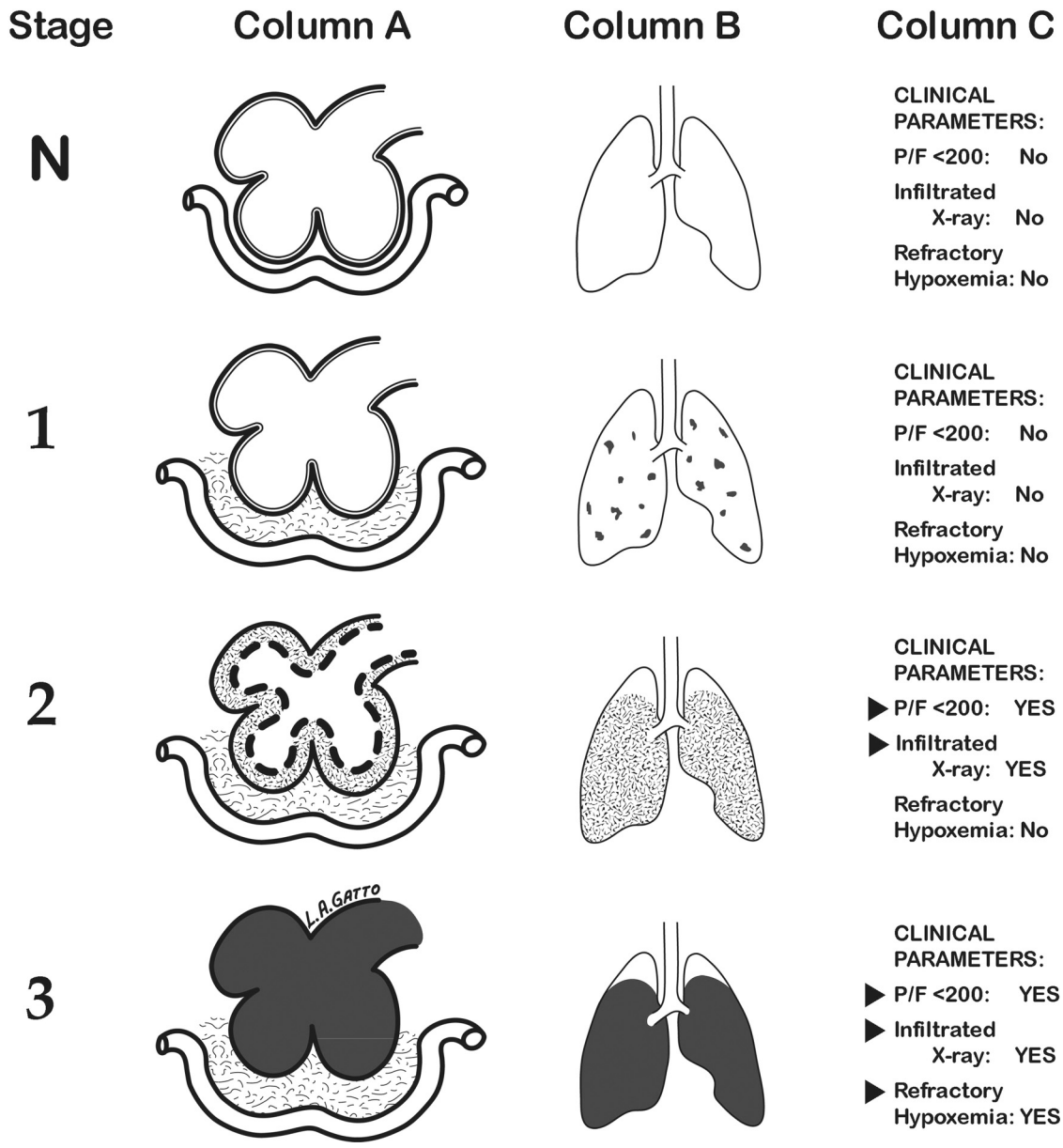

Fig. 4. Theoretical pathogenesis of ARDS development from normal (N) to established ARDS (*stage 3*). *Stages 1* and *2* are defined as pre-ARDS; *Stage 3* is the current ARDS Network definition of ARDS (5): *N*, normal alveoli no interstitial or alveolar edema; *stage 1*, early acute lung injury, interstitial edema in vascular cuffs (gray) without alveolar flooding or measurable clinical symptoms; *stage 2*, insidious ARDS, interstitial edema (light gray) and partial flooding of alveoli (dark gray) with moderate surfactant deactivation (dotted lines) causing alveolar instability and hypoxemia (insidious ARDS has all of the clinical parameters of established ARDS except that hypoxemia is not refractory if ventilation with the appropriate mechanical breath profile is applied); *stage 3*, established ARDS, interstitial edema (light gray) and complete alveolar flooding with edema (black), severe surfactant deactivation and all clinical parameters as defined by the ARDS consensus conference including refractory hypoxemia even if appropriately set mechanical breath is applied. *Column A*, diagram of alveoli, interstitial space and capillary; *column B*, percent of the entire lung that these lesions occupy; *column C*, clinical presentation at each stage. [Published with permission (112)].

These data demonstrate that ARDS is a disease that progresses in stages (Fig. 4) (112). This fact, combined with the knowledge that ARDS almost always develops within a hospital setting (121) and, once established is refractory to treatment (82, 87), collectively support the hypothesis that a preferred strategy should be to block the disease in an early stage rather than treat it once it develops. Indeed, Villar and Slutsky (133) recently commented that "ARDS is no longer a syndrome that must be treated, but is a syndrome that should be prevented."

Pathophysiology of EALI

There is a large volume of data describing the molecular, cellular, physiological, and pathological components of established ARDS (25, 32, 83, 117, 135), but little information exists on the pathogenesis during the EALI stages before the development of clinical symptoms (Fig. 4, *Stage 1*). Established ARDS is characterized by *1*) dysfunction of both the endothelial and epithelial barriers leading to *2*) high-permeability pulmonary edema causing *3*) surfactant deactivation and

4) alveolar instability (Fig. 3) (1, 25, 32, 83, 117, 122, 135). The components of the pathological tetrad develop progressively and in a heterogeneous fashion. Over time pulmonary edema and surfactant loss will necessitate the use of mechanical ventilation to maintain oxygenation, which will add another hit (i.e., VILI with inappropriate ventilation), thereby exacerbating and accelerating lung damage. The effect of increased alveolar flooding and surfactant deactivation results in *1*) volutrauma, with small airways rupturing and pneumothorax and 2) atelectrauma, marked by alveolar collapse and reopening causing a dynamic strain-induced injury to the pulmonary parenchyma (96, 122). This mechanical damage to lung tissue results in release of inflammatory mediators causing a secondary biotrauma, which is a significant component in ARDS pathogenesis (127). Thus VILI is a combination of volutrauma, atelectrauma, and biotrauma.

Most of the data on EALI pathophysiology have come either from studies examining markers of patients at risk of developing ARDS (14, 15, 19, 26, 32, 36, 56, 65, 74, 99) or clinical studies investigating the development of ARDS secondary to mechanical ventilation in patients with presumably normal lungs (16, 45, 48, 49, 51, 52, 66, 75, 119). Multiple inflammatory biomarkers have been found in patients at high risk of developing ARDS, giving us more clues to EALI pathophysiology (32, 85). Not surprisingly, the same mediators associated with established ARDS are also associated with patients at high risk of developing the syndrome. E-selectin (99), for example, led to lower levels of surfactant proteins A and B (56) as well as tumor necrosis factor (TNF) (65). IL-6 and IL-8 (19, 36) and variant angiopoietin-2 (90) have all been found in the plasma or bronchoalveolar lavage fluid of patients before they were clinically diagnosed with ALI/ARDS. These data suggest that the same pulmonary pathophysiology is taking place before the clinical symptoms of ALI/ARDS are present. Thus it is likely that increased endothelial (76, 100) and epithelial (24, 76) permeability, surfactant deactivation (56), pulmonary edema (71), and altered alveolar mechanics suggested by chest X-ray and oxygen requirements (73) are all occurring unnoticed before a patient is diagnosed with ALI/ARDS, generating the conditions that will ultimately drive the pathological tetrad.

VILI Drives Progressive Acute Lung Injury

It is known that very high VT combined with low PEEP will cause VILI in normal lungs with the pathology being indistinguishable from the injury observed with ARDS (25, 117), suggesting that a significant portion of ARDS pathology is ventilator induced (37). At the very least, the initial lung injury caused by direct (pneumonia, aspiration) or indirect (trauma, sepsis, hemorrhagic shock) inflammation works synergistically with inappropriate mechanical ventilation to drive disease progression, thereby significantly increasing the incidence, morbidity, and mortality of ARDS (102). Indeed, it has been theorized that "Acute Lung Injury (ALI)/ARDS is a consequence of our efforts to ventilate patients, rather than progression of the underlying disease" (133). Strong clinical evidence supports this hypothesis because the only treatment in a phase III clinical trial that demonstrated a significant reduction in ARDS mortality was by decreasing VT (8) and using low VT in combination with proning (59). These studies demonstrated that minimizing the VILI component of ARDS could improve survival (8, 59). Because it is known that the mechanical breath can be made less harmful depending on the combination and magnitude of the breath parameters [VT, plateau airway pressure (Pplat), and PEEP], it is not a conceptual leap to postulate that further optimization of the mechanical breath may actually be protective and prevent ARDS before it develops. This supports the likelihood that properly adjusted mechanical ventilation can be used as a therapeutic tool to prevent rather than treat established ARDS (130, 131, 133).

There is evidence that the lungs of patients receiving mechanical ventilation without clinical ALI were not normal, but rather a significant portion of the lung was already damaged and in an EALI stage even though the criteria for ALI or ARDS had not been met (Fig. 4, *stage 1*) (44). Gajic et al. (52, 53), Determann et al. (35), and Jia et al. (66) independently showed that many patients in intensive care units (ICUs) who received mechanical ventilation but who did not meet ALI/ARDS criteria nevertheless had significant signs of EALI such as the need for increased $F_{I_{O_2}}$ and high peak airway pressures, low $Pa_{O_2}/F_{I_{O_2}}$ (P/F) ratios, acidemia, and elevated plasma levels of IL-6. In addition, patients receiving mechanical ventilation without AECC-defined ALI showed a positive correlation between high airway pressures and VT and the development of established ARDS, suggesting that VILI is in progress during the EALI stage and contributing significantly to the pathology (Fig. 4, *stage 1*) (49). Indeed, patients without clinical ALI (Fig. 4, *stage 1*) who are intubated would likely be placed on nonprotective ventilation with higher VT, further accelerating ARDS development.

In a recent clinical study, patients who underwent extensive abdominal surgery but with normal lungs received mechanical ventilation through two settings: *1*) VT 12 ml/kg + PEEP 0 cmH_2O; or *2*) VT 6–8 ml/kg+ PEEP 6–8 cmH_2O with a recruitment maneuver and the incidence of major complications recorded in each group. There were significantly more complications in the nonprotective group (VT 12 ml/kg + PEEP 0 cmH_2O) including acute respiratory failure, pneumonia, sepsis, septic shock, and death (50, 120). This study supports the early works suggesting that the settings on the mechanical ventilator play a critical role in the development of ALI in patients with normal lungs but at high risk due to systemic inflammation. Finally, in a recent review paper, Fuller et al. (49) summarize the role of mechanical ventilation in the development of ARDS by concluding that *1*) higher VT is causal in the development of ARDS; *2*) ARDS occurs early in the course of mechanical ventilation and thus prevention trials should also occur early; and *3*) the development of ARDS is associated with significant morbidity and mortality, suggesting that ARDS-prevention trials are needed (49).

It is clear from the above description that nonprotective mechanical ventilation can greatly accelerate the progression and increase the incidence of ARDS. It is the hypothesis of researchers in our laboratory (7, 41, 68, 69, 111–113) and multiple other investigators (16, 45, 48–52, 58, 66, 73, 119, 120) that if a protective mechanical breath is applied early, the incidence of ARDS can be significantly reduced. What remain to be determined are the settings needed to optimize protective mechanical ventilation.

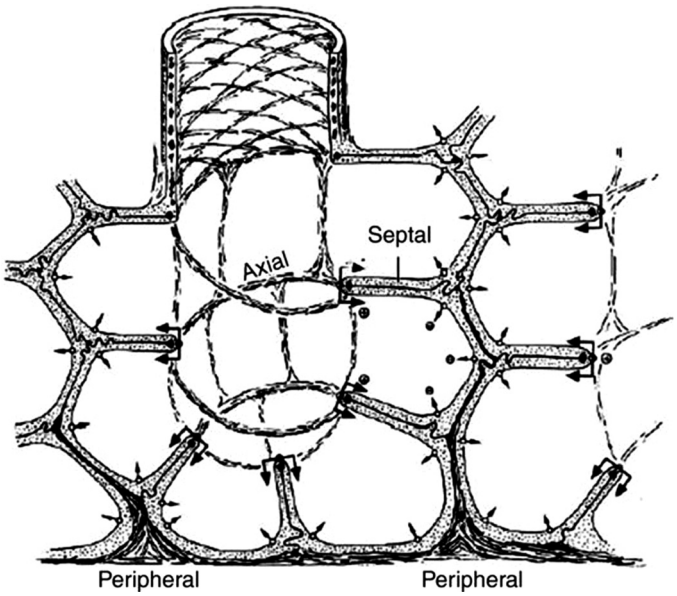

Fig. 5. Alveolar and alveolar duct architecture with the connective tissue systems (i.e., axial fibers observed as helical structure and peripheral fibers extending to the pleural surface). Note the interdependence of alveolar shared walls that maintain structural integrity as long as they are homogeneously inflated. Arrows depict distending action of surface tension. [Published with permission (137)].

What Do We Need to Know to Block Progressive ALI?

There is sufficient evidence to indicate that lung pathology identical to that observed with established ARDS unfolds in a matter of hours or days before clinical manifestations of the disease (14, 15, 19, 26, 32, 36, 56, 65, 73, 74, 90, 99). In addition, if mechanical ventilation with currently acceptable tidal volumes and pressures is applied during this period it can act as a second hit, exacerbating lung injury and resulting in a higher prevalence of established ARDS; however, if slight changes in VT or PEEP are applied early, then the incidence of established ARDS is reduced (16, 45, 48, 49, 51, 52, 66, 75, 119). These data, in addition to the fact that almost all ARDS develops in hospital settings (121), support the concept that preemptive application of a protective mechanical breath can block progressive ALI and reduce ARDS incidence. The next critical step is to ascertain *1*) the precise mechanism of ventilator-induced damage to the pulmonary microenvironment (the alveoli and alveolar ducts); and *2*) once the mechanism is known, identify the settings that would optimize the protective mechanical breath, thus preventing injury.

IDENTIFYING MICROENVIRONMENT VILI AND OPTIMIZING THE MECHANICAL BREATH

Microenvironment VILI

Structural design of the alveolus and alveolar duct. The healthy lung is a homogeneously ventilated organ that is structurally resistant to mechanical damage during ventilation. The shared walls of each alveolus with a two-fiber support system (i.e., the axial system anchored to the hilum and extending into the alveolar ducts and the peripheral system anchored to the visceral pleura distending into the central portion of the lung) are structurally very stable and resistant to either overdistension or collapse (Fig. 5) (137). The concept of this alveolar interdependence was first introduced by Mead et al. (88) and describes the structural mechanisms by which alveoli resist either collapse (Fig. 6*B*) or hyperinflation (Fig. 6*D*). In addition, Mead et al. (88) also demonstrated how heterogeneous collapse of alveoli created stress concentrators in the areas between open and collapsed alveoli (Fig. 6*B*). These stress concentrators greatly amplify the mechanical damage to tissue in the transitional zone between open and collapsed or edema-filled alveoli (31, 109).

Microenvironment VILI: mechanical or inflammatory? The logical sequence of events in progression of ALI caused by inappropriate mechanical ventilation would seem to be mechanical damage to pulmonary tissue caused by excess stress-induced strain as the primary injury, followed by biotrauma in response to physical damage caused by excessive strain (33, 140). D'Angelo et al. (33) showed that low-volume lung injury was caused by cyclic opening and closing of small airways and not by release of inflammatory cytokines. Likewise, Yoshikawa et al. (140) demonstrated that alveolar hyperpermeability occurred rapidly following exposure to high peak inflation pressure and was initially independent of an increase in inflammatory mediators (TNF-α, IL-1β, IL-6, and macrophage inflammatory protein-2), thus supporting the hypothesis that mechanical damage (dynamic strain and stress concentrators) causes the initial damage followed by a secondary inflammatory injury. Ultimately, this mechanical insult results in the release of inflammatory mediators that exacerbate the primary mechanical damage resulting in a secondary biotrauma (122). However, it appears that the key to preventing VILI is to block the mechanical insult to alveoli and alveolar ducts. To do this we need to understand whether the mechanism of mechanical injury is caused by overdistension or by dynamic strain of the pulmonary fine structures.

Microenvironment VILI: dynamic strain or overdistension? Most studies have shown that a high static airway pressure

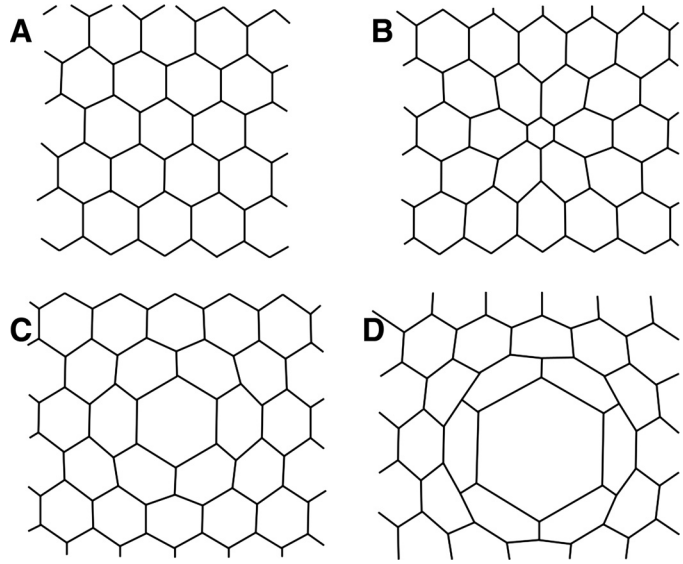

Fig. 6. Diagrammatic description of alveolar interdependence. Shared alveolar walls in homogeneous inflated lung (*A*) resist alveolar collapse (*B*) and overexpansion (*C*, *D*). Note the additional strain on the alveoli surrounding the center collapsing alveoli (*B*), which is the source of stress concentration. [Published with permission (88)].

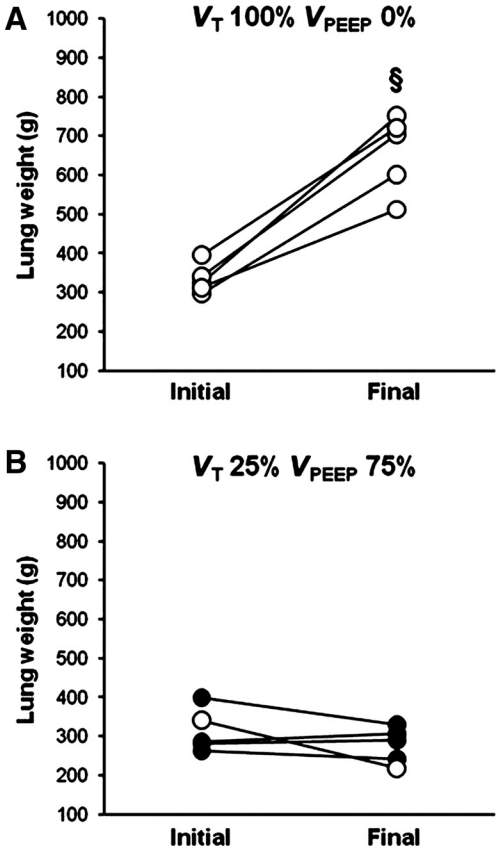

Fig. 7. Demonstration that high dynamic [tidal volume (VT) 100% and volume of positive end-expiratory pressure (V_{PEEP}) 0%] but not high static (VT 25% V_{PEEP} 75%) strain causes ARDS, assessed by development of pulmonary edema (lung weight). Pigs were ventilated for 54 h with an identical peak strain near total lung capacity (TLC) using a combination of VT and PEEP. When the strain was applied using VT without PEEP a high dynamic strain was subjected to the lung with each breath (VT 100% V_{PEEP} 0%). Static strain was applied by use of elevated PEEP with greatly reduced VT (VT 25% V_{PEEP} 75%). ARDS was assessed by a change in lung weight (i.e., pulmonary edema) from the baseline measurement (initial) and at the end of the experiment (final). All animals subjected to dynamic strain developed pulmonary edema, whereas animals with the identical static strain but minimal dynamic strain did not. [Published with permission (108)].

sufficient to significantly distend the lung in the absence of dynamic strain due to collapse of alveoli during expiration will not cause ARDS-like histopathology and edema. Multiple studies have shown that high static strain associated with lung overdistension alone (i.e., in the absence of dynamic strain) does not result in tissue histopathology typical of ARDS, even though it may cause rupture of small airways leading to pneumothorax (108, 118). However, with the identical total strain, increasing the dynamic strain component causes histopathology and pulmonary edema characteristic of ARDS (Fig. 7) (108).

The majority of the studies that measured change in alveolar size with high airway pressure showed a relative alveolar enlargement with increased airway pressure; however, alveolar size remained well within the range of normal alveolar anatomy (27, 89). These studies are supported by physiological evidence that high static strain, which should be sufficient to cause overdistension-induced tissue damage, is benign unless this strain is dynamic (108, 118). Large high VT causing a high static strain with sufficient PEEP to prevent high dynamic strain (i.e., large changes in alveolar volume with each breath) causes minimal lung injury. However, if PEEP is reduced, thereby creating excessive dynamic strain, significant lung damage will occur at the identical peak static strain (Fig. 7) (108). Thus it appears that dynamic strain, or atelectrauma, is the primary mechanical mechanism of injury to the pulmonary parenchyma. Volutrauma is also important because it can cause stress-failure in small airways leading to pneumonthoraces but it does not cause pulmonary edema or histopathology to the pulmonary parenchyma (Fig. 7).

More recently, another mechanical VILI mechanism has been identified (104, 109). Evidence has shown that the damage to the pulmonary parenchyma can be caused by heterogeneous ventilation, which occurs at the junction between collapsed (109) or edema-filled (104) alveoli and air-inflated alveoli. This heterogeneity causes stress concentrators that can significantly magnify the amount of alveolar and alveolar duct strain for any given stress and thus appears to be another mechanism of mechanical injury to the pulmonary tissue (Fig. 8) (104). The main pathological cause for both heterogeneous ventilation and altered alveolar and small airway mechanics is airway flooding with edema fluid and altered surfactant function (Fig. 3). Ventilator-induced loss of surfactant function (2) exacerbates edema formation (20, 95), which deactivates more surfactant (97). This leads to alveolar instability, which aggravates vascular permeability (40), causing more edema and deactivating more surfactant in a cycle that repeats until established ARDS is recognized. However, if a mechanical breath can be preemptively applied to maintain homogeneous lung ventilation (eliminate stress concentrators) and prevent alveolar collapse and reopening during ventilation (eliminate dynamic strain), it would ameliorate all components of the pathological tetrad and theoretically reduce ARDS incidence (Fig. 3).

Thus physiological evidence suggests that progressive ALI may be blocked by applying a preemptive mechanical breath directed to maintain homogenous lung inflation and not allowing alveoli to collapse during expiration. Lachmann in 1992 (70) identified the optimal way to protect a patient with established ARDS from VILI as "Open up the lung and keep the lung open." To reduce the incidence of ARDS in patients at high risk of using mechanical ventilation this statement should be modified to "never let the lung collapse."

Physiological Evidence That the Mechanical Breath Can Block Progressive ALI

ALI causes a pathological alteration in terminal airspace, generating extreme strains on the tissues in this microenvironment (i.e., alveoli and alveolar ducts). Excessive tissue strain results in a secondary VILI, which significantly increases ARDS incidence and mortality. Preemptive mechanical ventilation can minimize this severe strain and block progressive ALI. A component of this pathology is pulmonary edema, which is a hallmark of ARDS (Fig. 3*B*) (1, 25, 32, 83, 117, 122, 135). Is it possible that the same MB_P that minimizes tissue strain can also reduce pulmonary edema deposition?

Parameters comprising the mechanical breath profile. There are at least 10 components that comprise the MB_P and it is likely that a complex relationship among these components

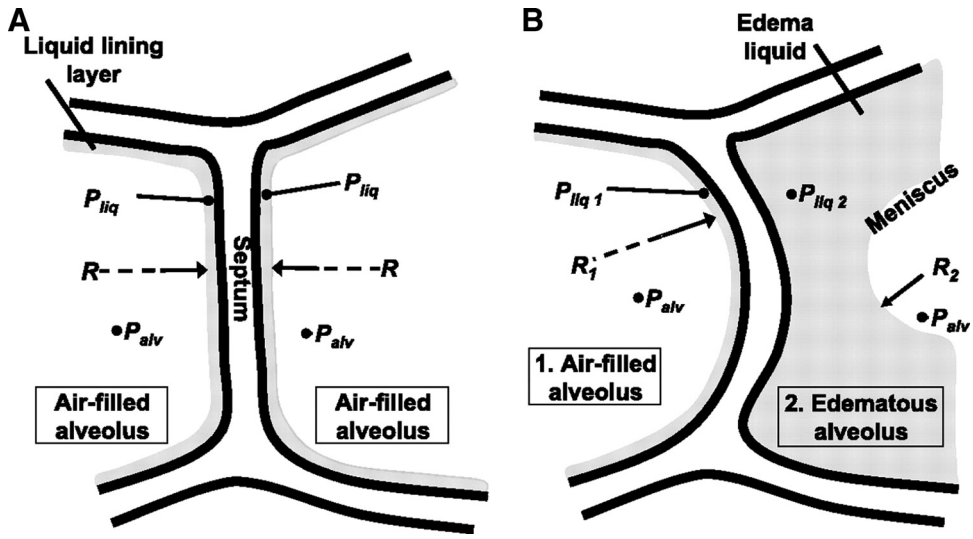

Fig. 8. An example of stress concentration between an air-filled and edematous alveolus. *A*: a model of the forces between air-filled and air-filled alveoli. Alveolar pressure is depicted as P_{alv}. A thin liquid hypophase with liquid pressure lines each alveolus (P_{liq}). The radius (R) of the air-liquid interface is a straight line and thus infinite. All forces are in balance in adjacent air-filled alveoli and thus the septum is planar. *B*: a model of the forces between an air-filled and edematous alveolus. The meniscus results in a smaller radius (R_2) in the edematous alveolus compared with the air-filled alveolus (R_1). The difference in radius generates a greater pressure drop across the air-filled alveolar interface, which in turn results in a lower liquid phase pressure (Pl_{iq2}) in the edematous alveoli (P_{liq1}). The difference in P_{liq} causes the septum to bulge toward the edematous alveoli causing excessive strain. [Published with permission (104).]

plays a critical role in either preventing or inflecting lung injury. The 10 parameters that comprise the MB_P are time at inspiration (T_I), pressure at inspiration (P_I), time at expiration (T_E), pressure at expiration (P_E), transition time from P_E to P_I (ΔT_I), transition time from P_I to P_E (ΔT_E), respiratory rate (RR), tidal volume (VT), inspiratory flow (Q_i), and expiratory flow (Q_E). In addition, the volume of the lung at expiration (functional residual capacity) and at inspiration (% of total lung capacity) is likely to influence the effect of the mechanical breath at the alveolar level. Until we understand how all of the components in the MB_P affect the pulmonary parenchyma, we will not be able to scientifically manipulate the mechanical breath to be optimally protective.

Lung fluid balance and ARDS pathophysiology. To identify whether the MB_P that minimizes tissue strain will reduce pulmonary edema we must refer to the Starling equation for fluid flux and the mechanism of ARDS-induced edema formation. The major components of the Starling equation are the hydrostatic and oncotic pressure gradients between the capillary lumen and the surrounding interstitial tissue, the capillary surface area available for fluid flux, and the permeability of capillary membrane to liquids and proteins. Trauma or sepsis-induced systemic inflammation (SIRS) can increase vascular permeability, which results in edema-induced surfactant deactivation, both of which can cause a disruption in fluid balance described by the Starling equation: $Jv = Lp \cdot PS\ [(Pc - Pi) - \sigma(\pi p - \pi i)]$.

Capillary filtration rate (Jv) is governed by the balance between capillary hydrostatic pressure (Pc) and plasma colloid osmotic pressure (πp), interstitial hydrostatic pressure (Pi) and colloid osmotic pressure (πi), hydraulic conductivity (Lp), surface area available for filtration (PS), and vascular permeability expressed as a reflection coefficient (σ). The combination of low capillary hydrostatic pressure (~7 mmHg) and plasma osmotic pressure (~28 mmHg) provide a strong absorptive force. This positive gradient for absorption is partially offset by a high-baseline tissue protein concentration (πi) that reduces the effective transcapillary colloid osmotic absorptive pressure [$\sigma(\pi p - \pi i)$]. The overall result is a slight gradient favoring fluid movement out of the capillaries (54).

SIRS disrupts this delicate balance by increasing the vascular permeability (σ) causing a shift toward an increased capillary filtration rate (Jv), and by increasing alveolar surface tension, results in a decrease in interstitial hydrostatic pressure (Pi) (39, 54, 101). Recently, this classic Starling equation has been modified to incorporate what is defined as the glycocalyx model of transvascular fluid flux (138). In both Starling models the fluid flux occurs due to transendothelial pressure difference (Pc − Pi). The difference between the classical and glycocalyx Starling models is that the plasma-interstitial colloid osmotic pressure (COP) differences in the modified Starling model fluid flux are governed by transendothelial pressure difference and the plasma-subglycocalyx COP (πsg) difference ($\pi p - \pi sg$) rather than the COP difference between plasma and the interstitial space ($\pi p - \pi i$).

Multiple parameters of the MB_P could affect various components of the Starling equation including Pc, Pi, πsg, and σ, which could dramatically affect lung fluid balance. In addition, the mechanical breath can also directly damage pulmonary epithelial and endothelial cells by mechanical distortion secondary to microstress/strain (124) and inhibit or deactivate pulmonary surfactant (2). An inappropriately set MB_P can exacerbate lung fluid flux by multiple mechanisms, which would explain the ventilator-dependent increase in ARDS mortality (8). Conversely, appropriately adjusted ventilation can minimize stress concentrators (104, 109) and dynamic strain (68, 69) and has been shown to reduce ARDS incidence (58, 119). Thus is it possible that parameters in the MB_P can be set to not only minimize microstrain but to concurrently reduce edema formation?

To understand the effect of the MB_P on lung fluid balance physiology we must recognize the unique relationship of the alveolar vessels (AVs) and extra-alveolar vessels (EAVs) within the lung in their response to positive alveolar pressure delivered by mechanical ventilation. This understanding is key because alveolar pressure and lung inflation have opposite effects on fluid exudation from AVs vs. EAVs. AV capillaries collapse with increased alveolar airway pressure (77). EAVs are larger than capillaries (~100 μm) and expand with increased airway pressure and lung volume due to a reduction in

the interstitial pressure (Pi). Alveolar corner vessels have similar dimensions as AVs (10–20 μm), but like EAVs they expand with increased lung volume (77). Thus increased airway pressure and lung volume would collapse AVs, reducing the permeability surface area (PS) and increasing the Pi surrounding these vessels, both of which would decrease fluid exudate. On the other hand, the same mechanical breath would decrease the Pi surrounding the EAVs and corner vessels, expanding the vessels and increasing fluid exudation. When the lung is fully inflated approximately one-third of the total fluid filtration comes from each of the three vessel types (AVs, venous EAVs, and arterial EAVs) (3). Luchtel et al. (77) have shown that the interstitial space surrounding extra-alveolar veins is contiguous with that of the extra-alveolar arteries and edema fluid, which leaks from these collects up in the periarterial cuffs. Luchtel et al. also showed that the arterial extra-alveolar interstitium plus lymphatics within this interstitium are important for edema drainage, and thus lung volume may be an important edema safety factor.

Overview: MB_P and pulmonary edema. The literature investigating the effect of MB_P on lung fluid balance have focused almost exclusively on only two (VT and PEEP) of the 10 MB_P components. The majority of studies focused on the effect of changes in PEEP (23, 29, 37, 47, 55, 78, 93, 106, 115, 116, 136) with a smaller number investigating the effect of VT and PEEP on lung fluid balance (23, 29). The data demonstrate that if sufficient preemptive PEEP is applied, lung water will be significantly diminished in multiple lung injury models including high vascular pressure (23, 47, 106, 116), high alveolar surface tension (78), high endothelial permeability (29, 55, 93, 115), and high airway pressure (37, 136). Also, PEEP is most effective at reducing edema when applied soon after injury (47, 114). Studies demonstrating that PEEP does not prevent edema applied low levels of PEEP (8–10 cmH_2O) and sometimes reduced this level during the experiment, applied PEEP after edema had already developed, and often used what we have now identified as injurious tidal volumes (15–20 ml/kg) (17, 103, 107). Clinical trials have also shown no benefit of high PEEP when applied in patients with established ARDS in whom edema has presumably already developed (21, 103). This suggests that not only does the combination and magnitude of the MB_P parameters play a role in lung fluid balance, but the timing of application in the course of the disease is also critical to lung protection.

There are numerous possible mechanisms by which PEEP might affect lung fluid balance and edema formation. PEEP increases the vascular transmural pressure secondary to an increase in the interstitial hydrostatic pressure (Pi, Starling equation) opposing fluid movement out of the capillaries (47, 116, 136). For example, in an isolated perfused pig lung preparation Schumann et al. (116) hypothesized high pulmonary vascular pressure would result in edema but that PEEP would prevent the increase in lung water. The results of the experiment were mixed, with PEEP (8 cmH_2O) reducing edema with low perfusion pressures (hydrostatic reservoir 65 cm) but not at high perfusion pressures (hydrostatic reservoir 105 cm). The authors suggest that one reason why edema was not reduced with high vascular pressure may be the use of a relatively low PEEP (8 cmH_2O) and that higher values of PEEP, above the hydrostatic pressure in the vasculature, may yield different results. This makes sense because with very high Pc generated by the reservoir set at 105 cm, PEEP level would have to be sufficiently elevated to raise the Pi to a level at or above Pc to reduce fluid flux. Russell et al. (115) showed in an isolated perfused dog lung with oleic acid injury that PEEP must be higher than pulmonary artery pressure to prevent edema.

PEEP may act to support the integrity of the interstitial matrix. An intact interstitial matrix functions as a low compliance glove surrounding the capillary and plays a key role in restricting capillary fluid filtration (92). As long as the extracellular matrix is intact, edema is contained within the interstitial space. Severe edema develops rapidly once damage to the extracellular matrix reaches a critical tipping point when the fluid restrictive component of the matrix is lost, allowing rapid efflux of fluid from the capillaries through the interstitial space and into the alveolar space (5, 94). The pressure transmitted to the interstitial space (Pi, Starling equation) with PEEP would prevent edema and swelling-induced injury to the extracellular matrix, maintaining this important edema safety factor, preventing the rapid influx of edema and alveolar flooding. These data clearly show that one component of the MB_P, PEEP, can reduce edema accumulation, which is a key pathological component of ARDS (Fig. 3).

It is known that edema can be caused by four basic mechanisms: high capillary pressure, high alveolar surface tension, high capillary endothelial permeability, and high alveolar epithelial permeability. It is important to know whether adjustments to the MB_P can prevent or reduce pulmonary edema accumulation secondary to all four mechanisms, because they may play active role in clinical ARDS pathogenesis.

MB_P (PEEP) effects on high vascular pressure edema. Multiple studies have shown that PEEP can reduce edema accumulation caused by increased vascular pressure (Pc, Starling equation) (23, 47, 106, 116). Fernández Mondéjar et al. (47) used a dog model and elevated pulmonary capillary hydrostatic pressure (Pc, Starling equation) by increasing left atrial pressure (Pla). They demonstrated that a PEEP of 10 or 20 cmH_2O, applied 30 min after Pla was increased prevented further accumulation of edema (but it did not reduce the edema that existed before PEEP application); a PEEP of 20 cmH_2O applied 90 min after Pla was elevated did not prevent edema. Thus PEEP was effective only if it was applied early in the course of the disease. Fernández Mondéjar et al. also showed that 10 but not 20 cmH_2O PEEP increased thoracic duct lymph flow. The mechanism of reduced edema was hypothesized to be a reduction in the transmural pressure gradient [Pla − pleural pressure (Ppl)] where Pla is an approximation of Pc and Ppl is an approximation of Pi [(Pc − Pi), Starling equation].

Bshouty et al. (23) used an in situ canine upper lobe preparation and tested the effect of VT, PEEP, and lung volume on edema formation secondary to elevated vascular pressure. They hypothesized that changes in VT may affect fluid filtration (Jv) but not via the mechanism of changing lung volume. Specifically, Bshouty et al. postulated that increased VT would reduce edema because higher lung volume reduces fluid filtration (Starling equation) and increases fluid removal secondary to increased lymph flow. Surprisingly, their data demonstrated that the rate of edema formation ($\Delta W/\Delta t$) was significantly increased with higher (as compared with lower) VT, but if mean airway pressure was elevated by raising PEEP

to levels equal to those during high VT, the rate of edema formation fell below baseline levels.

Bshouty et al. reasoned that VT-induced edema was not due to reduced lymph flow but rather to an increase in permeability (Lp), or area (PS), or both without changing Pi, πc, πi, or σ. They came to this conclusion because Pcrit (i.e., the critical pressure needed to initiate lung weight gain measured as the intercept of the linear regression of vascular pressure and edema formation) was unaffected during the development of edema (Starling equation). $\Delta W/\Delta t$ increased with large VT and decreased with PEEP even though effective filtration pressure was not significantly different. Because the increase in lung volume was the same in both high VT and high PEEP but the effect on $\Delta W/\Delta t$ was in the opposite direction, the mechanism could not be due to differences in microvascular surface area.

The main difference between the two lung volumes was that large VT was associated with a high lung volume during part of the cycle, and a low volume during the remainder of the ventilator cycle. Because the rate of $\Delta W/\Delta t$ was higher with dynamic ventilation, these data suggest that the effect of lung volume on fluid flux is not linear; rather, it functions in a nonlinear fashion, with a much greater effect on fluid flux taking place at higher volumes. It is possible that the change in Pi with lung inflation may be time dependent, and thus sustained pressure cycles (PEEP) have a greater effect on Pi than dynamic pressure cycles (high VT). Increasing Pi would decrease fluid filtration and reduce edema accumulation, which may be the mechanism of sustained PEEP-induced reduction in edema formation.

These studies demonstrate that both VT and PEEP can reduce edema caused by increased vascular pressure. In addition, the study by Bshouty et al. supports our current understanding of the MB_P parameters that are key to lung protection. Their data showed that dynamic strain caused by high VT caused more edema than a static strain at the same pressures caused by high PEEP. Their data also suggest that the effect of MB_P on Pi is time dependent and thus PEEP is more protective because a higher airway pressure is applied to the alveolus over a longer period of time during each breath. This supports the current studies showing that an extended time at inspiration and a minimal time at expiration reduces ARDS incidence in animals (41, 111–113, 123) and in patients with trauma at high risk of developing ALI (7).

MB_P (PEEP) effects on high surface tension and edema. Luecke et al. (78) in a sheep surfactant deactivation ARDS model (saline lavage) showed by thermal dye dilution technique that sequentially increasing PEEP (0, 7, 14, or 21 cmH_2O) effectively reduced pulmonary edema measured as the extravascular lung water. Following saline lavage, lungs were ventilated with 0 cmH_2O PEEP for 60 min to establish lung injury, and then PEEP was increased in 60-min intervals. Luecke et al. demonstrated that PEEP effectively reduced pulmonary edema accumulation. Some edema had already developed following surfactant washout before application of PEEP, and this edema was not reduced. This supports the findings in high vascular pressure edema (47, 114) that PEEP is most effective at preventing edema before it develops.

Albert (2) recently published a hypothesis stating that ventilation (mechanical or spontaneous)-induced deactivation of surfactant is the initiating pathologic event in EALI rather than increased alveolar capillary permeability, which ultimately leads to established ARDS. If this hypothesis is correct, then mechanical ventilation is the initiating factor in the development of ARDS, and thus blocking at this point will significantly reduce incidence.

It is well established that mechanical ventilation with large VT and low PEEP can cause irreversible compression of surfactant, in turn causing surfactant molecules to be driven toward the airways resulting in surfactant depletion, and that elevating PEEP reduces or prevents this deactivation (42, 57, 84, 136, 139). Maruscak et al. (81) showed that mechanical ventilation with low stretch (VT 8 ml/kg + PEEP 5 cmH_2O) prevented surfactant deactivation compared with high stretch (VT 30 ml/kg + PEEP 0 cmH_2O). More importantly, they demonstrated that alterations in surfactant were a consequence of the ventilation strategy and thereby contribute directly to lung dysfunction over time. Arold et al. (9) demonstrated that variable ventilation in a saline lavage ARDS model improved oxygenation and increased surfactant and attenuated alveolar protein concentrations without the need for high airway pressures and volumes (9). Surfactant deactivation secondary to mechanical ventilation can be slowed or prevented by application of sufficient PEEP. Malloy et al. (80) showed in sepsis-induced lung injury that application of PEEP (5 cmH_2O) significantly reduced surfactant deactivation and preserved lung function. Thus surfactant dysfunction caused by inappropriate mechanical ventilation could be the engine that drives progressive ALI. However, just slighting modifying the MB_P by increasing PEEP or decreasing VT can have a dramatic effect on preventing ventilation-induced surfactant deactivation and on accumulation of pulmonary edema.

MB_P and vascular permeability. Many studies have also shown that altering the MB_P can reduce edema formation in high vascular permeability-induced edema (29, 55, 93, 115). In a pig oleic acid model, Colmenero-Ruiz (29) showed that application of PEEP (10 cmH_2O) immediately following oleic acid infusion reduced pulmonary edema, and that a concomitant reduction in VT further reduced the accumulation of lung water. Similarly, Russell et al. (115) showed that if PEEP were set higher than the pulmonary artery pressure, edema would be blocked in an in situ isolated perfused lung model with oleic acid injury. One possible mechanism is that PEEP normalizes σ by stabilizing alveoli and thus preventing the cyclic stretch of the alveolar endothelium (34, 61). It has been shown that rapid Ca^{2+} entry through transient receptor potential vanilloid-4 (TRPV4) channels is the major determinant of an increase in alveolar capillary permeability (61, 98). TRPV4 receptors are stretch sensitive and are thus likely candidates for a stretch-activated increase in alveolar capillary permeability secondary to cyclic stretch (i.e., alveolar instability) during tidal ventilation (5). Another mechanism could be elevation of Pi thus shifting the balance of the Starling equation away from fluid egress from the capillaries even with an increase in σ. This hypothesis is supported by the work of Russell et al. (115) who demonstrated that if PEEP were higher than pulmonary artery pressure, then edema would be prevented.

MB_P and complex pathophysiology. Pulmonary edema caused by an increase in vascular flow and pulmonary artery pressure (35 mmHg) was significantly reduced with the addition of PEEP (15 cmH_2O), however, the protective effect of PEEP was lost when a second hit (oleic acid) was infused into the circuit of an isolated perfused rabbit lung preparation (106).

These data suggest that edemogenic factors are cumulative and that altering a mechanical breath parameter, in this case increasing PEEP to prevent edema following a single insult may not be effective with multiple insults. This is an important concept because patients being treated for sepsis or trauma are often exposed to many edemogenic alterations (i.e., changes in vascular permeability, increased vascular pressures with fluid and blood infusions, reduction in plasma oncotic pressures) concomitantly.

In a study using HCl instillation to increase Lp, σ, and alveolar surface tension in dogs, it was shown that surfactant replacement combined with PEEP was necessary to reduce edema accumulation (142). Exogenous surfactant treatment, PEEP, or both were applied 1 h after HCl injury. Edema that accumulated before treatment was not reduced, again supporting the hypothesis that protective ventilation works only if applied very early, but further increases in edema were prevented only in the surfactant + PEEP group. Although Lp and σ were not directly measured, Zucker et al. (142) believed that these were not a mechanism to explain surfactant or PEEP-induced normalization of these values that were very likely altered by exposure to HCl. Zucker et al. concluded that reestablishment of normal surface tension would increase pulmonary interstitial pressure (Pi, Starling equation), reduce the hydrostatic pressure gradient across the extra-alveolar vessels, and thus prevent further edema formation. PEEP was necessary to open alveoli and redistribute edema so that the exogenous surfactant could reestablish normal surface tension on the alveolar surface. In addition, PEEP would also increase Pi and thus would additively or synergistically result in lower alveolar surface tension. Finally, Mead et al. (88) hypothesized that the combination of PEEP and surfactant replacement might result in a more homogeneous ventilation, thus restoring alveolar interdependence (Fig. 6) and reducing the development of stress concentrators (104, 109).

This hypothesis was supported by Corbridge et al. (30) who showed that lowering VT + increasing PEEP led to significantly reduced edema in an HCl-induced lung injury model in dogs. Surfactant function was assessed using whole lung pressure volume curves, and Corbridge et al. hypothesized that the larger VT and lower PEEP led to depleted surfactant, which was preserved by a reduction in VT and an increase in PEEP. An alternative hypothesis would be that the low PEEP and higher PEEP opened the lung-reducing stress concentrators and minimized dynamic strain by preventing alveolar collapse and reopening. It is very possible that minimizing strain injury to the alveolus combined with preservation of surfactant function worked synergistically to reduce edema formation.

Summary. Modification of the MB_P early in ARDS pathogenesis can reduce pulmonary edema. The vast majority of studies have investigated only singularly the role of one MB_P parameter, PEEP, on edema development. These studies have shown that adequate PEEP applied early can block edema accumulation in high capillary pressure, high alveolar surface tension, high airway pressure, and high permeability-induced lung injury. Deconstruction of the entire mechanical breath will be necessary to identify the optimal combination of MB_P parameters, in addition to PEEP, necessary to optimally prevent edema formation. In conjunction with using mechanical ventilation to reduce edema formation, conservative fluid management should also be part of the total treatment package (110).

Optimizing the Mechanical Breath

Designing the optimally protective mechanical breath. To effectively block progressive ALI we must use the physiological knowledge that the primary mechanisms of VILI are stress concentrators and dynamic strain, and then design a mechanical breath that will block both. A critical need exists to identify the effect of mechanical breath on pathophysiology at the alveolar level; if we overlook alveolar function we in fact would subject patients to ventilation by trial and error. An inappropriately set mechanical breath intensifies the pathological tetrad (Fig. 3), exacerbating the damage caused by either primary (pneumonia) or secondary (sepsis, trauma, hemorrhagic shock) injuries that can progress into established ARDS. A major reason why identification of this optimally protective breath has been so difficult is the reductionist approach used in an attempt to answer the question. The mechanical breath consists of multiple parameters (i.e., airway pressures, volumes, rates, flows, and the duration these parameters are applied during each breath), all of which individually and in combination may cause structural damage to the alveoli. The current standard-of-care ventilation for established ARDS focuses on only three of these breath parameters: VT, Pplat, and PEEP (8). To identify the optimally protective breath we need to deconstruct the mechanical breath and determine which parameters in which combination and magnitude minimize the pathological progression of ALI.

Time is a key MB_P parameter in lung protection. In principle, the combination of MB_P parameters that would maintain a homogeneously ventilated lung and alveolar stability would be most protective. A mechanical breath with an extended duration at inspiration (T_I) during each breath would in theory recruit and maintain lung homogeneity. A small VT or a very short duration at expiration (T_E) would theoretically stabilize alveoli, preventing subsequent collapse and reopening. It could be argued that the MB_P that would seem to maximize both of these components may be high-frequency oscillatory ventilation (HFOV). However, early application of HFOV in patients with ALI did not improve clinical outcomes and indeed actually increased mortality (43, 141). From a purely physiological perspective it is hard to understand why these studies did not show improvement because this MB_P was targeted to what we currently believe to be the primary mechanisms of mechanical damage to the lung parenchyma. It has been postulated that the lack of efficacy in these studies was not due to failure to prevent mechanical damage to the pulmonary parenchyma, but rather to multiple other factors, including hemodynamic compromise in the HFOV group requiring increased pressor medication, end-organ failures, and application after rather than before established lung injury (79).

Multiple studies have shown that a combination of low VT, recruitment maneuvers, and PEEP do reduce the incidence of ARDS among high-risk patients undergoing surgery or being cared for in an ICU (7, 35, 49, 50, 52, 53, 58, 66, 72, 119). The low VT breath should reduce dynamic alveolar strain but it may not be as effective as HFOV at homogeneous lung ventilation (which would reduce stress concentrators) unless recruitment maneuvers with sufficient PEEP were added to

prevent the newly opened alveoli from recollapsing (60). Although HFOV was applied during early ARDS, the patients nevertheless had significant lung injury at the time of treatment. In all of the preemptive low-VT studies, the treatment was applied prophylactically, when the lungs were still normal. This suggests that the timing of the treatment may be essential to improved outcomes.

A major problem with the current standard of care is that it is a one-size-fits-all strategy with all patients receiving a VT of 6 ml/kg and a sliding PEEP, and FI_{O_2} on the basis of oxygenation (8). Thus the ability to personalize the mechanical breath to the lung pathology of each patient remains a significant clinical problem. The "Open Lung" strategy attempts to personalize the mechanical breath by optimally setting PEEP following a recruitment maneuver (RM) based on physiological parameters that include best dynamic tidal compliance (125), best Pa_{O_2} (18), best stress index (126), and upper and lower infection points (6). Although the approach is sound in principle, it has multiple problems: *1*) it is not preemptive and sufficient lung damage has already occurred necessitating an RM; *2*) there can be negative side effects so RMs cannot be conducted very often; *3*) because RMs can be applied so infrequently the lung may recollapse resulting in heterogeneous ventilation; and *4*) alveoli may become more unstable

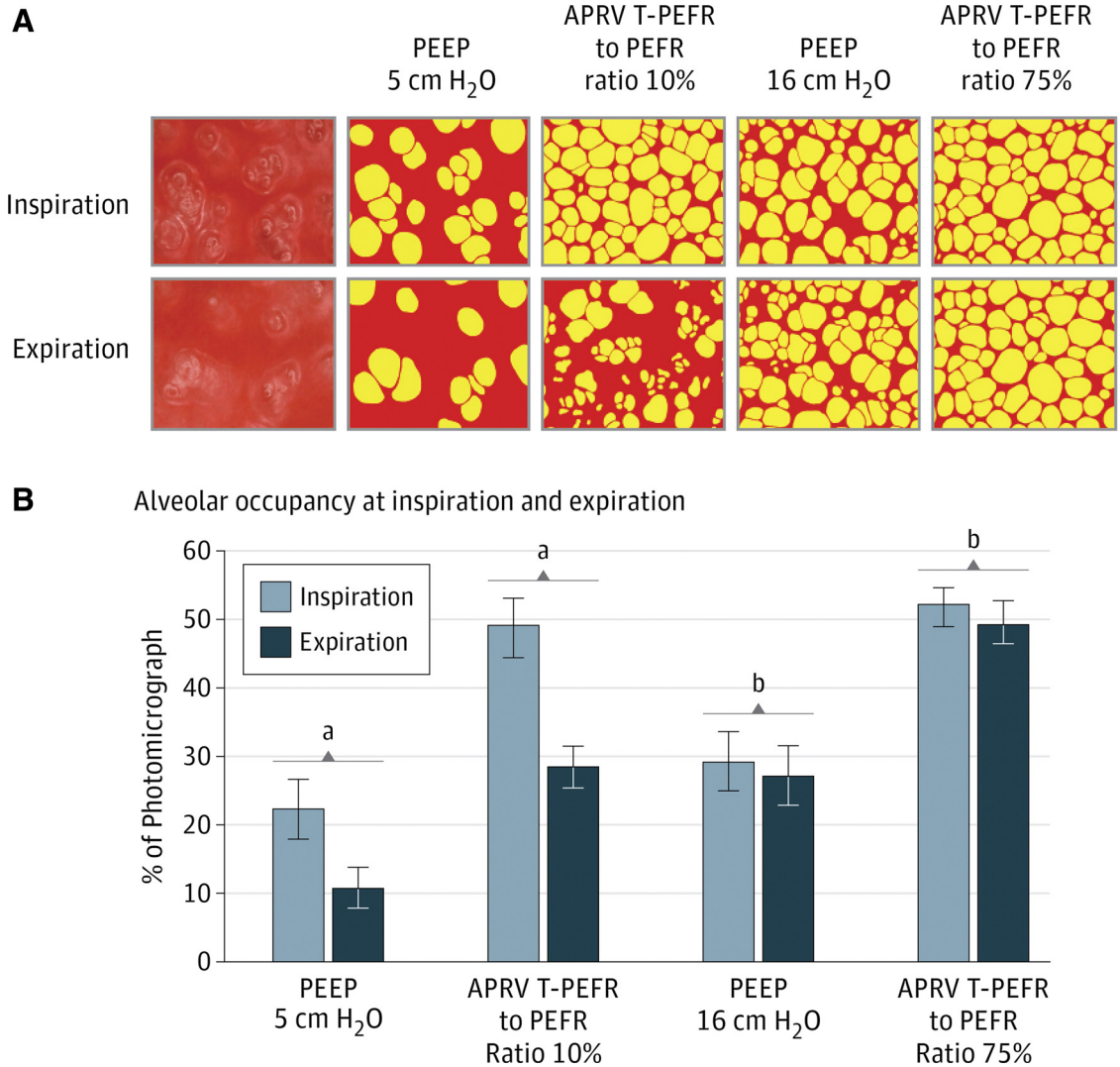

Fig. 9. Effect of four different mechanical breath strategies on both dynamic alveolar strain (DS) and generation of stress concentrators (S-C). In vivo videomicroscopy of subpleural alveoli in a surfactant deactivation model of ARDS was used to identify areas of S-C (i.e., areas of heterogeneous alveolar ventilation) and DS (i.e., a large change in alveolar size during tidal ventilation). Inflated alveoli appear yellow, and collapsed alveoli appear as an amorphous red mass. Areas of both inflated and collapsed alveoli were measured using computer image analysis. *A*: photomicrographs of the same subpleural alveoli at inspiration and expiration subjected to four different mechanical breath strategies: *1*) low VT (6 ml/kg) + PEEP (5 cmH_2O); *2*) low VT + PEEP 16; *3*) airway pressure release ventilation (APRV) with the time at expiration (T_{Low}, not indicated on the figure) set inappropriately long at ratio 10% of the ratio of termination of peak expiratory flow rate (T-PEFR) to the peak expiratory flow rate (PEFR); and *4*) APRV with an appropriately set very short T_{Low} at ratio 75% T-PEFR/PEFR. Heterogeneous ventilation is defined as collapsed alveoli adjacent to inflated and have been show to generate stress concentrators (109). *B*: alveolar homogeneity and stability were assessed as the percent of the microscopic field occupied by inflated alveoli at inspiration and expiration. Few alveoli were open at inspiration with Low VT +PEEP 5 (high S-C), and many alveoli collapsed and reopened during ventilation (high DS). APRV ratio 10% resulted in homogeneous alveolar inflation (low S-C) at inspiration but many alveoli collapsed during expiration (high DS). Low VT PEEP 16 did not result in homogeneous alveolar inflation at inspiration (high S-C) but it did stabilize alveoli (low DS). APRV ratio 75% resulted in homogeneous ventilation (low S-C) and alveolar stability (low DS). [Published with permission (68)].

with disease progression such that the PEEP initially necessary to prevent alveolar collapse may no longer be sufficient, resulting in alveolar micro-strain-induced lung damage.

Bellardine Black et al. (11) have shown that dynamic respiratory resistance and elastance can be used to personalize the PEEP setting to each patient. That study demonstrated that dynamic respiratory mechanics are very sensitive to mechanical heterogeneities in the lung and that minimizing mechanical heterogeneities, with personalized PEEP, maximizes Pa_{O_2} and minimizes peak-to-peak airway pressure (11). Another possible technique to personalize the protective breath is the use of the expiratory flow curve to identify changes in lung mechanics with airway pressure release ventilation (APRV) (111). It has been shown that using the expiratory flow curve to set the time at expiration (T_{Low}) will stabilize alveoli (68, 69, 113) and reduce acute lung injury (113). In combination, these studies show that it is possible to personalize the protective breath to lung pathology.

The role of an extended duration during inspiration (T_I) and minimal duration at expiration (T_E) in reducing ARDS incidence was tested in multiple animal models and in a clinical meta-analysis (7, 41, 68, 69, 111–113). In these studies the APRV mode was used as a tool to precisely control the duration of inspiration and expiration. As with HFOV, an extended T_I and minimal T_E should maintain homogeneous ventilation and prevent alveolar collapse using APRV. The animal studies clearly show that an MB_P with this time profile will indeed reduce ARDS incidence (41, 111–113), and this suggests that the mechanism of protection occurs by reducing both stress concentrators (Fig. 8) with homogeneous inflation and by minimizing dynamic strain by preventing subsequent alveolar collapse and reopening with each breath (Fig. 9) (68). Computational modeling has confirmed that this time-dependent MB_P with an extended time at high pressure and minimal time at low pressure both recruited and stabilized alveoli (123). Although the only clinical study investigating this time-dependent MB_P was a statistical analysis, it clearly demonstrated a reduction in ARDS incidence compared with the current standard of care in 16 other hospitals (7). It is important to note that in these animal experiments the time-dependent MB_P was applied when the lungs were still clinically normal (41, 111–113). Thus these studies support the clinical evidence that early application of low VT and PEEP will reduce ARDS incidence in high-risk patients undergoing surgery or receiving care in an ICU (58, 119).

Summary. The homogeneously ventilated lung is structurally sound and alveoli are very resistant to overdistension or collapse (Figs. 5 and 6) (88, 137). However, trauma, sepsis, or hemorrhagic shock can result in a serious systemic inflammatory response syndrome (SIRS) that initiates a pathological tetrad (Fig. 3) (4, 62, 67, 86), which significantly disrupts normal homogeneous ventilation resulting in stress concentrators (Fig. 8) (104, 109) and dynamic strain (Fig. 9) (68). If preemptive mechanical ventilation is applied following SIRS but before clinical symptoms of the tetrad appear, the incidence of ARDS can be reduced (Fig. 2) (58, 119). The entire MB_P must be deconstructed to determine the optimal breath to reduce ARDS incidence. Currently, physiological studies suggest that an MB_P with an extended time at inspiration and minimal time at expiration is optimal at blocking progressive ALI (41, 111–113). One systematic review supports this finding in patients being treated for trauma (7).

CONCLUSIONS

Once established, ARDS is refractory to treatment with only low VT and proning showing any improvement in mortality in phase III clinical trials. Even with these treatment strategies it has been shown that ARDS mortality has not significantly declined, remaining recalcitrant at nearly 40% (105, 131, 134). Evidence shows that ARDS is a progressive disease, and if treatment is applied early, then disease progression can be blocked. Numerous clinical studies have shown that the incidence of ARDS can be significantly reduced through a combination of low VT, lung recruitment, and PEEP applied to patients with normal lungs undergoing surgery or being treated in an ICU (58, 119). However, one study has shown that low VT with low PEEP led to an increase in mortality and thus the optimally preemptive mechanical breath necessary to block progressive ALI remains unknown (72). Studies in several animals models (41, 111–113) and a clinical statistical analysis (7) have shown that a mechanical breath with an extended duration at peak inspiration and minimal duration at end expiration is effective at reducing ARDS incidence, suggesting that the parameter of time during which the airway pressures are applied to the lung in each breath is an important component in lung protection. The primary mechanical mechanisms of progressive ALI are *1*) stress concentrators on alveolar walls between adjacent air-filled and collapsed or edema-filled alveoli; *2*) dynamic strain on alveolar walls during collapse and reopening; and *3*) stress-failure of overdistended small airways with high pressure leading to pneumothorax. The mechanical breath that will be effective at preventing this mechanical injury must convert heterogeneously to a homogeneously ventilated lung to eliminate stress concentrators and prevent alveolar collapse and reopening, thus minimizing dynamic strain. This must occur without having to apply excessively high airway pressures to prevent airway stress-failure. In addition to minimizing mechanical damage to the lung, a properly adjusted mechanical breath can reduce or prevent pulmonary edema development and preserve surfactant function, both of which are hallmarks of ARDS pathophysiology. Application of such an MB_P before the lung is injured and begins to remodel may also be critical. These data combined suggest that a properly adjusted mechanical breath can dramatically reduce the mechanical damage to the lung known as VILI and also prevent two of the primary pathologies associated with ARDS: pulmonary edema and surfactant deactivation.

Future work must expand upon the current reductionist strategy of testing the protective potential of just one mechanical breath parameter at a time. The entire mechanical breath profile containing all airway pressures, flows, volumes, rates, and time during each breath that these parameters are applied to the lung must be concomitantly analyzed to identify the optimally protective breath. Some of the MB_P parameters have been shown to reduce mechanical damage to lung tissue and reduce edema and preserve surfactant function. Low VT, adequate PEEP, an extended duration at peak pressure and minimal duration at end-expiration have all been shown to be important components in the protective mechanical breath. Ultimately, we need to identify which mechanical breath pa-

rameters, in which combination and at which magnitude, are most effective at preventing progressive ALI. Once the MB_P is identified and applied to all patients before the onset of lung injury, the incidence of ARDS may be reduced to near zero.

DISCLOSURES

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

AUTHOR CONTRIBUTIONS

G.F.N. drafted manuscript; G.F.N., L.A.G., and N.M.H. edited and revised manuscript; G.F.N., L.A.G., and N.M.H. approved final version of manuscript.

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