Mechanical Breath Profile of Airway Pressure Release Ventilation
The Effect on Alveolar Recruitment and Microstrain in Acute Lung Injury

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Importance
Improper mechanical ventilation settings can exacerbate acute lung injury by causing a secondary ventilator-induced lung injury. It is therefore important to establish the mechanism by which the ventilator induces lung injury to develop protective ventilation strategies. It has been postulated that the mechanism of ventilator-induced lung injury is the result of heterogeneous, elevated strain on the pulmonary parenchyma. Acute lung injury has been associated with increases in whole-lung macrostrain, which is correlated with increased pathology. However, the effect of mechanical ventilation on alveolar microstrain remains unknown.

Objective
To examine whether the mechanical breath profile of airway pressure release ventilation (APRV), consisting of a prolonged pressure-time profile and brief expiratory release phase, reduces microstrain.

Design, Setting, and Participants
In a randomized, nonblinded laboratory animal study, rats were randomized into a controlled mandatory ventilation group (n = 3) and an APRV group (n = 3). Lung injury was induced by polysorbate lavage. A thoracotomy was performed and an in vivo microscope was placed on the lungs to measure alveolar mechanics.

Main Outcomes and Measures
In the controlled mandatory ventilation group, multiple levels of positive end-expiratory pressure (PEEP; 5, 10, 16, 20, and 24 cm H2O) were tested. In the APRV group, decreasing durations of expiratory release (time at low pressure [Tlow]) were tested. The Tlow was set to achieve ratios of termination of peak expiratory flow rate (T-PEFR) to peak expiratory flow rate (PEFR) of 10%, 25%, 50%, and 75% (the smaller this ratio is [ie, 10%]), the more time the lung is exposed to low pressure during the release phase, which decreases end-expiratory lung volume and potentiates derecruitment). Alveolar perimeters were measured at peak inspiration and end expiration using digital image analysis, and strain was calculated by normalizing the change in alveolar perimeter length to the original length. Macrostrain was measured by volume displacement.

Results
Higher PEEP (16-24 cm H2O) and a brief Tlow (APRV T-PEFR to PEFR ratio of 75%) reduced microstrain. Microstrain was minimized with an APRV T-PEFR to PEFR ratio of 75% (mean [SEM], 0.05 [0.03]) and PEEP of 16 cm H2O (mean [SEM], 0.09 [0.08]), but an APRV T-PEFR to PEFR ratio of 75% also promoted alveolar recruitment compared with PEEP of 16 cm H2O (mean [SEM] total inspiratory area, 52.0% [2.9%] vs 29.4% [4.3%], respectively; P < .05). Whole-lung strain was correlated with alveolar microstrain in tested settings (P < .05) except PEEP of 16 cm H2O (P > .05).

Conclusions and Relevance
Increased positive-end expiratory pressure and reduced time at low pressure (decreased Tlow) reduced alveolar microstrain. Reduced microstrain and improved alveolar recruitment using an APRV T-PEFR to PEFR ratio of 75% may be the mechanism of lung protection seen in previous clinical and animal studies.

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In patients with acute lung injury, mechanical ventilation is a lifesaving treatment. However, mechanical ventilation may cause a secondary ventilator-induced lung injury (VILI) exacerbating the original acute lung injury. Several mechanisms of VILI have been described, including pressure gradient-induced tissue trauma from repetitive alveolar collapse and expansion, also known as atelectrauma and volutrauma. Alveolar heterogeneity and instability exacerbates these mechanisms. Despite implementation of ventilation strategies to protect against both atelectrauma and volutrauma, mortality from acute respiratory distress syndrome (ARDS) remains unacceptably high. Protti et al developed a technique of measuring whole-lung stress and strain and demonstrated that dynamic lung strain was more injurious than static strain. Their data suggest a novel method of determining the effects of the different components that compose the mechanical breath profile (MBP), including volumes, flows, pressures, rates, and the time that these forces are applied, on lung pathology. This knowledge may be used to optimize protective ventilation and reduce injury. Mechanical ventilation (CMV) was verified by demonstrating regional and alveolar inhomogeneity of mechanical ventilation. Prior to randomization, in order to standardize the volume history of the lungs, the animals were maintained on low tracheal VT ventilation (tracheal VT = 6 mL/kg) with a respiratory rate of 55 breaths/min and positive end-expiratory pressure (PEEP) of 5 cm H₂O with incrementally increasing PEEP (10, 16, 20, and 24 cm H₂O). Animals were ventilated at each setting for 5 minutes to acclimate and standardize the volume history. The in vivo microscope was placed as described and videos were recorded with a high-definition video camera (Allyed Visions Stingray F-145C) for 5 ventilator cycles at each ventilation setting.

**CMV Group**

Rats were maintained on low tracheal VT ventilation (tracheal VT = 6 mL/kg) with a respiratory rate of 55 breaths/min and PEEP of 5 cm H₂O with incrementally increasing PEEP (10, 16, 20, and 24 cm H₂O). Animals were ventilated at each setting for 5 minutes to acclimate and standardize the volume history. The in vivo microscope was placed as described and videos were recorded with a high-definition video camera (Allyed Visions Stingray F-145C) for 5 ventilator cycles at each ventilation setting.

**APRV Group**

Rats were maintained at a Pₜₕₕₜ of 35 to 40 cm H₂O for a time (Tₜₕₕₜ) of 1.9 to 2.0 seconds, which was set to occupy approximately 90% of the ventilator cycle. The release pressure (Pₑₕₑₕₑₜ = 0 cm H₂O) was applied for a time (Tₑₕₑₕₑₜ) between 0.13 and 0.40 second. The peak expiratory flow rate (PEFR) is defined as the greatest absolute flow rate during the release from Pₑₕₑₕₑₜ. The flow rate at the termination of PEFR (T-PEFR) was altered by varying the Tₑₕₑₕₑₜ to set the ratio between T-PEFR and PEFR to be 10%, 25%, 50%, or 75%. Rats were acclimated to each ventilator setting for 5 minutes prior to having in vivo microscopic fields recorded for 5 ventilator cycles.
veoli at both peak inspiration and end expiration (Figure 1A) using PhotoShop CS6 (Adobe Inc). Individual alveolar perimeters and areas were quantified using Image-Pro Plus (Media-Cybernetics). Individual alveolar area and total alveolar air space area were calculated as a percentage of total frame area. For each ventilation mode, the mean and standard deviation of the individual alveolar area were calculated. Change in individual alveolar area between inspiration and expiration, representing a surrogate for alveolar Vₜ, was then calculated and the number of pixels along the perimeter of each alveolus was measured to analyze microstrain. Alveoli that were visually lost between inspiration and expiration were assumed to have totally collapsed and were designated values of 0% for area and 0 pixels for perimeter.

The primary outcome of interest was microstrain, which was calculated as the change in length of the alveolar wall normalized by the original length: microstrain = ΔL/L₀, where ΔL is the change in perimeter length between inspiration and expiration and L₀ is the original perimeter length at expiration.

As previously described, the pressure-time integral (PTI) was calculated using direct measurements from the ventilator. The PTI calculates the degree of pressure applied to the lung over a given ventilator cycle (inspiration plus expiration or expiration only release). It describes 1 ventilator cycle but does not take into account the difference between total cycle times in the 2 ventilation modes. To account for the ventilation frequency f, we define a normalized PTI over a minute, PTI · f.

Macrostrain
To define macrostrain for similar treatment conditions, another group of rats was randomized to CMV (n = 3) or APRV (n = 3). Rats were anesthetized and surfactant deactivation was induced via intratracheal polysorbate instillation as described earlier.

Macrostrain was calculated as the relative change in total lung volume: macrostrain = ΔV/V₀, where ΔV represents the change in lung volume between inspiration and expiration and V₀ represents the end-expiratory lung volume (EELV).

Lungs were excised via thoracotomy. Macrostrain for the settings with the least microstrain (PEEP 16 cm H₂O; APRV T-PEFR to PEFR ratio 75%) and greatest microstrain (PEEP 5 cm H₂O; APRV T-PEFR to PEFR ratio 10%) within each group was assessed. The excised lungs were ventilated for 5 minutes and then the trachea was clamped at peak inspiration (Vᵢ) and end expiration (Vₑ). The volumes were measured by the volume of water displaced in a graduated cylinder so that ΔV = Vᵢ - Vₑ.

### Results

Changing both PEEP and Tₗow dramatically affected alveolar recruitment at both peak inspiratory pressure and end-expiratory pressure (Figure 1). The APRV T-PEFR to PEFR ratios of both 10% and 75% caused greater alveolar recruitment at peak inspiratory pressure compared with CMV at PEEPs of 5 and 16 cm H₂O (Figure 1). The largest expiratory derecruitment was seen with PEEP of 5 cm H₂O and an APRV T-PEFR to PEFR ratio of 10%. An APRV T-PEFR to PEFR ratio of 75% caused maximal inspiratory recruitment and minimal expiratory derecruitment (Figure 1).

The values of microstrain and macrostrain, the percentage of the photomicrograph occupied by alveoli (total alveolar area), the alveolar Vₜ, the number of alveoli, and PTI · f are listed in the Table and eTable 1 in the Supplement. A PEEP of 16 cm H₂O and an APRV T-PEFR to PEFR ratio of 75% resulted in minimal microstrain (mean SEM, 0.09 [0.08] and 0.05 [0.03], respectively) and caused minimal change in alveolar Vₜ (mean [SEM], 0.06% [0.07%] and 0.07% [0.03%], respectively). With APRV, a greater number of alveoli were recruited at inspiration with all Tₗow settings (ie, a large percentage of total alveolar...
The relationship between the alveolar air space occupancy at inspiration (which represents the combined effects of alveolar recruitment and alveolar VT) and the microstrain at inspiration (which represents the combined effects of all ventilator settings in APRV) was significant. The PTI \(\cdot f\) value was higher in APRV compared with CMV at all ventilator settings. The APRV T-PEFR to PEFR ratio of 75% had the highest PTI \(\cdot f\) (mean [SEM], 34.46 [0.94] cm\(H_2O\) \cdot breaths/min), the greatest total alveolar area at both inspiration (mean [SEM], 52.0% [2.9%]) and expiration (mean [SEM], 49.6% [3.2%]), and the lowest microstrain (mean [SEM], 0.05 [0.03]) and alveolar VT (mean [SEM], 0.07% [0.03%]) of all ventilator settings within APRV.

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PEEP of 16 cm H₂O (macrostrain, 0.10 [0.04]; microstrain, 0.09 [0.08];  P > .05) (Figure 4).

Details of the mechanical breath profile settings for both CMV and APRV are shown in eTable 2 in the Supplement.

Discussion

This study provides novel insights into the effect of mechanical ventilation on dynamic alveolar strain in the acutely injured lung using in vivo microscopy. We have shown that alveoli can be stabilized and microstrain reduced by either setting PEEP in CMV above alveolar critical closing pressure or by setting a sufficiently brief T₀ in APRV to maintain the end-expiratory release pressure above alveolar critical closing pressure. We have also found that an APRV T-PEFR to PEFR ratio of 75% optimized both alveolar recruitment and alveolar stability (ie, minimized microstrain) compared with all other groups. In addition, we have shown that whole-lung measurements such as the delivered Vᵣ and macrostrain are not always adequate markers of the regional microenvironment, as described by alveolar Vᵣ and microstrain. Moreover, APRV represents a low alveolar Vᵣ ventilation strategy despite greater tracheal Vᵣ. This study suggests that the appropriately adjusted APRV MBP (APRV T-PEFR to PEFR ratio of 75%) may be optimal (of the MBPs tested in this study) to protect the acutely injured lung because it results in maximal alveolar recruitment and minimal alveolar microstrain.

Lung Stress and Strain and VILI

Brunner and Wysocki¹⁵ developed a stress-strain index to determine the optimal MBP to minimize both stress and strain. Using a computational model, they determined that the stress-strain index increased markedly when EELV is reduced. Reducing EELV presumably increased alveolar tidal recruitment and derecruitment, suggesting that the larger the change in lung volume is with each breath, the higher the stress-strain index is. Corroborating these findings in a porcine model, Protti et al⁶ induced dynamic strain by decreasing the level of PEEP (reducing EELV) and increasing the tracheal Vᵣ. The study...
by Protti and colleagues clearly demonstrated that dynamic strain significantly increased VILI compared with static strain, even though the global strain was identical. Tschumperlin et al\textsuperscript{6} described similar findings using an in vitro model in which alveolar epithelial type II cells were exposed to identical degrees of peak deformation but varying degrees of static or dynamic deformation. They showed that large deformation amplitudes increased cell death, and minimizing these amplitudes improved alveolar epithelial cell viability. This study combined with those by Brunner and Wysocki\textsuperscript{15} and Protti et al\textsuperscript{6} support the hypothesis that dynamic strain causes more pulmonary injury than the same level of static strain.\textsuperscript{20} Our study builds on the work of these investigations by elucidating the features of the MBP that minimize lung volume loss at end expiration, thereby reducing microstrain. Specifically, we demonstrate that reducing EELV by either increasing T\textsubscript{low} (T-PEFR to PEFR ratio of 10%) in the APRV group or decreasing PEEP (5 cm H\textsubscript{2}O) in the CMV group significantly increased microstrain.

To recruit the lung and maintain recruitment,\textsuperscript{17} inspiratory pressures must be greater than the critical opening pressure and PEEP must be set above the critical closing pressure to prevent derecruitment.\textsuperscript{18,19} In addition, there is latency to both recruitment and derecruitment such that a finite period is necessary for an alveolus to close when the airway pressure falls below the critical closing pressure.\textsuperscript{19,20} In a randomized trial of 20 patients, Hodgson et al\textsuperscript{21} assessed critical closing pressure and PEEP must be set above the critical closing pressure to prevent derecruitment. 6,15,16 Thesedata provide theoretical support for prior assertions that the technique of APRV application (ie, appropriate titration of the release phase) is essential to achieving the lung-protective outcomes described in prior articles.\textsuperscript{23}

### Alveolar Recruitment

All settings of the APRV MBP used in our study demonstrated a greater number of open alveoli at inspiration compared with all CMV settings. We hypothesize that the observed improvements in alveolar recruitment occurred because of the increased time at the plateau pressure and reduced time at the release phase (increased PTI).\textsuperscript{20,24} The plateau pressures of APRV and high PEEP (20 and 24 cm H\textsubscript{2}O) were similar but the time over which plateau pressure was applied was up to 5 times longer in the APRV group, yielding an increased PTI.\textsuperscript{20} There is a strong time dependence to alveolar reopening as demonstrated by continued recruitment over a 40-second period of sustained plateau pressure in a rat saline lung lavage–induced acute lung injury.\textsuperscript{20} Therefore, APRV favors recruitment due to sustained plateau pressures, which facilitate reopening, and brief excursions to low pressure that do not allow time for the recruited units to close.

### Macroventilation vs Microventilation

Previous studies demonstrated that APRV yields an increase in tracheal VT over time, raising concerns that APRV is not a low VT ventilation strategy.\textsuperscript{13,25,26} These findings bring to light the important distinction between macroventilation and microventilation. The VT measured at the endotracheal tube may not accurately reflect distribution of volume over the alveolar units. For example, a lung with 50% derecruitment ventilated at 6 mL/kg may have greater localized distention than an open lung ventilated at 10 mL/kg owing to the reduced number of ventilated alveoli in the collapsed lung. In our study, alveolar VT was similar between an APRV T-PEFR to PEFR ratio of 75% and PEEP of 16 cm H\textsubscript{2}O, but the APRV T-PEFR to PEFR ratio of 75% had a significantly greater tracheal VT (Figure 3). We postulate that this discordance occurred because the APRV T-PEFR to PEFR ratio of 75% increased the number of alveoli over which the tracheal VT was distributed. When describing volutrauma as a potential source of VILI, it is important to recognize that volutrauma does not describe the topographical distribution of regional VT. Volume distribution is strongly dependent on derecruitment. Therefore, regional or alveolar volutrauma may be a more important indicator of lung injury than whole-lung volume.\textsuperscript{3,6,27}
Calculating the distribution of stresses and strains in a living, 3-dimensional system with interdependence of the pulmonary units is extremely complex. Protti et al have pioneered a method for approximating global pulmonary stress and strain using transpulmonary pressure and volume change, respectively. Unfortunately, this technique does not provide insight into regional microstress and microstrain experienced by individual alveoli due to volutrauma and atelectrauma. As we have shown in this study, macrostrain is not indicative of microstrain at the alveolar level. For instance, small global strain in lungs may lead to significantly larger local strains owing to the heterogeneity and complex interdependence of alveoli, particularly in the injured lung. Current clinical management relies on global parameters even though these may not reflect the regional lung micromechanics. This approach does not explicitly account for regional heterogeneity; it does, however, represent the best possible approach given the limitations of current clinical diagnostic tools.

The importance of maintaining patency using techniques such as APRV is highlighted by Mead et al, who demonstrated that simulations of nonuniform alveoli result in a 13% increase in stress compared with a uniform system. Similarly, Rausch et al determined that local strains could achieve levels up to 4 times that of the global strain in rat lungs using image-based 3-dimensional finite-element simulations. It is clear that use of global parameters to manage protective mechanical ventilation in patients may be inaccurate and knowledge of the effect of any MBP at the microanatomical level is essential. We have confirmed that there is a significant difference between measured microstrain and macrostrain in the heterogeneously injured lung.

Clinical Implications
We have found that an APRV T-PEFR to PEF ratio of 75% was the most effective MBP at both minimizing microstrain and maximizing alveolar recruitment (Figure 2A). Because others have shown that reduced dynamic strain decreases VILI, our data suggest that of the MBPs considered herein, an APRV T-PEFR to PEF ratio of 75% is the MBP most effective at minimizing lung injury caused by mechanical ventilation and optimizing the surface area available for oxygen exchange. These findings support our previous studies showing that preemptive application of an APRV T-PEFR to PEF ratio of 75% significantly reduced lung damage in a retrospective data analysis of severely injured trauma patients, a porcine sepsis and gut ischemia- and reperfusion-induced ARDS model, and a hemorrhagic shock-induced ARDS model. Our in vivo video microscopy shows that to understand the potential protective or deleterious properties of any MBP, it must be examined at the microanatomical level. Calculation of whole-lung stress and strain is limited in accurately determining the optimal MBP because it does not always correlate with the physical forces at the alveolar level (ie, the microanatomical environment). The importance of the time that the airway pressure is applied on alveolar recruitment and stabilization was also demonstrated in this study. An APRV T-PEFR to PEF ratio of 75% had a mean plateau pressure less than that of PEEP of 16 cm H2O but still recruited more alveoli, presumably owing to the application of plateau pressure for much longer during each breath. Because these factors may not be captured using current whole-lung stress and strain calculations, it is clear that further analysis of the time dependence of recruitment and derecruitment will be necessary to devise optimal MBPs.

Low Vt ventilation with PEEP adjusted to maintain satisfactory blood oxygen saturation is the current clinical standard-of-care ventilation for patients with established ARDS. The rationale for this strategy is that low tracheal Vt with adequate PEEP will minimize repetitive alveolar collapse and expansion, prevent atelectrauma, and protect the lung from VILI. The ARDS Network ventilation strategy allows much of the lung to collapse and attempts to ventilate and protect only the “baby lung” that remains relatively healthy. However, it has been shown that the combination of optimizing alveolar recruitment and minimizing alveolar instability reduces mechanical trauma to pulmonary tissue and inactivation of surfactant. The increased recruitment, reduced microstrain, and improved alveolar stability afforded by an APRV T-PEFR to PEF ratio of 75% suggest that this MBP may offer optimal protection from VILI.

Conclusions
This study demonstrates that changes in the MBP in both CMV and APRV modes can dramatically affect the degree of alveolar recruitment and stability in the heterogeneously injured lung. Our findings highlight the limitations of using whole-lung stress to identify the effect of the MBP on lung physiology. Because of the heterogeneous nature of the injured lung, alveolar microstrain provides a superior assessment of the injurious mechanical forces that cause VILI. We postulate that adjusting the MBP directed by microanatomical changes would assist in the development of the optimally protective mechanical breaths, potentially reducing VILI morbidity and mortality.
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Original Investigation

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