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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 H_2O) were tested. In the APRV group, decreasing durations of expiratory release (time at low pressure [T_{low}]) were tested. The T_{low} 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 H_2O) and a brief T_{low} (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 H_2O (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 H_2O (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 H_2O ($P > .05$).

CONCLUSIONS AND RELEVANCE Increased positive-end expiratory pressure and reduced time at low pressure (decreased T_{low}) 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[1,2] and alveolar overdistention (volutrauma).[3] Alveolar heterogeneity and instability exacerbate these mechanisms. Despite implementation of ventilation strategies to protect against both atelectrauma and volutrauma, mortality from acute respiratory distress syndrome (ARDS) remains unacceptably high.[4,5] Protti et al[6] developed a technique of measuring whole-lung stress or 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 VILI.[7] However, acute lung injury causes a heterogeneous injury such that whole-lung strain may not accurately reflect regional lung strain given the interdependence of alveolar architecture.[8]

Whole-lung stress and strain describe the global deformation of the lung but do not characterize the effect and distribution of forces generated by mechanical ventilation on lung microanatomy, including the alveoli and alveolar ducts. This is of particular importance in the injured lung because derecruitment may reduce the effective size of the lung so that overdistention occurs at lower tidal volumes.[9,10] Studying lung strain at this microanatomical level has been impeded by the complex geometry of the alveolar and conducting airway network.[8] An understanding of microventilation, the forces imparted to lung tissues at the microanatomical level, may provide insight into the development of optimal macroventilation strategies.[3] To better classify the strain associated with mechanical ventilation at the microanatomical level, we investigated alveolar microstrain using in vivo microscopy of subpleural alveoli during dynamic inflation and deflation. We hypothesized that whole-lung macrostrain is not correlated with alveolar microstrain for a given mechanical breath in the acutely injured lung. We further hypothesized that the MBP of airway pressure release ventilation (APRV), with a prolonged time at the plateau pressure (P_{high}) and minimal time at end-expiratory release pressure (P_{low}), minimizes microstrain.

Methods

Procedure

All experiments were performed in accordance with National Institutes of Health guidelines in the use of laboratory animals and approved by the State University of New York Upstate Medical University Institutional Animal Care and Use Committee. Male Sprague-Dawley rats (450-500 g) were anesthetized with a mixture of ketamine hydrochloride (90 mg/mL) and xylazine hydrochloride (10 mg/mL) dosed at 0.1 mg/kg of ketamine. Animals were intubated via tracheostomy with a 2.5-mm tracheal cannula (Harvard Apparatus), then placed on mechanical ventilation (Dräger Evita Infinity V500) with a positive end-expiratory pressure (PEEP) of 5 cm H_2O and a tracheal tidal volume (V_T) of 6 mL/kg, where tracheal V_T defines the whole-lung V_T measured by the ventilator at the level of the trachea. The carotid artery was cannulated with silastic tubing for hemodynamic monitoring and the external jugular vein was cannulated for fluid and medication administration. Surfactant deactivation was induced by intratracheal installation of 0.2% polysorbate 20 in normal saline (5 mL/kg, with half this volume into each lung). Rats were rotated into the right and left lateral decubitus positions for bilateral polysorbate distribution. Animals were then subjected to high V_T (tracheal V_T 16 mL/kg) and PEEP of 0 cm H_2O for 10 minutes. Peak airway pressures reached approximately 35 to 40 cm H_2O during this injurious mechanical ventilation. Prior to randomization, injury was verified by demonstrating regional and alveolar instability by gross observation and with in vivo microscopy.

Microstrain

The right lung was exposed via thoracotomy for in vivo assessment. A microscopic coverslip was lowered onto the pleural surface and the lung was held in place by gentle suction (5 cm H_2O) for in vivo video microscopy (epi-objective microscope with epi-illumination; Olympus America Inc) as previously described.[11] Animals were randomized into 2 treatment groups: controlled mandatory ventilation (CMV) (n = 3) and APRV (n = 3).

CMV Group

Rats were maintained on low tracheal V_T ventilation (tracheal V_T 6 mL/kg) with a respiratory rate of 55 breaths/min and PEEP of 5 cm H_2O with incrementally increasing PEEP (10, 16, 20, and 24 cm H_2O). 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 (Allied Visions Stingray F-145C) for 5 ventilator cycles at each ventilation setting.

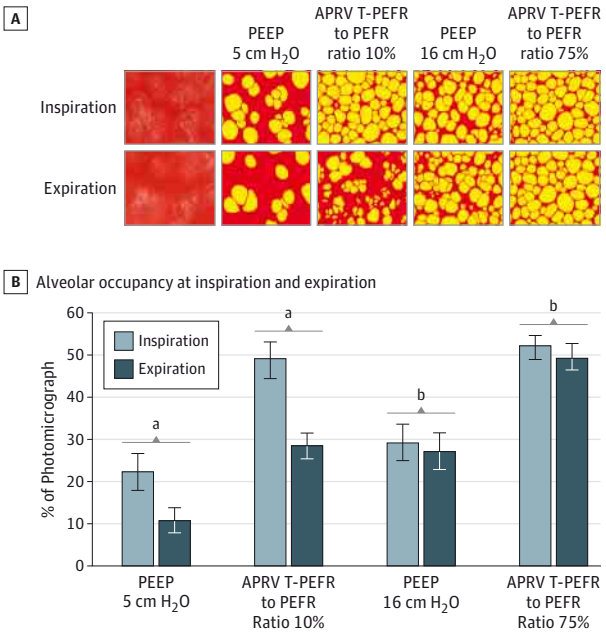
APRV Group

Rats were maintained at a P_{high} of 35 to 40 cm H_2O for a time (T_{high}) of 1.9 to 2.0 seconds, which was set to occupy approximately 90% of the ventilator cycle. The release pressure (P_{low} = 0 cm H_2O) was applied for a time (T_{low}) 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 P_{high}. The flow rate at the termination of PEFR (T-PEFR) was altered by varying the T_{low} 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.

Analysis of Alveoli

Microscopic images of alveoli were recorded for analysis using StreamPix 5 (Norpix Inc). The dynamic changes in alveolar size during ventilation were determined by outlining individual al-

Figure 1. In Vivo Photomicrographs and Percentage of Alveolar Air Space Occupancy at Inspiration and Expiration



A, In vivo photomicrographs at inspiration and expiration prior to coloring and for positive end-expiratory pressure (PEEP) of 5 cm H_2O, airway pressure release ventilation (APRV) ratio of termination of peak expiratory flow rate (T-PEFR) to peak expiratory flow rate (PEFR) of 10%, PEEP of 16 cm H_2O, and APRV T-PEFR to PEFR ratio of 75% (original magnification ×10). Alveoli are colored in yellow; nonalveolar tissue, red. B, Alveolar air space occupancy is expressed as a percentage of the photomicrograph containing inflated alveoli (yellow in A) at inspiration and expiration. Data are shown as the mean; error bars indicate standard error of the mean.

[a] $P < .05$ for PEEP of 5 cm H_2O vs APRV T-PEFR to PEFR ratio of 10%.

[b] $P < .05$ for PEEP of 16 cm H_2O vs APRV T-PEFR to PEFR ratio of 75%.

veoli at both peak inspiration and end expiration (**Figure 1**A) 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[12]: microstrain = $\Delta L_P/L_{Pe}$, where ΔL_P is the change in perimeter length between inspiration and expiration and L_{Pe} is the original perimeter length at expiration.

As previously described, the pressure-time integral (PTI) was calculated using direct measurements from the ventilator.[13] The PTI calculates the degree of pressure applied to the lung over a given ventilator cycle (inspiration plus expiration or expiratory release). It describes 1 ventilator cycle but does not take into account the difference between total cycle times in the 2 ventilator 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[14]: macrostrain = $\Delta V/V_o$, where ΔV represents the change in lung volume between inspiration and expiration and V_o represents the end-expiratory lung volume (EELV).

Lungs were excised via thoracotomy. Macrostrain for the settings with the least microstrain (PEEP 16 cm H_2O; APRV T-PEFR to PEFR ratio 75%) and greatest microstrain (PEEP 5 cm H_2O; 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 (V_i) and end expiration (V_o). The volumes were measured by the volume of water displaced in a graduated cylinder so that $\Delta V = V_i - V_o$.

Statistical Analysis

Results are reported as mean (standard error of the mean). Continuous variables were analyzed using analysis of variance within each group and Tukey test was used for post hoc multiple comparisons. The settings within each group that yielded the greatest and least microstrain were compared pairwise using *t* test. All tests were 2-tailed and $P \leq .05$ was considered statistically significant. We used Prism version 5.0 statistical software for analysis (GraphPad Software, Inc).

Results

Changing both PEEP and T_{low} 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 H_2O (Figure 1). The largest expiratory derecruitment was seen with PEEP of 5 cm H_2O 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 H_2O 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 T_{low} settings (ie, a large percentage of total alveo-

Table. Relationships Among Microstrain and Macrostrain, Total Alveolar Area at Inspiration and Expiration, and Number of Inflated Alveoli in APRV and CMV at Inspiration

	Mean (SEM)			
	APRV T-PEFR to PEFR Ratio		CMV PEEP	
Outcome	10%	75%	5 cm H_2O	16 cm H_2O
Microstrain	0.66 (0.10)[a]	0.05 (0.03)[b,c]	0.84 (0.09)[a]	0.09 (0.08)[b,c]
Macrostrain	0.33 (0.07)[a,b]	0.14 (0.07)[c]	0.15 (0.03)[c]	0.10 (0.04)[c]
Total alveolar area, %				
Inspiration	49.0 (4.4)[a,b]	52.0 (2.9)[a,b]	22.4 (4.4)[c]	29.4 (4.3)[c]
Expiration	28.5 (3.0)[b]	49.6 (3.2)[a,b,c]	10.7 (2.9)[a,c]	27.1 (4.4)[b]
Alveolar tidal volume, %	0.40 (0.07)	0.07 (0.03)[b]	0.63 (0.18)[a]	0.06 (0.07)[b]
Inflated alveoli at inspiration, No.	55.8 (7.91)[a,b]	54.2 (6.8)[a,b]	28.2 (8.32)[c]	30.0 (4.28)[c]
PTI · *f*, cm H_2O · breaths/min[d]	31.42 (0.92)[a,b]	34.46 (0.94)[a,b]	4.21 (0.05)[c]	11.57 (0.06)[c]

Abbreviations: APRV, airway pressure release ventilation; CMV, controlled mandatory ventilation; PEEP, positive end-expiratory pressure; PEFR, peak expiratory flow rate; PTI, pressure-time integral; T-PEFR, termination of peak expiratory flow rate.

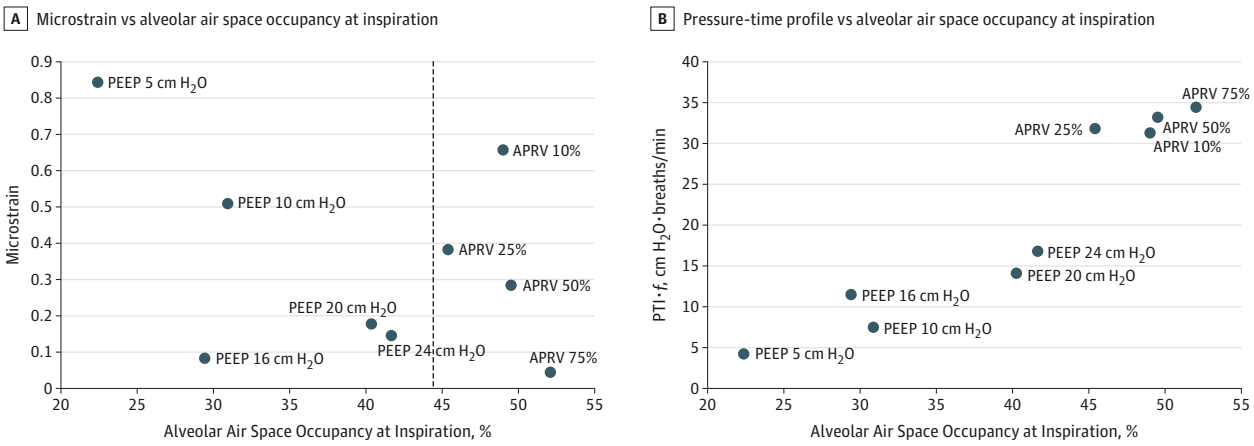
[a] $P < .05$ vs PEEP of 16 cm H_2O.

[b] $P < .05$ vs PEEP of 5 cm H_2O.

[c] $P < .05$ vs APRV T-PEFR to PEFR ratio of 10%.

[d] Indicates the PTI over 1 minute normalized by the ventilation frequency *f*.

Figure 2. Microstrain and Pressure-Time Profile vs Alveolar Air Space Occupancy at Inspiration



A, Microstrain vs alveolar air space occupancy at inspiration. Dashed line indicates difference in alveolar air space occupancy between airway pressure release ventilation (APRV) and controlled mandatory ventilation. B, Normalized pressure-time profile (pressure time integral [PTI] · *f*) over a minute vs alveolar air space occupancy at inspiration. PEEP indicates positive end-expiratory pressure. Percentages for APRV indicate the APRV ratio of termination of peak expiratory flow rate to peak expiratory flow rate.

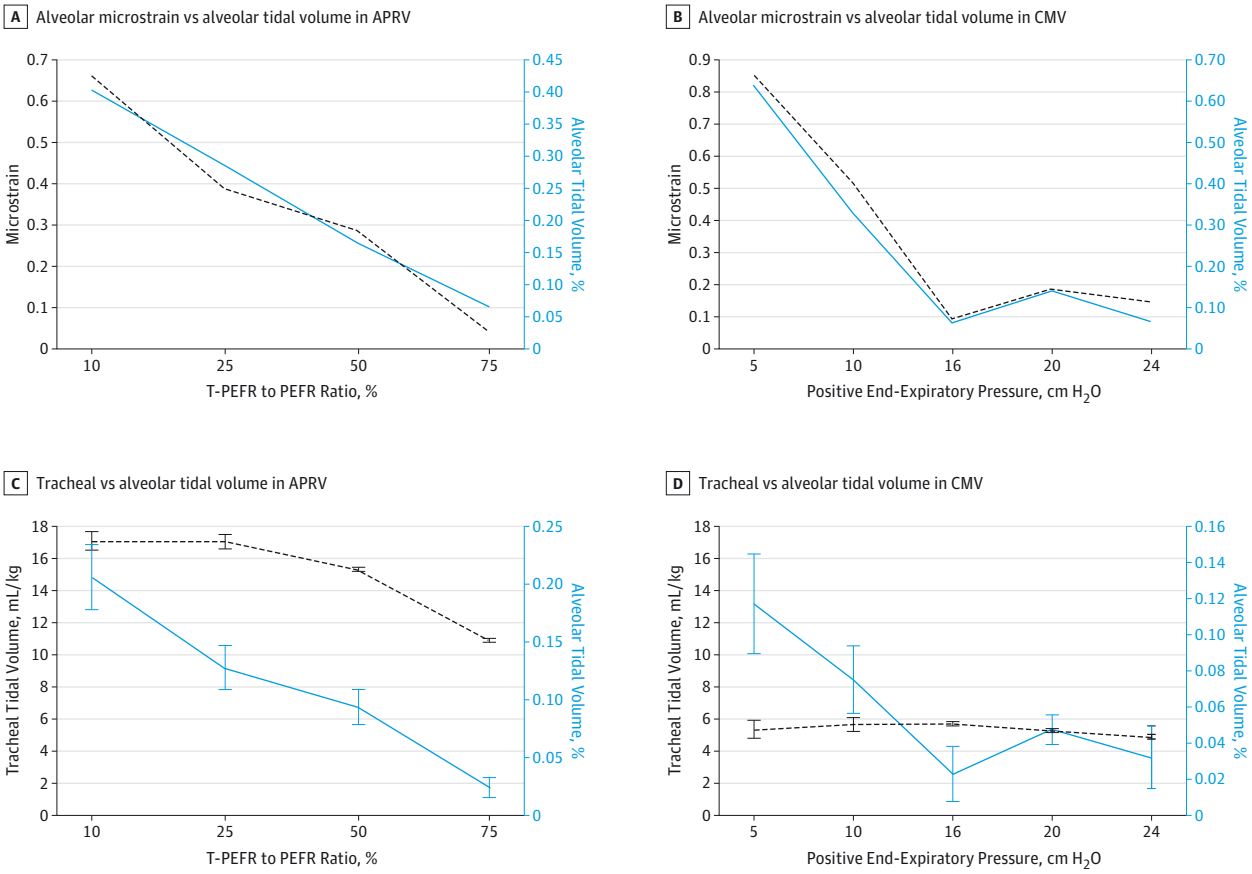
lar area and number of alveoli). The PTI · *f* value was higher in APRV compared with CMV at all ventilator settings. The APRV T-PEFR to PEFR ratio of 75% had the highest PTI · *f* (mean [SEM], 34.46 [0.94] cm H_2O · breaths/min), the greatest total alveolar area at both inspiration (mean [SEM], 52.0% [2.9%]) and expiration (mean [SEM], 49.6% [3.2%]), and the lowest microstrain (mean [SEM], 0.05 [0.03]) and alveolar V_T (mean [SEM], 0.07% [0.03%]) of all ventilator settings within APRV.

The relationship between the alveolar air space occupancy at inspiration (which represents the combined effects of alveolar recruitment and alveolar V_T) and the microstrain and PTI · *f* are shown in **Figure 2**. Figure 2B indicates that high PTI · *f*, which occurred in all APRV modes, was associated with alveolar recruitment. High PEEP (16 to 24 cm H_2O) reduced microstrain but recruited fewer alveoli than APRV (mean [SEM] total inspiratory area, 52.0% [2.9%] for APRV T-PEFR to PEFR ratio of 75% vs 29.4% [4.3%] for PEEP of 16 cm H_2O; $P < .05$). The APRV T-PEFR to PEFR ratio of 75% was optimal at both recruiting alveoli and minimizing microstrain (Figure 2A).

Alveolar V_T (the change in the size of individual alveoli during ventilation) and microstrain both decreased in response to reductions in T_{low} (T-PEFR to PEFR ratios increased from 10% to 75%) (**Figure 3**A). Increasing PEEP from 5 to 16 cm H_2O also decreased both alveolar V_T and microstrain, which did not change significantly with further increases in PEEP (Figure 3B). Tracheal V_T decreased during APRV with reduced T_{low} (T-PEFR to PEFR ratio increased from 10% to 75%) (Figure 3C). Increasing PEEP with a set tracheal V_T reduced alveolar V_T from PEEP of 5 to 16 cm H_2O; however, minimal changes were seen with further PEEP increases (Figure 3D).

There was a significant difference in mean (SEM) macrostrain between PEEP of 5 cm H_2O (0.15 [0.03]) and an APRV T-PEFR to PEFR ratio of 10% (0.33 [0.07]) ($P < .05$), which was not reflected in the microstrain (**Figure 4**). Mean (SEM) macrostrain and microstrain were also significantly different within both PEEP of 5 cm H_2O (macrostrain, 0.15 [0.03]; microstrain, 0.84 [0.09]; $P < .05$) and an APRV T-PEFR to PEFR ratio of 10% (macrostrain, 0.33 [0.07]; microstrain, 0.66 [0.10]; $P < .05$). Likewise, there was a significant difference between mean (SEM) microstrain and macrostrain with an APRV T-PEFR to PEFR ratio of 75% (macrostrain, 0.14 [0.07]; microstrain, 0.05 [0.03]; $P < .05$); however, this difference was not present with a CMV

Figure 3. Microstrain vs Tidal Volume and Tracheal vs Alveolar Tidal Volume in Airway Pressure Release Ventilation (APRV) and Controlled Mandatory Ventilation (CMV)



A, Alveolar microstrain vs alveolar tidal volume in APRV. Decreasing the time at low pressure (T_{low}) (or increasing the ratio of termination of peak expiratory flow rate [T-PEFR] to peak expiratory flow rate [PEFR] from 10% to 75%) resulted in both reduced microstrain and alveolar tidal volume. B, Alveolar microstrain vs alveolar tidal volume in CMV. Increasing positive end-expiratory pressure from 5 to 16 cm H_2O reduced microstrain and alveolar tidal volume. C, Mean tracheal vs alveolar tidal volume with decreasing T_{low} in APRV. Error bars indicate standard error of the mean. D, Mean tracheal vs alveolar tidal volume with increasing positive end-expiratory pressure in CMV. Error bars indicate standard error of the mean.

PEEP of 16 cm H_2O (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.

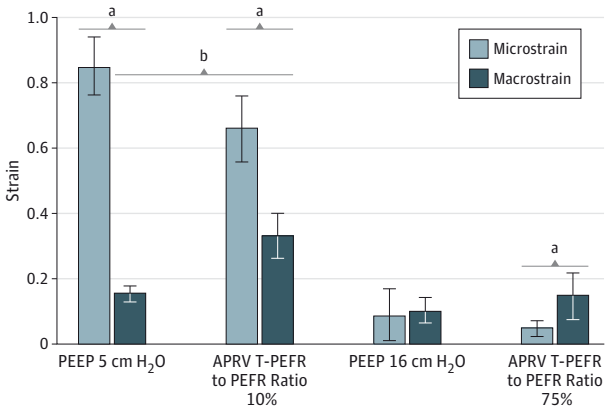
Discussion

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 T_{low} 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 VT and macrostrain are not always adequate markers of the regional microenvironment, as described by alveolar VT and microstrain. Moreover, APRV represents a low alveolar VT ventilation strategy despite greater tracheal VT. 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 Wysocki[15] 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 al[6] induced dynamic strain by decreasing the level of PEEP (reducing EELV) and increasing the tracheal VT. The study

Figure 4. Microstrain vs Macrostrain



Positive end-expiratory pressure (PEEP) of 16 cm H_2O had no difference between microstrain and macrostrain. However, PEEP of 5 cm H_2O and airway pressure release ventilation (APRV) ratios of termination of peak expiratory flow rate (T-PEFR) to peak expiratory flow rate (PEFR) of 10% and 75% demonstrated significant differences between microstrain and macrostrain. Error bars indicate standard error of the mean.

[a] $P < .05$ between microstrain and macrostrain.

[b] $P < .05$ between PEEP of 5 cm H_2O and APRV T-PEFR to PEFR ratio of 10%.

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[16] 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[15] and Protti et al[6] support the hypothesis that dynamic strain causes more pulmonary injury than the same level of static strain.[16] 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_{low} (T-PEFR to PEFR ratio of 10%) in the APRV group or decreasing PEEP (5 cm H_2O) in the CMV group significantly increased microstrain.

To recruit the lung and maintain recruitment,[17] inspiratory pressures must be greater than the critical opening pressure and PEEP must be set above the critical closing pressure to prevent derecruitment.[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.[19,20] In a randomized trial of 20 patients, Hodgson et al[21] assessed critical closing pressure by a stepwise reduction in PEEP until a decrease in oxygen saturation occurred. Patients ventilated with PEEP above critical closing pressure demonstrated a trend toward shorter duration of mechanical ventilation, intensive care unit stay, and hospital stay.[21] These results follow an earlier randomized trial by Villar et al[22] of 95 patients in whom PEEP was set just above the critical closing pressure as determined by the lower inflection point of the pressure and volume curve. Patients randomized to PEEP set with this strategy, as compared with a lower PEEP scale, demonstrated lower intensive care unit and hospital mortality and fewer ventilator-free days by day 28. In our study, PEEP set below the critical closing pressure demonstrated greater microstrain. Similarly, we have shown that extending T_{low} during APRV to yield an inappropriate T-PEFR to PEFR ratio is correlated with an increase in microstrain (Table), which has been shown to cause lung damage. In addition, APRV set with a longer T_{low} allows the lungs to deflate to airway pressures below critical closing pressure.[6,15,16] These data provide mechanistic 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.[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).[20,24] The plateau pressures of APRV and high PEEP (20 and 24 cm H_2O) 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 · *f*. 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.[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 V_T over time, raising concerns that APRV is not a low V_T ventilation strategy.[13,25,26] These findings bring to light the important distinction between macroventilation and microventilation. The V_T 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 V_T was similar between an APRV T-PEFR to PEFR ratio of 75% and PEEP of 16 cm H_2O, but the APRV T-PEFR to PEFR ratio of 75% had a significantly greater tracheal V_T (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 V_T 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 V_T. 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.[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[6] 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.[6,8,28,29] Current clinical management relies on global parameters even though these may not reflect the regional lung micromechanics.[30] 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,[29] who demonstrated that simulations of nonuniform alveoli result in a 13% increase in stress compared with a uniform system. Similarly, Rausch et al[8] 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 PEFR 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,[6,15] our data suggest that of the MBPs considered herein, an APRV T-PEFR to PEFR 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 PEFR ratio of 75% significantly reduced lung damage in a retrospective data analysis of severely injured trauma patients,[31] a porcine sepsis and gut ischemia- and reperfusion-induced ARDS model,[13,26] a rat VILI model,[25] and a hemorrhagic shock–induced ARDS model.[32]

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 PEFR ratio of 75% had a mean plateau pressure less than that of PEEP of 16 cm H_2O 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 V_T ventilation with PEEP adjusted to maintain satisfactory blood oxygen saturation is the current clinical standard-of-care ventilation for patients with established ARDS.[4] The rationale for this strategy is that low tracheal V_T with adequate PEEP will minimize repetitive alveolar collapse and expansion, prevent atelectrauma, and protect the lung from VILI.[4] 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.[33] 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.[3] The increased recruitment, reduced microstrain, and improved alveolar stability afforded by an APRV T-PEFR to PEFR 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 strain 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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