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Airway Pressure Release Ventilation Reduces Conducting Airway Micro-Strain in Lung Injury

Michaela Kollisch-Singule, MD¹, Bryanna Emr, MD¹, Bradford Smith, PhD², Cynthia Ruiz³, Shreyas Roy, MD¹, Qinghe Meng, MD¹, Sumeet Jain, MD¹, Joshua Satalin, BS¹, Kathy Snyder¹, Auyon Ghosh, MD¹, William Marx, DO¹, Penny Andrews, RN⁴, Nader Habashi, MD⁴, Gary F. Nieman, BA¹, and Louis A Gatto, PhD^{1,3}

¹SUNY Upstate Medical University, Syracuse, NY

²University of Vermont, Burlington, VT

³SUNY Cortland, Cortland, NY

⁴R Adams Cowley Shock Trauma Center, University of Maryland School of Medicine, Baltimore, MD

Abstract

BACKGROUND—Improper mechanical ventilation can exacerbate acute lung damage causing a secondary ventilator induced lung injury (VILI). We hypothesize that VILI can be reduced by modifying specific components of the ventilation waveform (mechanical breath) and studied the impact of airway pressure release ventilation (APRV) and controlled mandatory ventilation (CMV) on the lung micro-anatomy (alveoli and conducting airways). The distribution of gas during inspiration and expiration and the strain generated during mechanical ventilation in the micro-anatomy (micro-strain) were calculated.

STUDY DESIGN—Rats were anesthetized, surgically prepared and randomized into one uninjured Control group (n=2) and four groups with lung injury: 1)APRV 75% (n=2)—time at expiration (T_{Low}) set to terminate appropriately at 75% of Peak Expiratory Flow Rate (PEFR); 2)APRV 10% (n=2)— T_{Low} set to terminate inappropriately at 10% of PEFR; 3)CMV with PEEP 5cmH₂O (PEEP 5;n=2) or 4)PEEP 16cmH₂O (PEEP 16;n=2). Lung injury was induced in the experimental groups by Tween lavage and ventilated with their respective settings. Lungs were fixed at peak inspiration and end expiration for standard histology. Conducting airway and alveolar air space areas were quantified and conducting airway micro-strain calculated.

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Correspondence address: Josh Satalin, SUNY Upstate Medical University, 750 E. Adams Street, Syracuse, NY 13210, Office: 315-464-1696, Fax: 315-464-6237, satalinj@upstate.edu.

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RESULTS—All lung injury groups redistributed inspired gas away from alveoli into the conducting airways. APRV 75% minimized gas redistribution and micro-strain in the conducting airways and provided the alveolar air space occupancy most similar to Control at both inspiration and expiration.

CONCLUSIONS—In an injured lung, APRV 75% maintained micro-anatomical gas distribution similar to that of the normal lung. The lung protection demonstrated in previous studies using APRV 75% may be due to a more homogeneous distribution of gas at the micro-anatomical level as well as a reduction in conducting airway micro-strain.

Keywords

acute respiratory distress syndrome (ARDS); ventilator induced lung injury (VILI); micro-strain; airway pressure release ventilation (APRV); positive end expiratory pressure (PEEP); terminal airway; conducting airway; alveoli; histology

In patients with lung injury, mechanical ventilation is a necessary, life-saving treatment. However, improper mechanical ventilation settings can induce or exacerbate lung injury by causing a secondary ventilator induced lung injury (VILI).¹ Several mechanisms of VILI have been described including atelectrauma, which is caused by the large pressure gradients^{2,3} present during the reopening (recruitment) of closed airways and alveoli, as well as volutrauma, which is a consequence of parenchymal overdistension.⁴ Despite implementation of ventilation strategies to protect against these damaging stimuli, mortality from ARDS remains unacceptably high.^{5,6} Whole lung stress and strain have been used to identify the pathologic impact of a given mechanical ventilation pattern (mechanical breath) on the entire lung. Whole lung macro-strain (M-strain) is elevated in humans with lung injury⁷ and it has been suggested that dynamic strain is more injurious than static.⁸ However, because of lung heterogeneity, M-strain may not describe the substantial regional stress and strain heterogeneity in the distal air space, so the concept of regional micro-strain (μ -strain) has recently been described.⁹

Historically, study of the dynamic relationship between alveoli and conducting airways has been inhibited by the complex geometry of this micro-anatomical network.¹⁰ Thus the intricacies of dynamic micromechanics have not been fully elucidated.¹¹ Alveolar μ -strain was recently characterized in the injured lung using *in vivo* microscopy of subpleural alveoli.⁹ This study explored the effect of altering the timing and magnitude of the applied ventilation pressures on alveolar μ -strain and recruitment, demonstrating the importance of studying the impact of the mechanical breath at the micro-anatomical level.

Although *in vivo* microscopy provides a direct and dynamic view of alveolar mechanics, the analysis is limited to the subpleural alveoli and does not characterize the space-occupying relationship between the alveoli and conducting airways.⁹ In order to study the impact of varying mechanical breaths on the conducting airways, we utilize a novel histologic analysis of the terminal airway (i.e. alveoli and conducting airways) which allows quantification of conducting airway μ -strain.¹² Understanding the impact of specific components of the mechanical breath, such as the inspiratory pressure and the time at end expiration, at the

micro-anatomical level is important to the development of optimal protective ventilation strategies.⁴

METHODS

All experiments were performed in accordance with the National Institute of Health Guidelines in the Use of Laboratory Animals and approved by SUNY Upstate Medical University IACUC. Male Sprague-Dawley rats (450–500g) were acclimatized to the laboratory environment for one week prior to surgery. Each rat was anesthetized with a ketamine/xylazine mixture (90mg/mL/10mg/mL) at a dose of 0.1mg/kg of ketamine. Animals were intubated via tracheostomy with a 2.5mm tracheal cannula (Harvard Apparatus) then placed on mechanical ventilation (Dräger Evita Infinity V500) with a positive end-expiratory pressure (PEEP) of 5cmH₂O and tidal volume (V_t) of 6cc/kg.

The rats were randomized into one of three groups: Control (n=2), controlled mandatory ventilation (CMV; n=4) or airway pressure release ventilation (APRV; n=4). The Control rats were not subjected to injury but were briefly ventilated for five ventilatory cycles with V_t of 6cc/kg, PEEP 5 cmH₂O, F_iO_2 0.21, and respiratory rate of 55 breaths/minute prior to analysis as described below (*Terminal Airway Analysis*).

Surfactant Deactivation

In the treatment groups (CMV and APRV), surfactant deactivation was induced by intratracheal installation of 0.2% Tween-20 in normal saline (5cc/kg), half this volume into each lung. Rats were rotated into the right and left lateral decubitus position, respectively, for bilateral Tween distribution. Animals were then subjected to injurious mechanical ventilation with high tidal volumes (V_t 16cc/kg) and PEEP 0 cmH₂O for 10 minutes prior to initiating respective ventilator settings.

CMV Group—Rats were maintained on low tidal volume ventilation (V_t 6cc/kg) with respiratory rate 55 breaths/minute, I:E ratio of 1:2 and F_iO_2 of 0.21. They were further randomized into either PEEP 5 cmH₂O (PEEP 5; n=2) or PEEP 16 cmH₂O (PEEP 16; n=2). Animals were ventilated at each setting for 5 minutes to allow acclimatization and to standardize the volume history.

APRV Group—Rats were ventilated at a plateau pressure (P_{High}) of 35–40 cmH₂O for a prolonged time (T_{High}) of 1.9–2.0 seconds, which was set to occupy approximately 90% of the ventilatory cycle and a brief time (T_{Low}) at the release pressure (P_{Low} = 0 cmH₂O). 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 T_{Low} between 0.13–0.40 sec so that the ratio between T-PEFR and PEFR (T-PEFR:PEFR) was 10% (APRV 10%; n=2) or 75% (APRV 75%; n=2). Animals were ventilated with F_iO_2 of 0.21 at each setting for 5 minutes to allow acclimatization and to standardize the lung volume history.

Terminal Airway Analysis

Following ventilation with the respective settings, animals were euthanized and the lungs excised en bloc. The lungs were held at the same airway pressure after they were excised and one lung was clamped and fixed in formalin at peak inspiration and the other at end expiration for histologic analysis.

The lung lobes were sectioned and sliced to 10µm and stained with hematoxylin-eosin. Four photomicrographs from each of the Control and Experimental Groups at both inspiration and expiration were selected at random for analysis. Three main anatomical features were demarcated by our blinded histologist using PhotoShop CS6 (Adobe, Inc): 1) the *Conducting Airways* (demarcated in green, defined as the airways extending from the alveolar duct proximally), 2) the individual *Alveoli* (lilac) and 3) the remaining structures including interstitium, blood vessels, and lymphatics (magenta) (Figure 1).

The representative areas and perimeters of the conducting airway and alveolar air spaces were quantitatively measured using Image-Pro Plus (MediaCybernetics). Total air space areas were calculated as a percentage of the total frame area. Conducting airway perimeters were measured at inspiration and expiration and an average of each were taken. As previously described, μ -strain was calculated as the change in length of the conducting airway wall normalized by the original length¹³:

$$\mu\text{-strain} = \Delta L_P / L_{Pe} \quad (\text{Equation 1})$$

where L_P is the change in perimeter length between inspiration and expiration and L_{Pe} is the original perimeter length at expiration.

In order to describe the air space relationship between the conducting airways and alveoli, we defined the ratio between the conducting airway air space area (C_a) and alveolar area (A_a) = C_a/A_a .

Statistics

Results are reported as mean $\pm$ standard error. Continuous variables were analyzed using ANOVA. Dunnett's multiple comparison test was used for post hoc comparison of each experimental group to Control. All tests were 2-tailed and p-values ≤ 0.05 were considered statistically significant (Prism 5.0).

RESULTS

Qualitative Histology

In the Control group, the alveoli at both inspiration and expiration appear homogeneous and relatively round, with the alveoli at expiration being slightly smaller than those at inspiration (Figure 2). In the four treatment groups, the conducting airways appear to occupy more of the photomicrograph both at inspiration and expiration as compared with the Control group. In particular, the conducting airways dominate the photomicrograph in APRV 10%. In PEEP 5 and APRV 10%, the alveoli appear small and heterogeneous, both at inspiration and expiration. In PEEP 16 and APRV 75%, the alveoli appear more round and homogeneous,

more comparable to the Control group. The alveoli in the APRV 75% group appear larger than the rest of the experimental groups, both at inspiration and at expiration.

Terminal Airway Analysis

In the lungs injured by surfactant deactivation, gas was preferentially distributed to the conducting airways when compared with the Control group (Table 1, Figure 3A). However, experimental groups with higher end-expiratory pressure (i.e. PEEP 16) or shorter time at expiration (i.e. APRV 75%) reduced this gas redistribution to the conducting airways and improved gas distribution to the alveoli (Figure 3A, 3B). This was evidenced by smaller conducting airway air space occupancy (C_a) at inspiration, greater alveolar air space occupancy (A_a) at inspiration and expiration and a smaller ratio, C_a/A_a at inspiration (Table 1). Experimental groups with lower end expiratory pressure (i.e. PEEP 5) or longer time at expiration (i.e. APRV 10%) caused greater gas redistribution to the conducting airways, as supported by greater C_a as compared with A_a , measured by C_a/A_a (Table 1).

The Control group had the greatest A_a at inspiration and expiration, however this did not differ significantly from the A_a in APRV 75% (Table 1, Figure 3B). The remaining experimental groups had significantly less A_a than Control. The greatest change in C_a was in the PEEP 5 and APRV 10% group, which also had greater A_a at expiration as compared with inspiration (Figure 3A, 3B). This was likely due to additional alveoli being “pulled into” the photomicrograph at expiration as the size of the conducting airways was reduced. This artifact precluded analysis of alveolar dynamics between inspiration and expiration, including μ -strain.

APRV—APRV 75% caused the greatest A_a at both inspiration and expiration with values similar to Control ($p>0.05$), and resulted in the least conducting airway μ -strain (Figure 3B, Figure 4). APRV 10% had the least A_a at both inspiration and expiration and the greatest conducting airway μ -strain.

CMV—PEEP 16 demonstrated greater A_a than PEEP 5 at inspiration, but significantly less than Control ($p<0.05$) (Figure 3B). PEEP 16 also had less conducting airway μ -strain than PEEP 5 but greater than APRV 75% (Figure 4).

DISCUSSION

Current clinical ventilator management of the lung relies on organ-level parameters even though these may not reflect the regional lung micromechanics.^{9,14} Heterogeneous alveolar and alveolar duct compliance, which is a hallmark of lung injury, causes an abnormal distribution of strain during mechanical ventilation.¹⁵ Oeckler and Hubmayr assert that the micro-scale distribution of stress and strain remote from the pleura remains unknown. However, understanding the mathematical relationship between the mechanical breath and the distribution of micro-scale stress and strain is a critical component in the development of optimized macro-ventilation strategies.^{4,9} In the current study, we provide a novel description of the dynamic micromechanics in the lung interior utilizing a unique histologic technique⁴.

Our observations demonstrate that in the surfactant deficient lung, air was distributed preferentially to the conducting airways rather than the alveoli. We also found that APRV 75% minimized conducting airway μ -strain and optimized alveolar occupancy (A_a) as compared with the other experimental groups. Both clinical and animal studies have identified APRV 75% to be the optimal setting for lung protection.^{16–20} Conversely, inappropriately set APRV (10%) had the greatest conducting μ -strain and least A_a , suggesting that relatively minor changes in the components of the mechanical breath (~ 0.2 sec difference in T_{Low}) can have a large impact on the micro-environment.

Air Space Distribution

In a corollary study which employed *in vivo* microscopy, we measured air space occupancy of the subpleural alveoli as we varied pressure and time components of the mechanical breath profile during CMV and APRV (eVideo 1).⁹ As visualized in the video, that study demonstrated that APRV 75%, with P_{High} maintained for 90% of the breath, provided the greatest degree of alveolar air space occupancy at both inspiration and expiration. In contrast, APRV 10% with similar prolonged time at P_{High} but a long release phase at P_{Low} had similar A_a at inspiration but demonstrated a significant reduction in alveolar occupancy at end expiration. Thus, the current study supports our previous *in vivo* observations which indicate that that APRV 75% with a prolonged time at T_{High} improves and maintains alveolar recruitment. However, unlike the subpleural alveoli in our previous investigation, the current study shows that APRV 10% does not optimize alveolar occupancy in the terminal airway at inspiration. The differences in these two studies suggest that alveoli in the proximal lung respond differently to the mechanical breath than subpleural alveoli.

The distribution of the mechanical breath to the terminal airway has remained elusive despite decades of research. It is still unknown whether only the alveolar ducts expand during breathing while the alveoli remain relatively constant or whether the alveoli change during tidal ventilation.²¹ The results of the current study suggest that the alveolar ducts expand and contract during tidal ventilation in the injured lung.

μ -strain

In the healthy lung, an intimate micromechanical relationship between the alveoli and conducting airways is maintained. This balance is disturbed in the diseased state, particularly when ventilated with settings that have been shown harmful and associated with VILI.¹ It is possible that the mechanism by which inappropriate ventilator setting harms the lung is by altering the μ -strain of alveoli and connecting airways.^{8,9,22}

Protti et al. demonstrated that increasing degrees of whole lung dynamic strain increased the risk of developing VILI.⁸ It is also known that cyclic non-physiologic strain injures the lung subunits, particularly dynamic strain.²³ In the corollary study, we demonstrated that APRV 75% generated the smallest subpleural alveolar μ -strain and CMV with PEEP 5 the greatest (eVideo 1).⁹ In the current study, however, APRV 75% demonstrated the smallest conducting airway μ -strain and APRV 10% the greatest. Taken together, these data suggest that APRV 75% reduces alveolar⁹ and conducting airway μ -strain, both of which may be important components in preventing VILI.^{16–20}

The Sensitivity of Micromechanics to Macro-Ventilation Settings

APRV with an appropriate release phase duration (T-PEFR:PEFR 75%) has demonstrated promising results in a retrospective data analysis of severely injured trauma patients¹⁹, a porcine sepsis and gut ischemia/reperfusion-induced ARDS model^{17,18}, as well as in rat VILI¹⁶ and hemorrhagic shock-induced ARDS models²⁰. In the current study and our previous *in vivo* microscopy investigation, we have shown that inappropriately set APRV (i.e. T-PEFR:PEFR = 10%) increases alveolar⁹ and conducting airway μ -strain as well as preferential gas distribution away from the alveoli to the conducting airways.

In a randomized trial of 58 patients comparing APRV to synchronized intermittent mandatory ventilation (SIMV), Varpula et al. determined that there was no difference between APRV and SIMV in terms of clinically applicable outcomes; however, in that study, patients on APRV had a T_{Low} set to allow the expiratory flow to decay to zero.²⁴ The difference between the T_{Low} of APRV 75% (0.14 ± 0.01) and APRV 10% (0.34 ± 0.02) in the current study was only 0.20 seconds. With all other breath parameters held constant, this slight difference in the T_{Low} allowed the expiratory flow to decay to nearly zero and caused marked changes in gas distribution at the terminal airway. Similarly, in a randomized prospective trial of 63 patients, Maxwell et al. determined that many clinical outcome variables were similar between APRV and low tidal volume ventilation, however the T-PEFR:PEFR ratio was set between 25% and 75%.²⁵ Although the difference in the T_{Low} between a ratio of 25% and 75% may seem insignificant, our studies have shown that the distribution of the mechanical breath to the micro-environment is markedly different.⁹ When interpreting outcome studies comparing *any* ventilator mode(s), attention to the breath settings remains of critical importance.²⁶

Terminal Airway Analysis

Several innovative techniques have been developed to investigate the terminal airway and air distribution to the lung sub-units but very few have used these techniques to compare the impact of different ventilation strategies on the terminal airway. Many are limited by reduced resolution, inability to visualize structures deeper than the subpleural alveoli or inability to distinguish the conducting airways from the alveoli. In general, three-dimensional techniques offer a more complete view of the lung but are often limited by resolution or estimation by stereologic methods from serial sections in order to assess the individual acinar segments.²⁷ Standard computed tomography (CT) images of the thorax are useful clinically, however CT does not afford the necessary resolution to be able to characterize the structure and composition of the terminal airway and therefore does not yield information regarding tissue stretch or strain.^{21,28} Micro-CT has been used to investigate the lung microstructure and quantify alveolar surface area, density, and volume. However, the resolution decreases with increasing sample thickness and the technique has a lower resolution than standard histopathology such that very thin alveolar septae may not be visible. This suggests that histology may provide a more accurate, albeit two-dimensional, assessment of terminal airway morphology.^{27,29,30}

Optical coherence tomography (OCT) is a high-resolution, three-dimensional approach, which is non-destructive and may be performed such that it avoids contact with the

alveolus.³¹ OCT has the advantage of being able to track individual alveoli through the entire ventilator cycle, however it has a tendency to overestimate the area of alveolar walls and underestimate the alveolar space.³¹ Unfortunately, OCT is limited to visualization of only the first 500µm of subpleural lung parenchyma; therefore, assessment of volume changes and strain in the inner lung is not feasible.^{31–33}

In vivo microscopy has been utilized successfully to garner information regarding alveolar morphology in different ventilator settings.^{9,34} However, observation is limited to the immediate subpleural alveoli and this approach requires a small opening in the chest wall and direct contact with the pleura, thus potentially disturbing alveolar dynamics. The use of suction to hold the tissue under the lens may cause compressive stress and deform the tissue, and the environment of the alveolus may change due to the loss the constricting effect of the chest wall.²⁷ The loss of a volume limit and transpulmonary pressure may not adequately mimic the *in vivo* conditions associated with an intact chest wall.¹¹ It also does not directly visualize the inner lung and cannot characterize the space-occupying relationship between the alveoli and conducting airways.^{35–37}

Electrical impedance tomography (EIT) has also been advocated as a potential non-invasive strategy of assessing regional lung expansion. The unit of measure in this technology is the pixel, but each pixel contains several alveoli therefore making individual alveolar assessment difficult. Furthermore, different alveoli may be included in the same EIT pixel at different stages of ventilation, therefore limiting certain dynamic measurements, including µ-strain.^{38,39} EIT is also limited by the inability to distinguish the conducting airways from the alveoli quantitatively.

Many currently held theories on alveolar mechanics are rooted in classic histopathology studies, and this approach has remained a gold standard for the static analysis of the terminal airway.^{40,41} The current study is unique in that it allows quantification of relative air space areas as well as a comparison of lungs fixed at various points during the ventilator cycle.

Limitations

It would not be clinically realistic to ventilate an ARDS lung with F_iO_2 0.21 if the study were designed to identify pathologic changes over time caused by multiple ventilator settings. However, we feel that F_iO_2 of 0.21 was appropriate for this study since it addressed how the inspired gas was accommodated by the terminal airways (i.e. the alveoli and conducting airways) and did not address lung pathology. It is unlikely that a higher oxygen concentration would impact the response of the terminal airway to the mechanical breath, however the F_iO_2 was standardized in both groups to ensure comparable results. Each group consisted of two rats but four photomicrographs from each rat at each of inspiration and expiration were analyzed. At inspiration, between 3989 and 7550 alveoli were analyzed for a given group suggesting that this is still a robust analysis despite smaller group sizes. As noted previously, due to the artifact created by the large conducting airway occupancy at inspiration, alveolar µ-strain could not be reliably calculated.⁹ Since the terminal airway analysis was performed by isolating one lung at inspiration and the other at expiration, a specific lung region could not be compared at both levels of inflation. In order to calculate µ-strain, the average conducting airway perimeters at inspiration and expiration were

calculated, such that statistical significance could not be determined. Despite these limitations, the study provides a unique method of analyzing the terminal airway using standard histopathology techniques. To our knowledge, this is the first study to analyze the impact of various mechanical ventilation strategies on the conducting airways.

CONCLUSIONS

In this study, we present a novel methodology to assess the impact of the mechanical breath on the terminal airway in both the injured and uninjured lung. We have shown that the gas distribution of the APRV 75% mechanical breath is more similar to the normal lung than other ventilation modes despite surfactant deactivation. Because APRV 75% improves alveolar gas delivery, conducting airway μ -strain is concurrently reduced. Our findings highlight the importance of selecting appropriate ventilation parameters so that the inspired gas reaches the alveolus. When settings are adjusted on the mechanical ventilator, consideration is not always given to how those settings impact the terminal airway. We have therefore also demonstrated the importance of considering the impact of the macro-ventilation settings we set with the ventilator on the micro-anatomy of the lung.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations and Acronyms

VILI	ventilator induced lung injury
APRV	airway pressure release ventilation
CMV	controlled mandatory ventilation
T_{Low}	time during expiratory release
PEFR	peak expiratory flow rate
T-PEFR	termination of peak expiratory flow rate
PEEP	positive end expiratory pressure
M-Strain	macro-strain
μ-strain	micro-strain
V_t	tidal volume
L_p	change in perimeter length between inspiration and expiration

L_{pe}	original perimeter length at expiration
C_a	conducting airway air space area
A_a	alveolar area
SIMV	synchronized intermittent mandatory ventilation
CT	computed tomography
OCT	optical coherence tomography
EIT	electrical impedance tomography
Ins	inspiration
Exp	expiration
I-E	difference in area between inspiration and expiration

References

1. Gajic O, Dara SI, Mendez JL, et al. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Critical Care Med.* 2004; 32:1817–1824. [PubMed: 15343007]
2. Bilek AM, Dee KC, Gaver DP 3rd. Mechanisms of surface-tension-induced epithelial cell damage in a model of pulmonary airway reopening. *J Appl Physiol.* 2003; 94:770–783. [PubMed: 12433851]
3. Kay SS, Bilek AM, Dee KC, Gaver DP 3rd. Pressure gradient, not exposure duration, determines the extent of epithelial cell damage in a model of pulmonary airway reopening. *J Applied Physiol.* 2004; 97:269–276. [PubMed: 15004001]
4. Oeckler RA, Hubmayr RD. Alveolar microstrain and the dark side of the lung. *Crit Care.* 2007; 11:177. [PubMed: 18036270]
5. Network A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med.* 2000; 342:1301–1308. [PubMed: 10793162]
6. Villar J, Blanco J, Anon JM, et al. The ALIEN study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. *Intensive Care Med.* 2011; 37:1932–1941. [PubMed: 21997128]
7. Chiumello D, Carlesso E, Cadringer P, et al. Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2008; 178:346–355. [PubMed: 18451319]
8. Protti A, Andreis DT, Monti M, et al. Lung stress and strain during mechanical ventilation: any difference between statics and dynamics? *Critical Care Med.* Feb 4.2013
9. Kollisch-Singule MEB, Smith B, Roy S, et al. Mechanical breath profile of aprv maximizes alveolar recruitment and minimizes micro-strain in acute lung injury. *JAMA Surg.* 2014 (in Press.).
10. Rausch SM, Haberthur D, Stampanoni M, et al. Local strain distribution in real three-dimensional alveolar geometries. *Ann Biomed Engineer.* 2011; 39:2835–2843.
11. Roan E, Waters CM. What do we know about mechanical strain in lung alveoli? *American journal of physiology Lung Cell Molec Physiol.* 2011; 301:L625–635.
12. Storey WF, Staub NC. Ventilation of terminal air units. *J Appl Physiol.* 1962; 17:391–397. [PubMed: 13917520]
13. Brewer KK, Sakai H, Alencar AM, et al. Lung and alveolar wall elastic and hysteretic behavior in rats: effects of in vivo elastase treatment. *J Appl Physiol.* 2003; 95:1926–1936. [PubMed: 12871961]

14. Bates JH, Davis GS, Majumdar A, et al. Linking parenchymal disease progression to changes in lung mechanical function by percolation. *Am J Respir Crit Care Med*. 2007; 176:617–623. [PubMed: 17575096]
15. de Ryk J, Thiesse J, Namati E, McLennan G. Stress distribution in a three dimensional, geometric alveolar sac under normal and emphysematous conditions. *Int J Chronic Obstruct Pulmonary Dis*. 2007; 2:81–91.
16. Emr B, Gatto L, Roy S, et al. Airway pressure release ventilation prevents ventilator-induced lung injury in normal lungs. *JAMA Surg*. 2013 published online 9/11/13.
17. Roy S, Habashi N, Sadowitz B, et al. Early airway pressure release ventilation prevents ards-a novel preventive approach to lung injury. *Shock Jan*. 2013; 39(1):28–38.
18. Roy S, Sadowitz B, Andrews P, et al. Early stabilizing alveolar ventilation prevents acute respiratory distress syndrome: a novel timing-based ventilatory intervention to avert lung injury. *J Trauma Acute Care Surg*. 2012; 73:391–400. [PubMed: 22846945]
19. Andrews PL, Shiber JR, Jaruga-Killeen E, et al. Early application of airway pressure release ventilation may reduce mortality in high-risk trauma patients: a systematic review of observational trauma ARDS literature. *J Trauma Acute Care Surg*. 2013; 75:635–641. [PubMed: 24064877]
20. Roy SK, Emr B, Sadowitz B, et al. Preemptive application of airway pressure release ventilation prevents development of acute respiratory distress syndrome in a rat traumatic hemorrhagic shock model. *Shock*. 2013; 40:210–216. [PubMed: 23799354]
21. Hubmayr RD. Perspective on lung injury and recruitment: a skeptical look at the opening and collapse story. *Am J Respir Crit Care Med*. 2002; 165:1647–1653. [PubMed: 12070067]
22. Suki B, Ito S, Stamenovic D, Lutchen KR, Ingenito EP. Biomechanics of the lung parenchyma: critical roles of collagen and mechanical forces. *J Applied Physiol*. 2005; 98:1892–1899. [PubMed: 15829722]
23. Gattinoni L, Protti A, Caironi P, Carlesso E. Ventilator-induced lung injury: the anatomical and physiological framework. *Crit Care Med*. 2010; 38:S539–548. [PubMed: 21164395]
24. Varpula T, Valta P, Niemi R, et al. Airway pressure release ventilation as a primary ventilatory mode in acute respiratory distress syndrome. *Acta Anaesthesiologica Scandinavica*. 2004; 48:722–731. [PubMed: 15196105]
25. Maxwell RA, Green JM, Waldrop J, et al. A randomized prospective trial of airway pressure release ventilation and low tidal volume ventilation in adult trauma patients with acute respiratory failure. *J Trauma*. 2010; 69:501–510. discussion 511. [PubMed: 20838119]
26. Andrews PL, Scalea T, Habashi NM. What's in a name? Mechanical ventilation is at the mercy of the operator. *J Trauma Acute Care Surg*. 2013; 74:1377–1378. [PubMed: 23609296]
27. Unglert CI, Namati E, Warger WC 2nd, et al. Evaluation of optical reflectance techniques for imaging of alveolar structure. *J Biomed Optics*. 2012; 17:071303.
28. Suki B, Sato S, Parameswaran H, et al. Emphysema and mechanical stress-induced lung remodeling. *Physiology*. 2013; 28:404–413. [PubMed: 24186935]
29. Litzlbauer HD, Neuhaeuser C, Moell A, et al. Three-dimensional imaging and morphometric analysis of alveolar tissue from microfocal X-ray-computed tomography. *American journal of physiology Lung Cell Molec Physiol*. 2006; 291:L535–545.
30. Kampschulte M, Schneider CR, Litzlbauer HD, et al. Quantitative 3D micro-CT imaging of human lung tissue. *RoFo : Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin*. 2013; 185:869–876. [PubMed: 23888470]
31. Meissner S, Knels L, Schnabel C, et al. Three-dimensional Fourier domain optical coherence tomography in vivo imaging of alveolar tissue in the intact thorax using the parietal pleura as a window. *J Biomed Optics*. 2010; 15:016030.
32. Popp A, Wendel M, Knels L, et al. Imaging of the three-dimensional alveolar structure and the alveolar mechanics of a ventilated and perfused isolated rabbit lung with Fourier domain optical coherence tomography. *J Biomed Optics*. 2006; 11:014015.
33. Namati E, Thiesse J, de Ryk J, McLennan G. Alveolar dynamics during respiration: are the pores of Kohn a pathway to recruitment? *Am J Respiratory Cell Molec Biol*. 2008; 38:572–578.
34. Pavone LA, Albert S, Carney D, et al. Injurious mechanical ventilation in the normal lung causes a progressive pathologic change in dynamic alveolar mechanics. *Crit Care Med*. 2007; 11:R64.

35. DiRocco JD, Pavone LA, Carney DE, et al. Dynamic alveolar mechanics in four models of lung injury. *Intensive Care Med.* 2006; 32:140–148. [PubMed: 16391949]
36. Carney D, DiRocco J, Nieman G. Dynamic alveolar mechanics and ventilator-induced lung injury. *Crit Care Med.* 2005; 33:S122–128. [PubMed: 15753717]
37. Halter JM, Steinberg JM, Gatto LA, et al. Effect of positive end-expiratory pressure and tidal volume on lung injury induced by alveolar instability. *Crit Care.* 2007; 11:R20. [PubMed: 17302983]
38. Muders T, Luepschen H, Zinserling J, et al. Tidal recruitment assessed by electrical impedance tomography and computed tomography in a porcine model of lung injury*. *Crit Care Med.* 2012; 40:903–911. [PubMed: 22202705]
39. Bikker IG, Leonhardt S, Reis Miranda D, Bakker J, Gommers D. Bedside measurement of changes in lung impedance to monitor alveolar ventilation in dependent and non-dependent parts by electrical impedance tomography during a positive end-expiratory pressure trial in mechanically ventilated intensive care unit patients. *Crit Care.* 2010; 14:R100. [PubMed: 20509966]
40. Wilson TA, Bachofen H. A model for mechanical structure of the alveolar duct. *J Applied Physiol.* 1982; 52:1064–1070. [PubMed: 7085408]
41. Bachofen H, Gehr P, Weibel ER. Alterations of mechanical properties and morphology in excised rabbit lungs rinsed with a detergent. *J Applied Physiol.* 1979; 47:1002–1010. [PubMed: 511700]

Figure 1.

(A) Schematic of the terminal airway before and after color demarcation. (B) A standard hematoxylin-eosin staining of the lung is first analyzed for conducting airway air spaces and demarcated in green. The alveoli are demarcated in lilac while the remaining interstitium, blood vessels and lymphatics are colored in magenta. (Histology and artwork courtesy Louis A Gatto.)

Figure 2. Terminal airway analysis at inspiration and expiration in control versus the four experimental groups. The conducting airways are depicted in green, alveoli in lilac and remaining interstitium, blood vessels and lymphatics in magenta.

Figure 3.

(A) Conducting airway air space occupancy at inspiration and expiration. (B) Alveolar air space occupancy at inspiration and expiration. * $p < 0.05$ vs. Control at inspiration. † $p < 0.05$ vs. Control at expiration. APRV, airway pressure release ventilation; PEEP, positive end expiratory pressure.

Figure 4. Conducting airway micro-strain (μ -strain), calculated based on conducting airway perimeters at inspiration and expiration. APRV, airway pressure release ventilation; PEEP, positive end expiratory pressure.

Table 1

Relationships among Total Conducting Airway and Alveolar Area at Inspiration and Expiration and the Difference between Inspiration and Expiration Conducting Airway Air Space Area in Controlled Mandatory Ventilation and Airway Pressure Release Ventilation

Group	Conducting airway area			Conducting airway perimeter		μ -strain	C_a/A_a		Alveolar area	
	Ins (%)	Exp (%)	I-E (%)	Ins (μ m)	Exp (μ m)		Ins	Exp	Ins (%)	Exp (%)
Control	19.0 $\pm$ 0.24	17.2 $\pm$ 0.22	1.8	324.7 $\pm$ 5.7	285.5 $\pm$ 3.45	0.137	0.33 $\pm$ 0.01	0.35 $\pm$ 0.01	57.5 $\pm$ 0.22	49.6 $\pm$ 0.25
APRV 75%	30.5 $\pm$ 0.70 [*]	24.6 $\pm$ 0.53 [†]	5.9	487.2 $\pm$ 10.9 [*]	405.2 $\pm$ 5.9 [†]	0.202	0.65 $\pm$ 0.03	0.51 $\pm$ 0.01	48.7 $\pm$ 0.74	48.3 $\pm$ 0.60
PEEP 16	33.5 $\pm$ 0.43 [*]	30.2 $\pm$ 0.68 [†]	3.3	539.1 $\pm$ 11.3 [*]	437.8 $\pm$ 10.6 [†]	0.231	0.81 $\pm$ 0.03	0.79 $\pm$ 0.03 [†]	43.8 $\pm$ 0.85 [*]	39.7 $\pm$ 0.66 [†]
PEEP 5	32.7 $\pm$ 0.57 [*]	24.7 $\pm$ 0.53 [†]	8	468.5 $\pm$ 10.7 [*]	350.7 $\pm$ 7.7	0.336	0.90 $\pm$ 0.02 [*]	0.60 $\pm$ 0.02	37.0 $\pm$ 0.37 [*]	41.7 $\pm$ 0.54 [†]
APRV 10%	50.2 $\pm$ 0.95 [*]	35.2 $\pm$ 0.77 [†]	15	655.4 $\pm$ 13.0 [*]	470.2 $\pm$ 10.9 [†]	0.394	2.07 $\pm$ 0.12 [*]	1.32 $\pm$ 0.06 [†]	26.5 $\pm$ 0.82 [*]	28.7 $\pm$ 1.12 [†]

Data are presented as mean $\pm$ SEM.

C_a/A_a , conducting airway to alveolar air space area ratio; EXP, expiration; I-E, difference in area between inspiration and expiration; INS, inspiration

^{*} p<0.05 vs Control at inspiration.

[†] p<0.05 vs Control at expiration.