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# Alveolar instability (atelectrauma) is not identified by arterial oxygenation predisposing the development of an occult ventilator-induced lung injury

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## Abstract

**Background:** Improperly set mechanical ventilation (MV) with normal lungs can advance lung injury and increase the incidence of acute respiratory distress syndrome (ARDS). A key mechanism of ventilator-induced lung injury (VILI) is an alteration in alveolar mechanics including alveolar instability or recruitment/derecruitment (R/D). We hypothesize that R/D cannot be identified by PaO<sub>2</sub> (masking *occult VILI*), and if protective ventilation is not applied, ARDS incidence will increase.

**Methods:** Sprague-Dawley rats ( $n = 8$ ) were anesthetized, surgically instrumented, and placed on MV. A thoracotomy was performed and an in vivo microscope attached to the pleural surface of the lung with baseline dynamic changes in alveolar size during MV recorded. Alveolar instability was induced by intra-tracheal instillation of Tween and alveolar R/D identified as a marked change in alveolar size from inspiration to expiration with increases in positive end-expiratory pressure (PEEP) levels.

**Results:** Despite maintaining a clinically acceptable PaO<sub>2</sub> (55–80 mmHg), the alveoli remained unstable with significant R/D at low PEEP levels. Although PaO<sub>2</sub> consistently increased with an increase in PEEP, R/D did not plateau until PEEP was >9 cmH<sub>2</sub>O.

**Conclusions:** PaO<sub>2</sub> remained clinically acceptable while alveolar instability persisted at all levels of PEEP (especially PEEP <9 cmH<sub>2</sub>O). Therefore, PaO<sub>2</sub> levels cannot be used reliably to guide protective MV strategies or infer that VILI is not occurring. Using PaO<sub>2</sub> to set a PEEP level necessary to stabilize the alveoli could underestimate the potential for VILI. These findings highlight the need for more accurate marker(s) of alveolar stability to guide protective MV necessary to prevent VILI.

## Background

The acute respiratory distress syndrome (ARDS) remains a serious clinical challenge affecting nearly 200,000 patients annually, claiming the lives of 30–40 % of those afflicted [1]. Although mechanical ventilation (MV) is applied to patients without lung injury, improperly set MV [2] can cause a secondary ventilator-induced lung injury (VILI) [3], playing a key role in the high incidence of ARDS (25 %) within 48 h of MV initiation [4, 5]. Most cases of ARDS evolve over 30–72 h after hospital admission where lung protective strategies are typically implemented *after* the development of

lung injury and clinically diagnosed by a deterioration of oxygenation characterized by a decline in  $\text{PaO}_2/\text{FiO}_2$  (P/F) ratio [6, 7]. Although there are alternative markers of optimizing mechanical ventilation, most definitions of ARDS [6, 7] rely on oxygenation ( $\text{PaO}_2$ ) as a marker of pulmonary function. Lung protection is generally instituted in a *reactive* rather than *proactive* approach with an emphasis on *treating* rather than *preventing* the progression of worsening lung injury. Further, clinicians target  $\text{PaO}_2$  or saturation ( $\text{SpO}_2$ ) [8] to determine if ventilator strategies are effective prior to and after the development of acute lung injury (ALI). However, reliance on  $\text{PaO}_2$  as a marker of lung function presumes there is no lung injury prior to ARDS perpetuating a binary concept of ARDS. A key to understanding lung-ventilator interactions may lie in sub-clinical mechanisms of lung injury and the impact of MV on the “micro-environment” at the alveolar/alveolar duct level rather than centering on the “macro-environment” and parameters displayed on the ventilator (i.e., tidal volume ( $V_t$ ), plateau pressure) using  $\text{PaO}_2$  and  $\text{SpO}_2$ .

Recently, it has been suggested that the primary mechanism of VILI is tidal alveolar recruitment/derecruitment (R/D) [9, 10]. Our group has shown that tidal R/D leads to persistent alveolar instability causing severe histologic lung injury and ARDS [11] and optimizing alveolar stability is critical to preventing VILI and limiting ARDS [12–14].  $\text{PaO}_2$  may not be an accurate surrogate of alveolar stability; therefore, preventing ARDS using preemptive MV requires clinicians to consider the potential for *occult alveolar instability* (i.e., R/D without a significant fall in  $\text{PaO}_2$ ) [6]. In this study, we hypothesized that in an acutely injured lung, alveolar instability would persist despite improvements in  $\text{PaO}_2$  with increasing levels of positive end-expiratory pressure (PEEP). Lack of correlation between  $\text{PaO}_2$  and alveolar stability would provide a mechanistic explanation of why patients with normal  $\text{PaO}_2$  evolve to ARDS after 48 h of MV [4, 15]. In this study, we show direct visual evidence using *in vivo* microscopy that alveolar R/D cannot be predicted using  $\text{PaO}_2$  as a surrogate for alveolar stability and protective MV.

## Methods

### Vertebrate animals

The Institutional Animal Care and Use Committee at Upstate Medical University, Syracuse, NY, approved the studies. All experiments were performed in adherence to the guidelines established by the National Institutes of Health for the use of experimental animals in research.

### Surgical preparation

Adult male Sprague-Dawley rats ( $n = 8$ ) weighing  $590 \pm 19.2$  g were anesthetized via an intraperitoneal injection of ketamine/xylazine (90 and 10 mg/kg, respectively) dosed at 0.1 mg/kg of ketamine before surgery as well as during the experiment to provide adequate anesthesia. To ensure that the  $V_t$  remained constant, the animals were paralyzed with rocuronium to inhibit spontaneous breathing. A tracheostomy was performed, and time-cycled/pressure-controlled mechanical ventilation was initiated with a PEEP of 3  $\text{cmH}_2\text{O}$ , pressure control ( $P_{\text{control}}$ ) of 15  $\text{cmH}_2\text{O}$ , respiratory rate of 30 breaths/min, and  $\text{FiO}_2$  of 100 % (Hamilton G5 ventilator; Hamilton Medical Inc., Reno, NV). A jugular vein

was cannulated for the administration of fluids and a carotid artery catheter placed for blood gas samples and hemodynamic monitoring.

#### **Hemodynamic, pulmonary, and blood gas measurements**

Hemodynamic and pulmonary parameters were continuously monitored (Philips Healthcare and Hamilton G5 ventilator). Arterial blood gas was sampled at baseline and each PEEP level, as defined in "Lung injury," to record pH, PaCO<sub>2</sub>, PaO<sub>2</sub>, and PaO<sub>2</sub>/FiO<sub>2</sub> (P/F) ratios (cobas b221, Roche Diagnostics).

#### **Lung injury**

Serial blood gases were taken and the respiratory rate adjusted until PaCO<sub>2</sub> was between 35 and 45 mmHg. A baseline blood gas was performed and lung injury induced via 0.2 % Tween-20 in normal saline (16 cc/kg) instillation via an endotracheal tube. This was repeated until a P/F <100 mmHg was reached.

#### **In vivo microscopy**

After induction of lung injury, a right thoracotomy was performed to expose the pleural surface of the right lung. The in vivo microscope (epi-objective microscope with epi-illumination; Olympus America Inc.) was approximated to the nondependent (anterior) portion of the right lung and 5 cmH<sub>2</sub>O suction applied to capture a steady field of the alveoli at ×10 magnification. Although dependent lung regions may be more susceptible to R/D, stability in dependent regions would be unlikely if alveolar stability in nondependent regions was not achieved. In this model, we used individual rats as their own control and documented alveolar stability at baseline. After Tween injury, alveolar behavior became unstable demonstrating R/D. Thirty seconds of video was recorded from an attached digital video camera (Sony CCD color video camera SSC-S20) and uploaded to a computer while maintaining a PEEP of 3 cmH<sub>2</sub>O and  $P_{\text{control}}$  of 15 cmH<sub>2</sub>O. Subsequently, PEEP was increased in 3 cmH<sub>2</sub>O increments and videos recorded from the in vivo microscopy at each setting until a PEEP of 18 cmH<sub>2</sub>O was achieved. This procedure was repeated at each PEEP level in five distinct parenchymal areas of the right nondependent lung.

#### **Image capture and processing**

Video was captured using Pinnacle Studio software (Corel Corp.) for analysis of alveolar mechanics. Individual frames were extracted and analyzed at the plateau pressure ( $P_{\text{plateau}}$ ) and peak expiration (PEEP) for five lung fields per PEEP level. The alveoli were identified in the frames and manually outlined using Photoshop CS6 (Adobe Inc.) with areas calculated using Image-Pro software (Media Cybernetics). The areas calculated represent alveolar inflation at end-inspiration (I) and end-expiration (E) and are each represented as a fraction of the total microscopic lung field. Alveolar instability was assessed by comparing the percent difference between I and E (%ΔI-E). A greater %ΔI-E is suggestive of increased R/D and alveolar instability.

## Statistics

Least squares regression was used to determine whether alveolar stability and arterial oxygenation were linearly related (Microsoft Excel, 2008).

## Results

### Physiologic parameters

All animals displayed severe lung injury after Tween instillation with average P/F ratio <100 mmHg. As PEEP was increased, there was a concomitant decrease in mean arterial pressure but no change in heart rate (Table 1). With increasing PEEP, there was no significant change in pH but there was a decrease in pCO<sub>2</sub> with PEEP above 6 cmH<sub>2</sub>O. Increasing PEEP led to a correspondent increase in the mean airway pressure (Paw) and P<sub>plateau</sub>. Tidal volumes were set at 6 cc/kg, and minute ventilation was similar between groups (Table 2).

### Alveolar stability and PaO<sub>2</sub>

Subpleural alveoli at I and E in both the uninjured and injured lungs are seen in Fig. 1 with individual alveoli outlined in *dots*. Measuring alveolar size change between I and E is used to assess alveolar stability.

### Uninjured alveolar stability and PaO<sub>2</sub>

There was a minimal size change during tidal ventilation in the normal lung with 12 cmH<sub>2</sub>O of PEEP compared to a large change in alveolar size in the injured lung indicating severe alveolar instability even with 18 cmH<sub>2</sub>O of PEEP (Fig. 1).

### Injured alveolar stability and PaO<sub>2</sub>

Examination of the aggregate data shows that a stepwise increase in PEEP (3–9 cmH<sub>2</sub>O) led to an increase in both alveolar stability and PaO<sub>2</sub> (Fig. 2). However, further increased levels of PEEP (12–18 cmH<sub>2</sub>O) improved PaO<sub>2</sub> without a concomitant increase in alveolar stability (Fig. 2). Examination of individual animals demonstrated that PaO<sub>2</sub> remained largely unchanged despite a spectrum of alveolar instability at a given PEEP level.

## Discussion

The most important findings of this study were as follows: (a) unstable alveoli oxygenated blood to nearly the same PaO<sub>2</sub> as stable alveoli, particularly at levels of PEEP of 3–9 cmH<sub>2</sub>O; (b) alveolar stability did not improve when PEEP was increased above 9 cmH<sub>2</sub>O despite continual improvement in PaO<sub>2</sub> up to PEEP of 18 cmH<sub>2</sub>O (Fig. 3); and (c) combined with our prior work, this shows that PEEP may have a greater effect recruiting and distending conducting airways rather than the alveoli [16]. In a previous study, we showed increasing levels of PEEP increases micro-strain of the conducting airways with less effect on alveolar area [16]. In the present study, low levels of PEEP may have recruited collapsed conducting airways initially stabilizing communicating alveoli (steep portion of alveolar stability curve in Fig. 2). However, an increase in PEEP may have caused progressive distention in the conducting airways rather than increasing alveolar area and stability. Despite increasing PEEP, alveolar stability plateaus above PEEP of 9 cmH<sub>2</sub>O and never reaches the complete stability (i.e., R/D = 0 %) of the

**Table 1** Hemodynamic and blood gas measurements

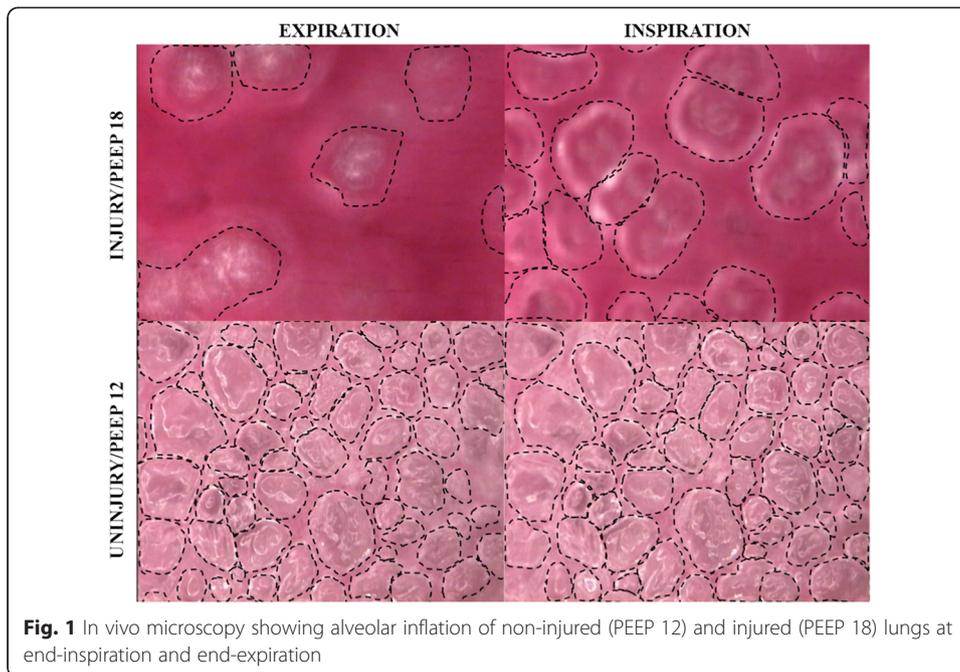
	BL-uninjured	Post-injury	PEEP 3	PEEP 6	PEEP 9	PEEP 12	PEEP 15	PEEP 18
HR (beats/min)	189.1 ± 59.1	186.4 ± 45.1	204.9 ± 44.5	172.2 ± 51.1	186.0 ± 38.3	176.7 ± 44.6	179.9 ± 61.5	150.5 ± 42.9
MAP (mmHg)	71.8 ± 21.1	61.3 ± 12.6	50.6 ± 16.2	52.5 ± 26.5	49.0 ± 24.1	47.4 ± 18.1*	44.5 ± 16.5*	39.1 ± 15.7*
pH	7.35 ± 0.07	7.246 ± 0.087	7.204 ± 0.049*	7.153 ± 0.101*	7.209 ± 0.066*	7.197 ± 0.109*	7.21 ± 0.15*	7.199 ± 0.195*
PaCO <sub>2</sub> (mmHg)	38.11 ± 11.67	53.58 ± 14.43*	47.42 ± 13.21	49.68 ± 11.22	36.49 ± 4.85	35.43 ± 5.99	32.0 ± 7.0	29.39 ± 7.17
PaO <sub>2</sub> (mmHg)	467.5 ± 163.5	54.03 ± 24.70*	60.07 ± 13.10*	106.3 ± 90.47*	169.7 ± 143.5*	221.5 ± 115.5*	266.0 ± 122.0*	352.0 ± 159.0
FiO <sub>2</sub> (%)	100	100	100	100	100	100	100	100
% Saturation	97.63 ± 1.26	56.43 ± 20.96*	64.76 ± 16.04*	65.12 ± 17.54	88.77 ± 5.74	92.26 ± 8.58	93.15 ± 8.11	95.1 ± 5.98
P/F	507.6	54.03*	60.07*	106.3*	169.7*	221.5*	266.0*	352.0*

\* $p \leq 0.05$  as compared to baseline (BL)

**Table 2** Pulmonary measurements

	BL-uninjured	Post-injury	PEEP 3	PEEP 6	PEEP 9	PEEP 12	PEEP 15	PEEP 18
Vt (ml)/kg	6.0 ± 0.5	5.9 ± 0.3	6.0 ± 0.5	5.9 ± 0.3	5.9 ± 0.3	5.9 ± 0.3	5.9 ± 0.3	5.875 ± 0.354
$P_{\text{control}}$ (cmH <sub>2</sub> O)	12.6 ± 2.5	16.9 ± 1.2*	17.6 ± 2.2*	16.6 ± 2.5*	15.5 ± 3.1	14.9 ± 3.1	14.7 ± 3.9	12.88 ± 5.0
$P_{\text{peak}}$ (cmH <sub>2</sub> O)	15.7 ± 2.6	20.1 ± 1.4*	20.7 ± 2.3*	22.5 ± 2.3*	24.5 ± 3.1*	27.0 ± 3.2*	29.7 ± 3.9*	30.88 ± 5.0*
$P_{\text{plateau}}$ (cmH <sub>2</sub> O)	15.7 ± 2.6	20.0 ± 1.3*	20.6 ± 2.2*	22.6 ± 2.5*	24.5 ± 3.1*	27.0 ± 3.2*	29.7 ± 3.9*	30.88 ± 5.0*
$P_{\text{mean}}$ (cmH <sub>2</sub> O)	6.59 ± 0.65	7.72 ± 0.43	7.94 ± 0.72	10.15 ± 0.95*	11.99 ± 1.35*	13.8 ± 1.9*	15.3 ± 3.6*	14.63 ± 2.8*
MV (l/min)	0.183 ± 0.009	0.187 ± 0.022	0.185 ± 0.022	0.184 ± 0.026	0.188 ± 0.019	0.187 ± 0.016	0.19 ± 0.028	0.175 ± 0.018
RR (breaths/min)	30.5 ± 1.6	30.4 ± 2.0	30.9 ± 2.5	32.0 ± 3.3	32.0 ± 3.3	31.6 ± 2.5	31.4 ± 2.9	30.13 ± 3.23

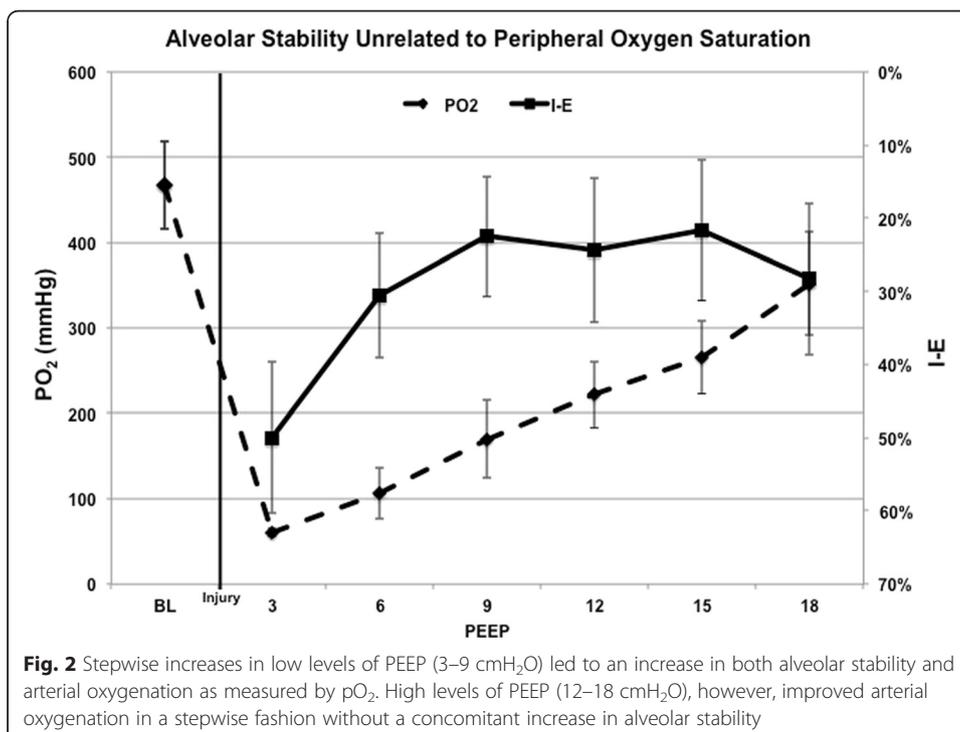
\* $p \leq 0.05$  as compared to baseline (BL)



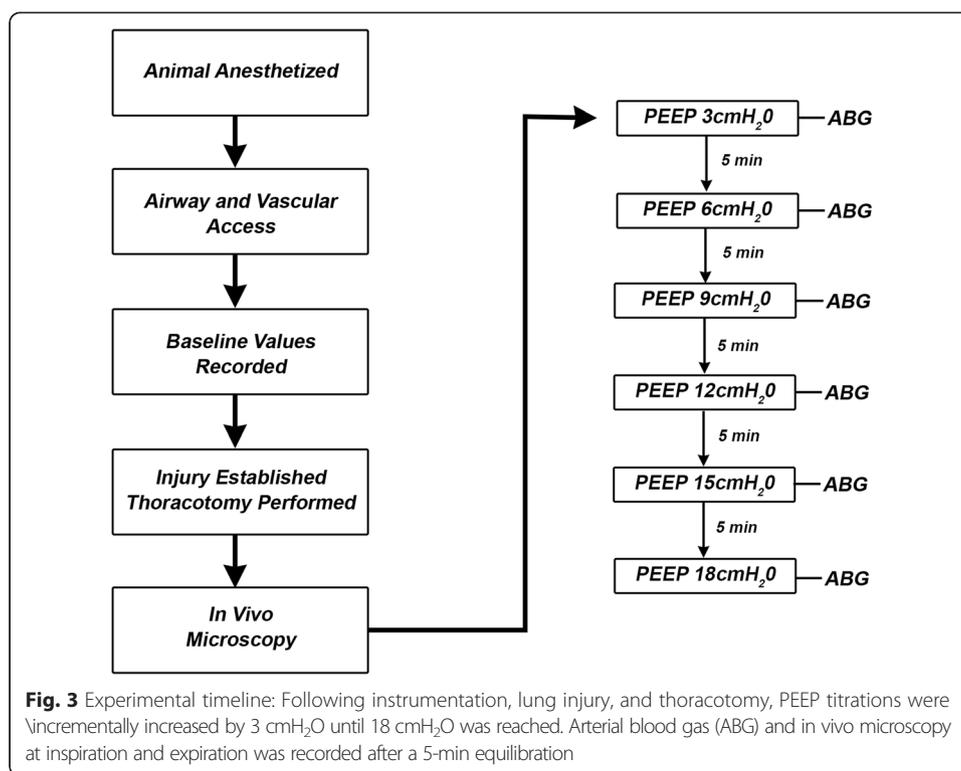
**Fig. 1** In vivo microscopy showing alveolar inflation of non-injured (PEEP 12) and injured (PEEP 18) lungs at end-inspiration and end-expiration

uninjured lung [17]. These data suggest that alveolar stability has a nonlinear relationship to PaO<sub>2</sub>.

We hypothesize that improvement in PaO<sub>2</sub> was due to end-inspiratory tidal recruitment of collapsed alveoli rather than recruitment of unstable alveoli throughout the ventilator cycle (i.e., both I and E). Oxygen would be exchanged during inspiration as the alveolus “pops” open and coupled with the rapid transit time of the erythrocyte,



**Fig. 2** Stepwise increases in low levels of PEEP (3–9 cmH<sub>2</sub>O) led to an increase in both alveolar stability and arterial oxygenation as measured by pO<sub>2</sub>. High levels of PEEP (12–18 cmH<sub>2</sub>O), however, improved arterial oxygenation in a stepwise fashion without a concomitant increase in alveolar stability



maintaining a relatively normal PaO<sub>2</sub>; however, the alveoli collapse during expiration. The linear improvement in PaO<sub>2</sub> without a corresponding increase in alveolar stability suggests persistent alveolar instability, and the potential to expose the lung to *occult VILI* exists and may silently progress to clinical ARDS.

Our data and others demonstrate that perhaps the most widely used marker for lung injury [PaO<sub>2</sub>] is insensitive to detect alveolar instability. Baumgardner et al. used a high-speed intravascular PaO<sub>2</sub> sensor in a saline lavage ARDS model and found that PaO<sub>2</sub> fluctuated within the respiratory cycle [18]. They postulated that PaO<sub>2</sub> rose during inflation when the alveoli were open and fell (during exhalation) when the alveoli collapsed [18]. Using a fiber optic oxygen sensor that detects rapid PaO<sub>2</sub> changes, Formenti and colleagues documented PaO<sub>2</sub> fluctuations between 37 and 375 mmHg between the I and E cycles as a result of cyclical atelectasis [19]. Caltabeloti et al. have shown, using ultrasound, that lung aeration decreases during fluid loading without any deterioration in PaO<sub>2</sub>. These data demonstrate that although oxygenation improves, alveolar R/D-induced VILI may persist but cannot be identified by standard clinical measurements (i.e., PaO<sub>2</sub>). Therefore, if solely guided by PaO<sub>2</sub>, ventilator adjustments may aggravate alveolar instability, particularly when lung injury is evolving secondary to volume resuscitation and a progressing systemic inflammatory response syndrome (SIRS) [20]. Furthermore, uncontrolled R/D increases lung inflammatory response and may propagate other organ dysfunctions and multisystem organ failure [21]. This potentially explains the dichotomy of results in the ARDSnet trial (i.e., improved oxygenation in the high Vt/end-inspiratory pressure group, yet an increase in mortality) [22]. The low tidal volume strategy with lower end-inspiratory pressure may have resulted in a greater regional lung collapse and lower oxygenation; but because these regions remain

collapsed throughout the breathing cycle, they are protected from tidal R/D, resulting in less alveolar instability rather than overdistension (Fig. 2) [23].

Although recruitment maneuvers (RM) were not used in this study, previous work from this lab using *in vivo* microscopy demonstrated that the alveoli open following an RM but remain unstable unless combined with sufficient amounts of PEEP to maintain alveolar patency [24]. Oxygenation significantly improves following RMs despite persistent alveolar R/D, suggesting that unstable alveoli participate in oxygenation during the portion of the ventilatory cycle in which they are open [11]. RMs improve oxygenation but have not demonstrated a mortality benefit [25, 26] supporting our postulate that despite improved PaO<sub>2</sub>, alveolar instability may persist causing progressive lung injury. Nontraditional approaches to MV such as high-frequency oscillatory ventilation (HFOV) use similar goals of PaO<sub>2</sub> or SpO<sub>2</sub> to guide adjustment of ventilator settings. Two recent trials used oxygenation triggers to adjust P<sub>aw</sub> and the decision to convert from HFOV back to conventional ventilation [27, 28]. However, experimentally, we have shown that adjusting P<sub>aw</sub> during HFOV based on PaO<sub>2</sub>-guided protocols resulted in significantly greater histologic lung injury as compared with maintaining a constant P<sub>aw</sub> after lung injury [27, 28]. Combined, these data support our hypothesis that PaO<sub>2</sub> does not correlate with alveolar stability with enough sensitivity to guide ventilator adjustments and relying solely on oxygenation to make ventilator adjustments could increase alveolar instability and promote occult VILI.

Clinically, these data may be important as discordance between PaO<sub>2</sub> and the degree of alveolar instability creates the potential for occult R/D-induced VILI. Robust clinical markers for evaluating alveolar stability are lacking; thus, VILI remains a genuine concern among clinicians who intend to minimize iatrogenic lung injury during MV. In clinical practice, PaO<sub>2</sub> or SpO<sub>2</sub> is routinely used to guide ventilator adjustments [8]. The commonly used PEEP/FiO<sub>2</sub> table derived from the ARDSnet strategy links a PaO<sub>2</sub> or SpO<sub>2</sub> goal to regulate PEEP and FiO<sub>2</sub>. Several investigators have suggested that the PEEP/FiO<sub>2</sub> scale does not impose a physiologic end-point for clinical or computed tomography-guided evidence of recruitment and alveolar stability [29, 30]. In addition, clinicians frequently underdiagnose ARDS suggesting that acceptable oxygenation may leave many without concern for ongoing lung injury [31]. In this study, all animals had an acceptable P/F ratio based on the PEEP/FiO<sub>2</sub> table despite a 25–60 % increase in alveolar instability from baseline. This suggests that achieving clinically acceptable oxygenation goals may not equate with decreased alveolar instability, allowing persistent R/D and the potential for VILI.

### Summary

This study has identified the need of detecting alveolar instability and optimizing MV settings to promote alveolar stability and lung homogeneity using methods other than PaO<sub>2</sub>. Possible methods include the following: (a) electrical impedance tomography (EIT) which provides an assessment of lung volume, PEEP level, and V<sub>t</sub> distribution rather than the relationship of V<sub>t</sub> to ideal body weight [32–34]; (b) routine evaluation of the respiratory system as a whole with transpulmonary pressure measurement to determine the effect of the chest wall and abdomen on lung mechanics [35–37]; and (c) monitoring the expiratory flow graphics when using modes such as airway pressure

release ventilation (APRV) to control expiratory time constants which has been shown to eliminate alveolar instability [38, 39]. These methods are all currently available and may guide ventilator adjustments rather than relying on the insensitivity of PaO<sub>2</sub> and SpO<sub>2</sub> or the macro-environment parameter such as Paw [14, 32–39].

The concept that preemptive ventilation strategies may be therapeutic is obverse to the current understanding that MV creates or aggravates lung injury (i.e., VILI). Although both concepts may be accurate, the key may be the method of MV and the timing of application in the pathogenesis of the disease (i.e., early vs. late) [13, 14, 39, 40]. The causal role of MV in progressing acute lung injury (ALI) may be determined by adjustment of ventilator settings to adequately prevent alveolar instability and heterogeneity. If adjusted properly, the ventilator may be used to halt the progression of ALI pathogenesis and reduce the incidence of ARDS [12–14, 16, 39, 40].

### Critique of the model

While we speculate that the steady increase observed in PaO<sub>2</sub> without a marked change in alveolar stability at PEEP levels of >9 cmH<sub>2</sub>O was likely due to increased alveolar recruitment, this recruitment was not confirmed by direct measurement. Also, our *in vivo* microscope has limitations such as the shallow depth of field (70 μm), limiting observations of alveolar mechanics to only two dimensions. We used gentle suction (≤5 cmH<sub>2</sub>O) to hold lung tissue in place underneath the glass coverslip in all experimental settings standardizing this artifact, which has been shown previously to have minimal effect on alveolar mechanics [41].

### Conclusions

Our data suggest that oxygenation (PaO<sub>2</sub>) may be a poor marker for alveolar stability and occult VILI may exist despite meeting acceptable clinical criteria. Further, using PaO<sub>2</sub> to guide titration of MV settings (PEEP and Pplat) may result in increased alveolar instability and increase the potential for VILI. New methods to identify alveolar stability are needed for clinical assessment and protection from occult VILI. In combination with judicious use of MV, the goal of eliminating VILI in the critical care population may eventually be realized.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

PLA and NMH had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. PLA, BS, MK-S, JS, SR, KS, LAG, GFN, and NMH contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. All authors read and approved the final manuscript.

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