Unstable Inflation Causing Injury

Insight from Prone Position and Paired Computed Tomography Scans

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Abstract

Rationale: It remains unclear how prone positioning improves survival in acute respiratory distress syndrome. Using serial computed tomography (CT), we previously reported that “unstable” inflation (i.e., partial aeration with large tidal density swings, indicating increased local strain) is associated with injury progression.

Objectives: We prospectively tested whether prone position contains the early propagation of experimental lung injury by stabilizing inflation.

Methods: Injury was induced by tracheal hydrochloric acid in rats; after randomization to supine or prone position, injurious ventilation was commenced using high tidal volume and low positive end-expiratory pressure. Paired end-inspiratory (EI) and end-expiratory (EE) CT scans were acquired at baseline and hourly up to 3 hours. Each sequential pair (EI, EE) of CT images was superimposed in parametric response maps to analyze inflation. Unstable inflation was then measured in each voxel in both dependent and nondependent

lung. In addition, five pigs were imaged (EI and EE) prone versus supine, before and (1 hour) after hydrochloric acid aspiration.

Measurements and Main Results: In rats, prone position limited lung injury propagation and increased survival (11/12 vs. 7/12 supine; $P = 0.01$). EI–EE densities, respiratory mechanics, and blood gases deteriorated more in supine versus prone rats. At baseline, more voxels with unstable inflation occurred in dependent versus nondependent regions when supine ($41 \pm 6\%$ vs. $18 \pm 7\%$; $P < 0.01$) but not when prone. In supine pigs, unstable inflation predominated in dorsal regions and was attenuated by prone positioning.

Conclusions: Prone position limits the radiologic progression of early lung injury. Minimizing unstable inflation in this setting may alleviate the burden of acute respiratory distress syndrome.

Keywords: acute respiratory distress syndrome; ventilator-associated lung injury; prone position ventilation; computed tomography; parametric response mapping

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At a Glance Commentary

Scientific Knowledge on the

Subject: Ventilation in the prone position increases oxygenation and improves survival in severe acute respiratory distress syndrome; however, the specific mechanism through which prone positioning improves survival is not known.

What This Study Adds to the

Field: Using paired, serial computed tomography scans taken at inspiration and at expiration, we identified regions of unstable inflation (partially aerated voxels with large tidal swings in tissue density) that indicate local lung stress. We report that prone positioning contains the early propagation of ventilator-associated lung injury, an effect that is related to reduced vertical gradients of unstable inflation. This imaging approach may ultimately improve clinical prognostication by identifying patients with acute respiratory distress syndrome who have a higher (or lower) probability of positive response to intervention.

Secondary lung injury caused by mechanical ventilation increases mortality in acute respiratory distress syndrome (ARDS) (1–3). Because clinical trials of ventilator strategy in ARDS over the last 15 years have not substantially improved on mortality,

new strategies for reducing ventilator-associated lung injury (VALI) are needed.

Although ventilating patients in the prone position increases survival (4), the improved gas exchange associated with this strategy (5) does not explain the survival benefit (6). Imaging studies using quantitative computed tomography (CT) (7) and positron emission tomography (8) report that prone positioning attenuates vertical gradients of aeration observed while supine. Such recruitment of atelectatic lung might lessen secondary VALI by reducing regional strain during inspiration (9). However, it is not known if the homogeneity of inflation in the prone position is responsible for attenuating the progression of lung injury; this is potentially important for clinical management, because attenuation in the early stages might lessen the burden of established ARDS.

In our previous studies of experimental ARDS, we used sequential CT imaging to show that regional lung strain drives the propagation of early lung injury (10). Tidal inflation was imaged after primary injury, and the resultant parametric response maps of paired CT scans (i.e., paired scans at end-inspiration [EI] and at end-expiration [EE]) showed areas with partially aerated voxels and large tidal swings in tissue density. We termed this “unstable inflation,” and it was associated with the radiologic propagation of secondary lung injury. Moreover, in both experimental lung injury and in patients with ARDS, the proportion of (voxels with)

unstable inflation was directly related to the extent of injury progression (10).

In the current study, we used these insights to explore the mechanisms of protection afforded by prone (vs. supine) positioning in early lung injury. By linking the regional distribution of inflation with the subsequent trajectory of injury, we were able to successfully test two hypotheses. First, ventilation in the prone position limits the early progression of secondary lung injury following a primary insult. Second, this effect is related to a reduction of the vertical gradients of unstable inflation associated with supine positioning. In an additional series of ventilated pigs, we verified the effects of prone position on unstable inflation in a large animal model. Some of these results have been presented in abstract form (11, 12).

Methods

Outline

All animal studies were approved by the Animal Care and Use Committee of the University of Pennsylvania. The outline of the small animal experiments is illustrated in Figure 1. Methodologic details are fully described in the online supplement.

Animal Preparation: Rats

Twenty-four male Sprague-Dawley rats (365 ± 21 g) were anesthetized with intraperitoneal pentobarbital, orally intubated, and paralyzed with pancuronium bromide. The carotid artery was catheterized.

Figure 1. Experimental timeline in rats ventilated in supine versus prone position after hydrochloric acid aspiration. Identical ventilator settings were used in both groups. In the prone group, additional inspiratory and expiratory computed tomography scans were acquired at baseline (after hydrochloric acid) in the supine position to assess the acute effects of prone ventilation on inflation distribution and to compare injury distribution with supine ventilation group. CT = computed tomography; EE = end-expiration; EI = end-inspiration; HCl = hydrochloric acid; PEEP = positive end-expiratory pressure; TV = tidal volume.

Figure 2. Group statistics (mean and SD) of (A) respiratory system compliance, (B) total lung volumes, and (C) lung mass normalized to baseline. All measurements were obtained at baseline (after hydrochloric acid) and after 1 and 2 hours of ventilation. [†] $P < 0.05$ between cohorts; [§] $P < 0.05$ versus baseline in the same group. EE = end-expiration; EI = end-inspiration.

Heart rate and oxygen saturation were monitored by pulse-oximetry.

Mechanical Ventilation

Animals were ventilated with V_T (6 ml/kg) and positive end-expiratory pressure

(PEEP; 10 cm H₂O) using a custom-built ventilator (13). Peak inspiratory airway pressure and PEEP were recorded, and dynamic compliance was calculated as $C_{dyn} = V_T \cdot (\text{peak inspiratory airway pressure} - \text{PEEP})^{-1}$.

Lung Injury

All rats received 2.5 ml/kg hydrochloric acid (HCl; pH 1.25) through the endotracheal tube in two aliquots (10, 14), while in the right and left lateral decubitus. After 1 hour of supine stabilization (V_T 6 ml/kg; PEEP 10 cm H₂O), rats were randomized to ventilation in supine or prone position (12 rats in each group) for up to 3 hours, using settings known to induce secondary VALI (10, 14): V_T 12 ml/kg, PEEP 3 cm H₂O, FiO_2 1.0, and frequency 53 min⁻¹.

Small Animal Imaging

Whole-lung CT was performed at baseline (when stabilized after HCl) and hourly thereafter. Imaging was performed at EI and EE. In the prone group, additional supine images were obtained at baseline to allow between-group comparisons of primary injury severity.

Image Analysis

The lung boundaries were semiautomatically delineated using a previously developed algorithm (15), yielding whole-lung regions of interest. EI and EE images were registered (aligned) to each other using methodology to superimpose anatomic features when distorted by respiration (10). To assess the effect of gravity and position on regional inflation (and on lung injury progression), lungs were partitioned into three coronal bins of equal thickness (ventral, middle, and dorsal). Parametric response maps were then generated for the whole lung, and for each bin by matching individual voxels in each set of paired EI and EE images (10, 16–19). Voxels were categorized as severe injury if both EI and

Table 1. Physiologic Characteristics of Two Groups of Rats Ventilated in the Prone versus Supine Position after Hydrochloric Acid Instillation in the Trachea

	Supine			Prone		
	Baseline	1 h	2 h	Baseline	1 h	2 h*
Arterial blood pressure, mm Hg	113.8 ± 12.3	108.9 ± 19.9	82.9 ± 41.9 [†]	126.0 ± 8.4	118.2 ± 23.1	104.8 ± 28.5 [†]
Driving pressure, cm H ₂ O	19.1 ± 2.9	23.3 ± 5.6 [†]	28.7 ± 6.6 [†]	19.9 ± 2.2	20.7 ± 3.3	21.8 ± 4.0 [†]
P _{O₂} , mm Hg	396.3 ± 79.7	107.5 ± 56.5 [†]	43.6 ± 7.5 [†]	388.8 ± 65.9	217.0 ± 109.3 ^{††}	142.9 ± 108.1
P _{CO₂} , mm Hg	45.9 ± 8.2	50.0 ± 11.2	50.6 ± 10.2	46.4 ± 6.7	44.8 ± 7.8	48.7 ± 11.1
pH	7.34 ± 0.06	7.26 ± 0.06 [†]	7.19 ± 0.04 [†]	7.32 ± 0.07	7.29 ± 0.01	7.30 ± 0.06
Sp _{O₂} , %	99.9 ± 0.1	94.5 ± 4.9 [†]	65.9 ± 11.7 [†]	99.9 ± 0.1	99.0 ± 0.8	94.4 ± 7.5 ^{††}
Blood lactate, mmol/L	1.28 ± 0.40	2.50 ± 1.29 [†]	4.82 ± 3.26 [†]	1.54 ± 0.72	1.89 ± 1.38	1.49 ± 0.08

Definition of abbreviation: Sp_{O₂} = oxygen saturation as measured by pulse.

*In the prone group, arterial blood gases were available at 2 hours in only three rats because of positional difficulties drawing blood through the carotid catheter after 1 hour of prone ventilation.

[†] $P < 0.05$ versus baseline in the same group.

^{††} $P < 0.05$ between cohorts.

EE densities were greater than -300 Hounsfield units (HU), indicating pulmonary edema and stable atelectasis, and as unstable inflation if densities fell in the range (EE, 0 to -600 HU; EI, -300 to -700 HU) that we previously found to indicate a high probability of injury progression (10).

Large Animals

Five Yorkshire pigs (32.4 ± 2.7 kg) were anesthetized, intubated, ventilated with V_T 8 ml/kg, and received tracheal HCl (pH 1.25 , ml/kg into each lung). EI and EE CT scans were obtained at baseline and 1 hour after HCl, during ventilation in prone and supine position and with PEEP 5 and 10 cm H_2O . All images were analyzed as described for the rats.

Statistical Analysis

Image analysis was performed using Matlab 2016b software applications developed in the authors' laboratory. Statistical analysis was performed using R (R Foundation for Statistical Computing). Group mean and SD of all the computed quantities were calculated. *Post hoc* Student's *t* tests were used to identify differences among means, and Bonferroni adjustment was performed. The Fisher exact test was used for proportions. *P* less than 0.05 was considered statistically significant.

Results

Small Animal Studies

Survival. Ventilation in the prone position significantly improved survival; five rats in the supine group died between 2 and 3 hours of ventilation, compared with one in the prone group (Fisher, $P = 0.013$).

Respiratory and vital parameters.

Compliance (Figure 2A) and driving pressure (Table 1) were comparable between groups at baseline. In the supine group, compliance decreased at 1 hour and again at 2 hours of ventilation ($P < 0.01$ vs. baseline), reaching lower values than in the prone group ($P < 0.01$ at both times) (Figure 2A).

Baseline oxygenation was similar between groups (Table 1), but Pa_{O_2} was lower in the supine than in the prone group after 1 hour of ventilation ($P < 0.01$), and further decreased in the supine group over time. No significant effect of time or body position on Pa_{CO_2} was detected.

Oxygen saturation followed a similar trend to Pa_{O_2} (Table 1). Blood pH was lower in the supine group than in the prone group after 1 hour of ventilation ($P < 0.05$) because of higher lactic acid concentration in the former group (Table 1).

Arterial blood pressure decreased from baseline after 2 hours of ventilation in both groups ($P < 0.01$), although it was higher in prone than in supine rats at this time (Table 1).

Distribution and progression of lung injury. Baseline CT scans, obtained supine in both groups, confirmed that the distribution of primary injury was similar and that primary lesions were dorsal, irrespective of group assignment (Figure 3).

In supine animals, injury propagated rapidly over the entire lung (Figure 3, top), as previously described (10). Changing

from supine to prone position resulted in the attenuation of dorsal hyperdensities, which remained stable thereafter for the duration of the experiment (Figure 3, bottom).

Quantitative CT analysis demonstrated that EI and EE lung gas volumes were smaller in supine versus prone animals during the course of the experiment ($P < 0.01$); EI and EE values also decreased to a greater extent in supine versus prone rats (Figure 2B). CT estimates of lung weight (reflecting tissue edema) increased only in the supine group (Figure 2C).

Baseline parametric response maps in the supine position were similar in the two groups, indicating comparable inflation conditions after the primary (acid instillation) lung injury (Figure 4). At each subsequent time point, maps showed an

Figure 3. Radiologic injury propagation in four representative rats ventilated in prone versus supine position (two rats in each group) and imaged at end-inspiration. Baseline (after hydrochloric acid) supine images are also shown for the two prone rats (#3 and #4). In all rats, primary injury was initially localized in the dorsal lung regions. In the rats ventilated supine (#1 and #2), injury rapidly spread over the entire lung. In the prone rats, position change improved aeration in the dorsal lung regions (black arrows) and subsequent injury propagation was more contained. The blue triangles indicate body position (up-pointing, supine; down-pointing, prone).

Figure 4. Whole-lung parametric response maps obtained at baseline after hydrochloric acid aspiration and hourly until the end of the experiment in the two experimental cohorts. Each map shows a cumulative voxel distribution for each condition, obtained by incorporating all rats in each group and averaging the distributions. The blue triangles indicate body position (up-pointing, supine; down-pointing, prone). In the supine rats, maps evolved with increased representation of voxels with nonreversible high-density (square), indicating edema and/or nonreversible atelectasis (severe injury). In this group, voxels with complete expiratory loss of gas content and inspiratory re-aeration (indicating reversible atelectasis) appeared only after 1 and 2 hours of ventilation (arrow). In the prone rats, the voxel distributions were more stable over time. HU = Hounsfield units.

evolving distribution of voxels in the supine group (Figure 4, top), with more voxels developing in the higher (> -300 HU) domains of EI and EE density, indicating severe injury (square); voxels with reversible expiratory loss of gas content (indicating cyclic recruitment) appeared only after 1 hour of ventilation (arrow). Low-density voxels were prevalent at all times in the prone rats, and density distribution evolved only minimally (Figure 4, bottom). Categorization of voxels showed a progressive increase in the fraction of unstable inflation voxels in supine (baseline, $28.5 \pm 6.7\%$; end, $44.1 \pm 22.8\%$; $P < 0.01$), but not in prone position (baseline, $26.9 \pm 3.2\%$; end, $28.7 \pm 4.9\%$; $P = 0.35$). Representative EI-EE images are shown in Figure E1 in the online supplement.

Regional injury. Analysis of the three horizontal bins showed that time-dependent increases of EI-EE density were more prominent in the dependent (i.e., dorsal) versus nondependent lung in the supine group (Figure 5).

In baseline supine scans, the averaged voxel distribution was of lower density in

nondependent lung regions, and of higher density in the dependent lung (Figure 5). This shift was characterized by the changing position of the distribution centroid (Figure 5, dashed line).

In the prone position, minimal gravity-related change of the voxel distributions (or the respective centroids) was observed (Figure 5), and evolution was comparable between dependent (ventral) and nondependent (dorsal) bins.

Categorization of voxel distribution at baseline showed that unstable inflation and severely injured voxels were significantly affected by gravity in the supine position, but not in the prone position (Figure 6A). In supine animals, significantly higher fractions of unstable inflation and severe injury tissue voxels were present in the dependent (dorsal) regions of the lungs compared with the other regions.

Finally, the baseline fraction of unstable inflation voxels in the dorsal bins (dependent in supine, nondependent in prone) was positively correlated with the decrease in respiratory system compliance ($R = 0.71$; Figure 6B), but not with severe injury.

Large Animal Studies

In the pig experiments, HCl aspiration caused mild oxygenation impairment, worsened mechanics, and relatively small dorsal hyperdensities on CT (Table E1 and Figure E2). Prone positioning attenuated functional abnormalities and dorsal opacities. After HCl, parametric response maps showed the appearance of more voxels with unstable inflation in the dorsal bin (Figures 7 and Figure E4). This abnormal inflation was attenuated but not abolished in the prone position with PEEP 5 cm H₂O. PEEP 10 cm H₂O also produced a decrease in dorsal voxels with unstable inflation, but inflation distribution was further improved in the prone position.

Discussion

In this study, prone positioning limited the early propagation of radiologic abnormalities after experimental lung injury and improved survival during mechanical ventilation. The effect of prone positioning was likely related to its ability to decrease areas of unstable inflation in the dependent

Figure 5. Cumulative parametric response maps of end-inspiration/end-expiration voxels partitioned in nondependent, mid-level, and dependent regions of the lungs (indicated by the solid blue color in the triangle) in the prone and supine position (indicated by the tip of the triangle). In the supine position at baseline, the centroid of the voxel distribution shifted toward higher density following the gravitational gradient. Over time, changes in the voxel distributions were more evident in the dependent lung regions than in the nondependent ones. In the prone position, the centroid and the voxel distribution changed minimally in the three regions at baseline (minimal deviation from white vertical reference line); evolution in the dorsal lung regions was less than in the supine rats. The area including voxels with unstable inflation is highlighted (green border) in the dorsal maps. HU = Hounsfield units.

Figure 6. (A) Unstable inflation and severely injured voxels are shown (as a percent of total) in the nondependent, mid-level, and dependent lung regions of the baseline images obtained in supine and prone rats. (B) Correlation between change in compliance (between baseline and the end of the experiment) and baseline percent fraction of unstable inflation voxels in the dependent lung regions. Solid triangles indicate rats that died before 2 hours of ventilation. † $P < 0.05$ between cohorts.

regions of the lungs. Thus, prone positioning could prevent severe ARDS by protecting the lungs from the progression of injury in its early stages.

Although prone positioning has been introduced as a rescue therapy for severely hypoxemic ARDS (20–22), the improved oxygenation that it produces does not explain the observed improvement in survival among patients with severe ARDS (6). Using serial CT, our study showed that prone positioning reduced the regional propagation of CT densities compared with supine positioning, while also attenuating the deterioration of respiratory mechanics and development of pulmonary edema (estimated from tissue weight). These results suggest that prone positioning may improve ARDS outcomes by alleviating the early evolution of secondary (ventilator-associated) lung injury, before it becomes severe.

In a previous study of mechanical ventilation with nonprotective settings in experimental ARDS (14), we reported that radiologic propagation is the visual manifestation of evolving lung injury. Using analysis of longitudinal CT scans in a similar model (10), we then observed that this secondary propagation was more severe in lungs that displayed larger areas of tissue with unstable inflation. In that same study, unstable inflation was also found to be associated with higher mortality in a small group of patients with early ARDS (10). Partial inflation includes areas with

stable poor aeration, but it is dominated by large tidal density changes within partially aerated tissue. Studies using diffusion magnetic resonance imaging suggest that this pattern of inflation indicates overstretched airspaces embedded in voxels with reduced (but not abolished) gas content (13, 23, 24). Although unstable inflation may be simply a marker of heterogeneous gas distribution, such stress concentration can regionally increase the risk of VALI (25, 26). Unstable inflation is distinct from cyclic recruitment of atelectasis, which is defined as complete but reversible loss of aeration (27). As with unstable inflation, cyclic recruitment was not correlated with propagation of injury after acid aspiration (14).

In the current study, regional analysis revealed a vertical gradient of abnormal inflation in supine rats that was not present in prone rats. Voxels with unstable inflation were more abundant in the dependent (dorsal) lung of supine rats, where the radiologic signs of both primary injury and its progression were more visible. We also observed that, irrespective of body position, the baseline fraction of unstable inflation in the dorsal lung predicted worsening mechanics (Figure 6B). Overall, the findings of this study suggest that prone positioning reduced the harmful effects of mechanical ventilation in dependent regions of tissue with unstable inflation, thereby mitigating the radiologic propagation of the injury to the rest of the lung. Further studies are

needed to confirm that tissue inflammation is attenuated by this strategy.

Other authors have studied the effects of the prone position on regional lung mechanics and VALI, finding that prone position attenuated vertical gradients of pleural pressure and regional strain, in addition to improving dorsal atelectasis (28, 29) and ventral hyperinflation (30). Using CT in established ARDS, prone position was shown to augment recruitment by PEEP (9). Nuclear medicine studies have shown less heterogeneity of both lung aeration and perfusion in prone versus supine sheep with surfactant depletion (31). Another study showed that prone position delayed the progression of lung injury in previously healthy lungs receiving high stretch ventilation (32), supporting a causal relation between improved mechanics and milder injury. Finally, in a study of preinjured lungs (oleic acid) receiving ventilation with elevated inflation pressure, prone positioning attenuated injury in the dorsal lung (33), suggesting that attenuation of airspace collapse in dependent regions may be crucial to the success of positional therapy.

Our work differs from these previous studies (9, 28–32, 34) in that it is the first to demonstrate that prone positioning can attenuate the radiologic and functional progression of lung injury, before it becomes established and severe. This finding was enabled by our use of longitudinal imaging, which allowed us to link unstable inflation, future propagation of lung injury, and response to body position. Furthermore, our model recapitulates the early evolution of lung injury, when hypoxemia is still mild and radiologic abnormalities are spatially limited. Our short-term studies in pigs showed that, similar to the rats, prone position decreased unstable inflation in the dorsal lung, supporting long-term experiments to test this approach in large animals. Similar to our previous studies (10, 14), we used a model of secondary VALI superimposed on mild primary injury, as indicated by the relatively mild oxygenation impairment at 1 hour after acid aspiration in both rat cohorts (Table 1). In addition to helping understand how positional therapy improves outcomes, this study's findings suggest a potential new use for prone positioning: it could be used in patients with early lung injury to prevent the development of severe ARDS.

Figure 7. Cumulative parametric response maps in five pigs imaged before and 1 hour after HCl aspiration. Pigs were ventilated in the prone versus supine position with tidal volume 8 ml/kg and PEEP 5 and 10 cm H₂O. Similar to the rats, we observed a gravitational gradient of inflation distribution when the animals were supine, with more representation of unstable inflation voxels in dependent lung after injury. This maldistribution improved at higher PEEP, but it persisted in the supine position. Prone positioning caused a more homogeneous voxel distribution at both PEEP levels. The triangles follow the same format as in Figure 5. HCl = hydrochloric acid; HU = Hounsfield units; PEEP = positive end-expiratory pressure.

In a clinical trial that recruited only patients with severe hypoxemia, Guerin and colleagues (4) reported better outcomes with prone versus supine position; in contrast, outcomes were mixed in earlier clinical trials that included patients with less severe ARDS (35). However, this does not mean that prone position is ineffective in carefully selected subjects with milder hypoxemia, because the discrepancy may be related to heterogeneity of patient characteristics within the study populations (36). In fact, a one-time measurement of oxygenation impairment is a worse prognostic indicator than either treatment responsiveness (37) or imaging-derived metrics (10, 38). Although we do not yet propose clinical implementation of this evidence, the current study suggests that the effectiveness of prone position may be related to the characteristics described in the dependent lung. In addition to CT scanning, other methodologies (e.g., lung ultrasound [39], and electrical impedance tomography [40]) may allow for the efficient measurement of unstable dorsal inflation to assess the early risk of injury progression.

There are several limitations inherent to this study. First, as shown by our previous studies, injury progression is variable in this animal model, and could be affected by intergroup differences of baseline severity rather than by treatment. However, measured treatment effects were large, and the primary injury was consistent between groups. In addition, the baseline images obtained while supine showed similar injury morphology in animals before randomization into prone and supine cohorts (Figure 3) and in parametric response maps (Figures 4 and 5).

Second, we used nonprotective ventilator settings (i.e., large tidal volume and low PEEP). The choice of such settings diminishes the clinical relevance of our study but was motivated by the need to visualize injury progression within the time

frame of the experiment. However, relatively high tidal volumes and low PEEP continue to be used in clinical practice (1). Smaller tidal volumes and higher PEEP could have attenuated injury, while redistributing mixed and heterogeneous aeration to more ventral lung regions (41) as a consequence of dorsal recruitment. However, in the pig studies (V_T 8 ml/kg), dorsal unstable inflation persisted at PEEP 10 cm H_2O and was decreased by prone positioning; the efficacy of prone positioning thus was maintained at higher PEEP levels (Figures 7 and Figure E4).

Third, the dorsal lung was more involved by the primary injury, which was an intentional consequence of the HCl injection technique meant to mimic human aspiration injury. The efficacy of position with other injury distributions (e.g. ventral predominance) was not explored in the current study and could be different if prone position does not improve regional inflation patterns.

Finally, the rat model may be less affected by gravity than larger animals and humans. Inflation distribution may be governed by changes in thoracic geometry rather than by gravity vector (32), as suggested by the larger chest wall diameters in prone versus supine rats (see Table E2). Irrespective of the mechanism, however, we were able to find vertical gradients of inflation distribution in rats that qualitatively resembled those observed in the pigs. We may expect similar effects of prone positioning on injury propagation in large animal models, although this needs verification.

We used radiologic and functional variables as surrogates for tissue inflammation, rather than attempting direct measurements. The distributions of histologic injury and radiologic densities are similar in spatially matched tissue and CT slices (14). Furthermore, respiratory compliance is a surrogate of VALI in animal models (42). Further studies are

required to characterize the spatial relationships between severe injury, unstable inflation, and tissue inflammation. Although lung inflammation is often detectable in the nondependent lung that receives most of the inspired gas (43–45), this may be a characteristic of established ARDS: studies on the early stages of injury showed inflammation in dependent lung regions with poor aeration, which could be a consequence of local stress (46). Mechanisms other than redistribution of inflation and attenuation of VALI may influence the effects of prone positioning on injury progression. These include reduced secretions and increased bacterial clearance, and reduced blood flow to areas of injury (47). Furthermore, reduced cardiac output could decrease capillary perfusion and lessen pulmonary edema. However, mean intrathoracic pressure was likely similar in both positions, because the same ventilator settings were maintained in both conditions. In addition, blood pressure was greater (and lactate lower) in the prone position, suggesting hemodynamic advantage as previously described (48). Finally, left heart failure, hypotension, and acute cor pulmonale could have exacerbated edema and caused greater mechanical impairment in the supine group (49).

Conclusions

This experimental study indicates that prone position attenuates the trajectory of early lung injury, suggesting a possible use of this strategy in selected patients, to prevent progression to severe ARDS. Further experimental and clinical studies are required to confirm whether unstable inflation can be used as a predictor of both ARDS progression and of treatment success. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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