Lung ventilation injures areas with discrete alveolar flooding, in a surface tension-dependent fashion

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Wu Y, Kharge AB, Perlman CE. Lung ventilation injures areas with discrete alveolar flooding, in a surface tension-dependent fashion. J Appl Physiol 117: 788–796, 2014. First published July 31, 2014; doi:10.1152/japplphysiol.00569.2014.—With proteinaceous-liquid flooding of discrete alveoli, a model of the edema pattern in the acute respiratory distress syndrome, lung inflation over expands aerated alveoli adjacent to flooded alveoli. Theoretical considerations suggest that the overexpansion may be proportional to surface tension, T. Yet recent evidence indicates proteinaceous edema liquid may not elevate T. Thus whether the overexpansion is injurious is not known. Here, working in the isolated, perfused rat lung, we quantify fluorescence movement from the vasculature to the alveolar liquid phase as a measure of overdistension injury to the alveolar-capillary barrier. We label the perfusate with fluorescence; micropuncture a surface alveolus and instill a controlled volume of nonfluorescent liquid to obtain a micropunctured-but-aerated region (control group) or a region with discrete alveolar flooding: image the region at a constant transpulmonary pressure of 5 cmH₂O; apply five ventilation cycles with a positive end-expiratory pressure of 0–20 cmH₂O and tidal volume of 6 or 12 ml/kg; return the lung to a constant transpulmonary pressure of 5 cmH₂O; and image for an additional 10 min. In aerated areas, ventilation is not injurious. With discrete alveolar flooding, all ventilation protocols cause sustained injury. Greater positive end-expiratory pressure or tidal volume increases injury. Furthermore, we determine T and find injury increases with T. Inclusion of either plasma proteins or Survanta in the flooding liquid does not alter T or injury. Inclusion of 2.7–10% albumin and 1% Survanta together, however, lowers T and injury. Contrary to expectation, albumin or Survanta in the flooding liquid does not alter T. Yet recent evidence indicates, proteinaceous edema liquid may not elevate T. Thus whether the overexpansion is injurious is not known.

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of an edematous area with heterogeneous alveolar flooding. We subject the lung to five ventilation cycles. We quantify dye leakage from vasculature to alveolus as an indicator of the injury imposed by varied ventilation protocols. Furthermore, investigating the interaction between plasma proteins and exogenous surfactant, we find that plasma proteins have the potential to play an unexpected role in protecting against ventilation injury.

METHODS

In an excised rat lung model, we assess ventilation injury and determine alveolar liquid-phase surface tension.

Isolated, Perfused Rat Lung

We handle all animals in accord with a protocol approved by the Stevens Institute of Technology Institutional Animal Care and Use Committee. We anesthetize male Sprague-Dawley rats (n = 94, 250–425 g) and prepare the isolated, perfused rat lung as previously described (34). We inflate the lung to a transpulmonary pressure of 30 cmH2O and then deflate it to 5 cmH2O. In the isolated lung, transpulmonary pressure equals alveolar air pressure, \( P_{AVL} \). Unless otherwise specified, we perfuse the isolated lung with 10 ml of autologous blood plus 18 ml of 5% albumin (Sigma Aldrich, St. Louis, MO) in normal saline and 23 \( \mu \)M calcein red-orange AM (Life Technologies, Grand Island, NY) in the instilled liquid to label the epithelium and thus verify the location of the aerated alveolar liquid lining layer.

Injury Assay

We assess ventilation-induced injury by tracking ventilation-induced fluorescence movement across the alveolar-capillary barrier.

Determination of ventilation settings. To determine the end-expiratory transpulmonary pressure, \( P_{AVL\ MIN} \), to apply during ventilation of the isolated rat lung for simulation of clinical PEEP (end-expiratory airway pressure with intact chest wall), we rely on a relation obtained by Pelosi et al. (21) in an instrumented, closed-chested canine lung injury model. We use data from Pelosi et al. obtained by pleural pressure transducer and the curve for the most normally aerated, independent portion of the lung: \( P_{AVL\ MIN} = 3.3 + 0.6 \) PEEP, where pressures are in cmH2O.

With our experimental setup, we can precisely control airway entrance pressure. As described previously, we pass compressed air through a series of regulators to step down the pressure and then bleed most of the air flow through a manually operated side valve. By closing the side valve we inflate the lung, and by opening the side valve we deflate the lung (16). Given our ability to control inflation pressure and our desire to specify tidal volume (\( V_T \)), we perform preliminary volume-controlled ventilation experiments to determine the peak inspiratory transpulmonary pressure, \( P_{AVL\ MAX} \), generated by a given PEEP/\( V_T \) combination in an animal of a given body weight and then, subsequently, use pressure-controlled ventilation to mimic volume-controlled ventilation. We use a 10-ml glass syringe to ventilate manually the isolated, nonperfused rat lung. We ventilate with a \( P_{AVL\ MIN} \) corresponding to a PEEP of 0, 5, 10, 15, or 20 cmH2O; a \( V_T \) of 6 or 12 ml/kg actual body weight; and a frequency of 0.33 Hz. We subject each set of lungs to four replicates of each combination of ventilation settings and record \( P_{AVL\ MAX} \) under each condition, noting that lack of perfusion may introduce a small error into our \( P_{AVL\ MAX} \) determinations under dynamic conditions (25). We perform subsequent ventilation injury experiments by ventilating the isolated, perfused lung at 0.33 Hz between the determined \( P_{AVL\ MIN} \) and \( P_{AVL\ MAX} \) that correspond to the targeted PEEP and \( V_T \).

Alveolar flooding. To generate a local model of heterogeneous alveolar flooding, we micropuncture a subpleural alveolus and inject \( \approx 300 \) nl of model edema liquid. Following injection, 43 ± 6% of surface alveoli in the microscopic field remain flooded (n = 6 randomly selected flooded fields, each from a different animal). These flooded alveoli are interspersed with aerated alveoli. To generate a control area in which we have micropunctured but not generated an edema model, we flood only 5–10 surface alveoli and then wait 1 min, during which time the very low volume of instilled liquid spontaneously clears from all alveoli (33). We repeat the procedure three times. We are left with an entirely aerated region (34).

In testing the injuriousness of different ventilation protocols, we use as the model edema liquid 3% albumin in normal saline. In testing the effect of model edema liquid composition on barrier injury, we vary the instilled liquid as follows. To test the effect of plasma protein concentration or type, we use an alternative albumin concentration of 0, 1, 2, 5, 10, 11, 12, or 30% or replace albumin with 5% fibrinogen (Sigma Aldrich). As an osmotic control, we replace albumin with 5% 70-kDa dextran (Sigma Aldrich). To test negatively charged dextran, we add 10 \( \mu \)M NaOH (VWR, Radnor, PA) to a 5% dextran solution. As a control for the 10 \( \mu \)M NaOH plus 5% dextran solution, we test 10 \( \mu \)M NaOH alone. To test the effect of exogenous surfactant, we add 1% Survanta (Abbott Nutrition, Columbus, OH) to the above solutions.

In a subset of control experiments in aerated regions, we include calcein red-orange AM (Life Technologies, Grand Island, NY) in the instilled liquid to label the epithelium and thus verify the location of the aerated alveolar liquid lining layer.

Microscopy. We image subpleural fluorescence in the isolated rat lung using a ×40 (0.8 N.A.) water immersion objective in conjunction with a coverslip (34). We excite/collect the fluorescence of calcein at 488/493–535 nm and of calcein red-orange AM at 543/560–750 nm. Image size is 369 \( \mu \)m square for flooded areas, 100 \( \mu \)m square for aerated areas. We collect Z-stacks of optical sections (slice thickness of 2 \( \mu \)m, center-to-center interslice distance of 4 \( \mu \)m) from the pleural surface to a depth of 30 \( \mu \)m.

Protocol. With calcein in the perfusate, we instill nonfluorescent liquid in subpleural alveoli to generate an experimental area with discrete alveolar flooding or a control, aerated area. We obtain two baseline images of the area 5 min apart at \( P_{AVL} \) of 5 cmH2O. We remove the coverslip and apply five ventilation cycles to the lung at 0.33 Hz with specified PEEP and \( V_T \). Then we return the lung to a constant \( P_{AVL} \) of 5 cmH2O, replace the coverslip, and reimage the area at 1, 6, and 11 min postventilation.

Analysis. As an indicator of injury, we quantify fluorescence (ImageJ, National Institutes of Health, Bethesda, MD) at a subpleural depth of 20 \( \mu \)m in the liquid lining layer of aerated alveoli in control areas or in the liquid phase of flooded alveoli in experimental areas. We also quantify fluorescence in each of the four capillaries, 5.0–6.5 \( \mu \)m.
in diameter, in each imaged area at each time point. We then at each time point normalize alveolar liquid fluorescence by average vascular fluorescence. All fluorescence intensity measurements are made in raw, unprocessed images.

We report data in two forms. Over the time course of the experiment, we report increase in normalized alveolar fluorescence above that at the first baseline time point. As a single “injury score” for a given condition, we report the increase in normalized fluorescence above baseline at the last (11 min postventilation) time point.

Surface Tension Determination

We prepare the lung for T-determination experiments as for injury-assessment experiments above, but with the following differences. We determine T in isolated, unperfused rat lungs. For T determination, we instill a greater volume, ~1.2 μl, of model edema liquid (interinvestigator variation) that we label with 31 μM fluorescein (16). Within the imaging field, this volume floods the same percentage of surface alveoli such that flooded and aerated alveoli are still interspersed. We test model edema liquids of similar composition to those used for the injury assay. To normal saline we add 0, 0.9, 1.8, 2.7, 4.6, 10, 11, 12, or 28% albumin; 4.6% fibrinogen; 4.6% 70-kDa dextran; 4.6% 70-kDa dextran plus 10 μM NaOH; or 10 μM NaOH alone. We test each liquid in the absence and presence of 0.9% Survanta. Following two ventilation cycles between PALV·5 and 15 cmH2O, we employ the Laplace relation to determine T at PALV·15 cmH2O, as previously described (16).

Statistics

We assess statistical differences by ANOVA and Tukey’s post hoc analysis and accept significance at P < 0.05. We report data as mean ± standard deviation.

RESULTS

In preliminary volume-controlled ventilation experiments, we investigate the dependence of peak inspiratory transpulmonary pressure, PALV·MAX, on animal body weight, tidal volume, and end-expiratory transpulmonary pressure, PALV·MIN. We select PALV·MIN values corresponding to clinical PEEP settings, as detailed in METHODS. We find that within the body weight range of 320–360 g, PALV·MAX is independent of body weight (R² = 0.06 ± 0.09, n = 10) (Fig. 2). Thus for each combination of PALV·MIN and VT, we average PALV·MAX values from within this body weight range (Table 1). We perform all subsequent ventilation injury experiments using animals with body weights between 320 and 360 g. We apply pressure-controlled ventilation at 0.33 Hz between PALV·MIN and PALV·MAX values that correspond, according to Table 1, to targeted PEEP and VT settings. We refer below to PEEP and VT rather than to PALV·MIN and PALV·MAX.

We find that ventilation causes injury in regions with discrete alveolar flooding. We assess injury by tracking fluorescence in the alveolar liquid phase over time (Fig. 3A). At baseline, nonfluorescent liquid instilled in the alveolus is not visible in unprocessed images of either flooded or control, aerated areas. In flooded areas, alveolar liquid fluorescence becomes evident following ventilation. In control areas, aerated alveolar liquid lining layer fluorescence is still not evident in unprocessed images even following ventilation. To identify the location of the liquid lining layer, therefore, we increase image brightness at all time points in a replicated set of control area images (Fig. 3A, bottom row). We confirm the identity of the liquid lining layer by its position with respect to the epithelium (Fig. 3B).

Over the baseline period in all groups, fluorescence of the alveolar liquid phase remains constant. Following five ventilation cycles, fluorescence of the liquid lining layer in control, aerated areas remains constant (Fig. 3, A and C). Control data for PEEP of 10 cmH2O and VT of 6 and 12 cmH2O are shown, combined, in the bottom curve of Fig. 3C. The control results for these two data groups are representative of the control groups for all ventilation settings (Fig. 4, control groups) and all model edema liquids (Fig. 5A, control groups) tested. The unchanged liquid lining layer fluorescence indicates that in a uniformly aerated region, over the time course of our experiments, the tested ventilation settings do not increase barrier permeability to fluorescein. These control experiments further demonstrate that our micropuncture method does not alter barrier permeability.

Following five ventilation cycles, alveolar liquid fluorescence increases in areas of heterogeneous alveolar flooding (Fig. 3, A and C). The increase in fluorescence indicates fluorescein movement from the vasculature into the alveolus, thus an increase in alveolar-capillary barrier permeability. If the increase in permeability were transient, present only during ventilation, then one would expect alveolar fluorescence to be increased following ventilation but constant over the observed postventilation period. Instead, we observe alveolar liquid fluorescence to continue to increase.

| Body weight, g | Palv·MIN, cmH2O | Palv·MAX, cmH2O
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End-expiratory transpulmonary pressure values, PALV·MIN, correspond to PEEP values as detailed in METHODS. VT, tidal volume.
over the postventilation period. This continued increase suggests that there is a sustained injury to the barrier, one that persists following ventilation arrest.

The rate of postventilation fluorescence increase in the alveolar liquid is greater with a $V_T$ of 12 than 6 ml/kg (Fig. 3C). Because there is greater clinical volutrauma with a $V_T$ of 12 than 6 ml/kg (6), detection of this difference lends clinical relevance to our injury assay.

Figure 4 presents results for all tested combinations of PEEP and $V_T$, in the form of injury score. In the presence of discrete alveolar flooding, all tested ventilation settings are injurious. An increase in either PEEP or $V_T$ increases overexpansion injury. With 3% albumin solution as the model edema liquid, addition of Survanta is protective under all ventilation settings except the least injurious. With a PEEP of 0 or 5 cmH₂O and $V_T$ of 6 or 12 ml/kg, ventilation is minimally injurious and addition of Survanta does not lessen the injury. With discrete alveolar flooding, however, these minimally injurious settings are still injurious.

In testing different albumin concentrations in the model edema liquid, we find that albumin concentration does not alter injury (Fig. 5A, black bars). We find that addition of Survanta can be protective, but only in the presence of a particular range of albumin concentrations (Fig. 5A, white bars). With an
base differs (Survanta. Among all groups with discrete flooding, a group with a letter above their error bars.

We find Survanta to lower C. We find that the degree of injury increases with increasing surface tension. In the absence of Survanta, the concentration of plasma proteins in our model edema liquid does not affect surface tension or injury. For Survanta to lower T and reduce injury, however, it is necessary that plasma proteins be present. Although Survanta can lessen injury, it cannot eliminate injury. Even the least injurious ventilation settings, irrespective of Survanta inclusion, cause injury to areas with discrete alveolar flooding.

### Assay for Ventilation Injury

Our assay detects ventilation-induced injury to the alveolar-capillary barrier. With this assay, we find that injury correlates with surface tension (Fig. 5C). Addition of Survanta to the model edema liquid, however, causes a greater % decrease in injury than in T (Figs. 5 and 6). Thus our ventilation assay is more responsive to differences between experimental groups than is our T-determination method.

We apply the ventilation assay in an idealized model, one in which the alveolar-capillary barrier is intact at baseline, and use fluorescein as a tracer. Fluorescein is a small tracer but one that binds to albumin (7). In human plasma, ~82% of fluorescein is bound to albumin. In our perfusate, a mixture of rat blood and 5% albumin solution, the bound fluorescein fraction should be comparable (8). Furthermore, the fluorescence of fluorescein is markedly quenched upon binding to albumin (7). Following ventilation, we detect an increase in fluorescence in the alveolar liquid that indicates an increase in barrier permeability. Whether the increase in permeability is sufficient to allow albumin passage across the barrier has not been determined. However, as detailed below, comparison of the protein concentration in cardiogenic edema (CE) liquid to that in the permeability edema liquid of ARDS suggests that ventilation might increase barrier permeability to albumin in our model.

Edeema liquid protein content is typically assessed by bronchoalveolar lavage. Protein concentration of bronchoalveolar lavage fluid (BALF) is markedly elevated in both CE and ARDS cases compared with controls, and more so in ARDS than in CE (10, 26, 32). Günther et al. (10), testing all three groups in a single study, find BALF total protein content to be 73, 271, and 699 pg/ml in control, CE, and ARDS cases, respectively. Because lavage is a qualitative technique, it is generally not known whether an elevated total protein (TP) concentration in lavage fluid, [TP]_{BALF}, is due to an elevated alveolar edema liquid protein concentration, [TP]_{ALV-LIQ}, or an elevated edema liquid volume as a fraction of total lavage volume, V_{ALV-LIQ}/V_{BALF}. However, Günther et al. (10) further use the relative area concentrations in the BALF and blood plasma to estimate, from the concentration of surfactant protein-B (SP-B) in the BALF, [SP-B]_{BALF}, the SP-B concentration in the edema liquid, [SP-B]_{ALV-LIQ}. Dividing Günther et al.’s values for [SP-B]_{BALF} by those for [SP-B]_{ALV-LIQ}, we obtain the values of the ratio V_{ALV-LIQ}/V_{BALF} for the three experimental groups (generally on the order of 0.01); dividing Günther et al.’s values for [TP]_{BALF} by those for V_{ALV-LIQ}/V_{BALF}, we obtain quantitative estimates of [TP]_{ALV-LIQ}: 0.9, 5.1, and 4.9% in control, CE, and ARDS.
An alternative method for determining alveolar edema liquid protein content is to suction directly the airspace liquid content (18). This method indicates protein concentrations of 4.1 ± 1.9% and 5.8 ± 1.7% in CE and ARDS, respectively, with the ARDS value greater than the CE value (P < 0.01). Although the samples of both the lavage and suction methods likely contain unknown fractions of upper airway liquid, average edema liquid protein content in CE, approximately 4–5%, appears to be comparable with that in ARDS, approximately 5–6%. We speculate that ventilation of
an area with discrete alveolar flooding and initially normal barrier permeability, as in both CE and our model, may increase permeability sufficiently to allow protein passage into the alveolus. This hypothesis requires direct testing.

In ARDS, where elevated barrier permeability is the cause of edema, we do not know whether ventilation would further increase barrier permeability in areas with heterogeneous alveolar flooding. Our assay is nonetheless relevant as an indicator of mechanical insult to the barrier. The principal mechanical insult is likely the application of excessive strain and stress to aerated alveolar septa, where strain and stress are coupled such that the effect of one cannot be isolated from that of the other. If overexpansion of the aerated alveolus thinned the liquid lining layer in that alveolus, then further insult might result from greater epithelial-interfacial contact (12, 27) or possibly, despite decreased aerated alveolar compliance (23), application of greater ventilation-induced fluid shear stress to the epithelium. For any of these mechanisms, however, the degree of mechanical insult should be independent of the degree of initial barrier permeability.

Our injury assay is sensitive to injury degree but not location. It lacks the spatial specificity of the propidium iodide injury detection method (14). We surmise from our assay that in a region with discrete alveolar flooding it is the hyperexpanded aerated alveoli that are injured (23). Ventilation, however, is likely to strain different aerated alveolar septa to different degrees. That is, a bowed septum between an aerated and a flooded alveolus; aerated alveolar septa contiguous with and roughly perpendicular to the bowed septum; and aerated alveolar septa across the alveolus from and roughly parallel to the bowed septum are likely to experience different degrees of strain. These relative strain levels have yet to be determined.

Another limitation of our method is our restriction to assessing subpleural alveoli, although subpleural alveoli, which do have some distinguishing characteristics (24). However, inflation expands subpleural and internal alveoli to comparable degrees. In subpleural alveoli, we find lung inflation from P_{ALV} of 5 to 15 cmH_2O to increase the alveolar perimeter in a plane parallel to the pleural by 15% (22). Perpendicular to the pleura, septal stretch is of comparable magnitude (24). Thus the inflation-induced increase in surface area is a little over 30%. In internal alveoli, the same degree of inflation increases surface area by 32% (20). We expect areas with discrete alveolar flooding to be injured to the same degree whether located in subpleural or internal regions.

Following cessation of ventilation, we track alveolar liquid fluorescence for 10 min. This analysis period is brief and we do not know whether the barrier might reseal at a later time. That low VT ventilation is less injurious than high VT ventilation is consistent with clinical results (6). Even low VT ventilation, however, is injurious. Furthermore, PEEP is effectively a prestress applied before further lung expansion by tidal volume delivery. In a lung with gross dependent alveolar flooding and discrete nondependent flooding, use of PEEP would be expected to contribute to nondependent alveolar injury yet benefit the dependent lung by maintaining recruitment of flooded units (17, 21). In maintaining recruitment, PEEP enables ventilation with a reduced fraction of inspired oxygen (3, 5). That is, PEEP may mechanically injure one lung region while assisting oxygenation in another. These contradictory effects of PEEP may in part explain why mortality is similar between groups ventilated with low or high PEEP values (5). Both microscopic (flooded vs. aerated alveolus) and macroscopic (dependent vs. nondependent lung) heterogeneities contribute to the difficulty of ventilating the edematous lung.

**Plasma Protein-Survanta Interaction**

Our finding that plasma proteins enable Survanta to lower surface tension counters the widely held belief that plasma proteins raise T in permeability edema. We have recently shown that with albumin inclusion in the model edema liquid and physiologic surface area compression, %ΔA, comparable to that during ventilation of the mildly edematous lung, T remains constant over 60 ventilation cycles (16). We surmise that with physiologic %ΔA the surfactant monolayer at the interface remains intact such that proteins are blocked from the interface. Here, given the P_{ALV} values between which we ventilate (Table 1), %ΔA should be within the physiologic range and an intact monolayer of native surfactant is likely present (2, 16).

The absence/presence of an existing, intact surfactant monolayer may influence exogenous surfactant activity. In vitro, surfactant lowers the surface tension of saline solution (13). In the premature neonate lacking native surfactant, exogenous surfactant therapy is a success (11). In the absence of an existing monolayer, exogenous surfactant presumably directly lowers T at the interface. In patients with ARDS who have native surfactant, exogenous surfactant therapy has failed to reduce mortality (4). In our model, we find that exogenous surfactant can lower T but postulate that it may act indirectly. Although plasma proteins facilitate Survanta activity (Figs. 5 and 6), they do not enhance the activity of native surfactant alone (16). It may be that Survanta in the bulk liquid phase in our model interacts with albumin to promote native and/or exogenous surfactant adsorption.

We find Survanta activity to be facilitated by negatively charged particles—either plasma proteins or negatively charged dextran (Fig. 5). Survanta is a complex aggregate of phospholipids, neutral lipids, and both hydrophilic and hydrophobic proteins that, altogether, carries a net negative charge (15, 31). It may be an electrostatic interaction between plasma proteins and Survanta that underlies protein facilitation of native or exogenous surfactant adsorption. The mechanism of this interaction remains to be determined.

If one assumes that exogenous surfactant instilled in the trachea distributes uniformly throughout the edematous lung, then the 1% Survanta concentration that we test is, as discussed previously (17), at least an order of magnitude lower than the clinical dosage of 50–100 mg phospholipids/kg body weight that is used in neonates and has been tested in ARDS (9, 28). Given the excessive instillation volume and cost of adminis-
tering the present clinical dosage to an adult with ARDS, the possibility that a lower exogenous surfactant dosage might be effective is intriguing. How the mechanism of Survanta activity in our local instillation model relates to that of exogenous surfactant instilled in the trachea and why Survanta is effective locally but not globally, however, are questions that require further investigation.

Furthermore, protein content in our local edema model is not precisely known. As discussed previously (16), there is likely diffusive efflux of protein from the area that we flood. That no protein concentration from 0 to 30% alters $T$ or injury in the absence of Survanta strongly suggests that plasma proteins do not alter native surfactant activity. When Survanta is added, it is facilitated by an albumin concentration of $\geq 2.7\%$ in the instilled solution (Fig. 5B). Due to diffusive efflux, the actual albumin concentration is likely lower than the instilled concentration; an even lower albumin concentration may facilitate Survanta activity. The maximum % albumin in our flooding solution that facilitates Survanta activity is 10% in injury-assay experiments and 11% in $T$-determination experiments (Fig. 6).

With instillation of a lower liquid volume when assessing injury ($\approx 300$ nl) than when determining $T$ ($\approx 1.2$ $\mu$l), greater diffusive efflux of albumin in the former case may underlie the difference in results between the two types of experiments. With unknown degrees of albumin efflux in both cases, we do not know precisely the peak albumin concentration up to which Survanta is protective. Generally, however, Survanta is effective in our model over a range of albumin concentrations that is likely to encompass the approximately 5–6% albumin present in ARDS (10, 18).

Conclusions

We find that mechanical ventilation injuries areas with discrete alveolar flooding. Injury increases with increasing $V_T$, but even low $V_T$ ventilation is injurious. The use of PEEP during ventilation, although beneficial to lung oxygenation, increases the injury of areas with heterogeneous alveolar flooding. Furthermore, the degree of injury correlates with surface tension. We find that Survanta inclusion in our local edema model lessens surface tension and injury, but only with plasma proteins present within a particular concentration range. The mechanism through which plasma proteins can facilitate exogenous surfactant activity requires further investigation.

GRANTS

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

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