The last decade has brought about many new insights into the mechanical properties of injured lungs that have profoundly altered ventilatory management of patients with acute respiratory distress syndrome (ARDS). The pioneering studies byGattinoni and colleagues (9, 11, 12) revealed a topographical heterogeneity in lung involvement and reinforced the idea that large portions of an injured lung are derecruited (i.e., they do not get aerated during positive-pressure breathing). This important insight formed the basis for the “baby lung” concept that explains why the lungs of patients with ARDS appear to be particularly prone to injury from overdistention. On the basis of an interpretation of computer tomographic (CT) images of the thorax, Gattinoni and colleagues attributed derecruitment of dependent lung to atelectasis and small airway collapse (9, 11, 13). In arriving at this conclusion, Gattinoni embraced the idea of a “fluid-like lung” in which dependent regions must bear the weight of the superimposed “heavy” edematous lung tissue (18) and are thus prone to cyclic opening and closure during positive-pressure breathing. This interpretation fits well within the conceptual framework of the open lung protective ventilation strategy (19) and provided an appealing rationale for the use of positive end-expiratory pressure (PEEP) and the prone posture as a means to promote lung recruitment (4, 9, 20, 31).

Because the interpretation of CT data hinges on the assumption that lung water (blood and edema) is uniformly distributed, we had in previous studies used the parenchymal marker technique to characterize regional lung deformation in oleic acid (OA)-injured dogs (24). In contrast to CT, the parenchymal marker technique provides absolute measures of regional tissue dimensions, as opposed to relative measures of regional air to liquid content (17). To our surprise, OA injury did not produce the collapse of dependent lung units; in addition, we detected no evidence for cyclic reopening and collapse of dependent lung regions during mechanical ventilation. On the basis of these findings we reinterpreted the CT data and proposed an alternative mechanism for the topographical variability in regional impedances and lung expansion after injury: namely, liquid and foam in alveoli and conducting airways (24).

We extend our observations on the regional mechanics of the OA-injured lung to PEEP and posture effects. We reaffirm the absence of dependent lung collapse in this injury model in three different body postures and interpret PEEP-related and posture-related changes in regional lung dimensions in the context of widespread alveolar flooding. Our observations provide the first direct evidence that for PEEP to produce recruitment it must increase the dimensions (total volume) of both nondependent and dependent lung regions beyond their normal tidal breathing range. We confirm that at the PEEP levels required to fully recruit dependent lung, nondependent lung parenchyma is often strained beyond its total lung capacity (TLC). In contrast, changes in posture readily promote the recruitment of
previously dependent regions without overdistending distant parts of the lung. Although these data in and of themselves do not speak to the potential risks and benefits of lung recruitment strategies, they do bring into question the widely held belief that the principal mechanism by which PEEP and posture protect the lung from injury is the minimizing of shear stress on acinar structures.

METHODS

Parenchymal marker technique. To measure regional lung expansion during mechanical ventilation, the parenchymal marker technique was used. It has been described in detail previously (17). Briefly, 1-mm metal beads were implanted transthoracically into the caudal lobe of 13 anesthetized dogs. In animals studied in a lateral decubitus position (groups LD-D and LD-ND; as defined in Table 1), contralateral upper lobes were also labeled with markers. Nine weeks later, experiments were conducted during which biplanar fluoroscopic images of the thorax were recorded on videotape. The orthogonal projection images of each bead were sampled at the rate of 5 Hz by use of an operator-interactive computer tracking system. The three-dimensional marker locations were derived from these data. Four markers define a volume (tetrahedron) that contains air, tissue, edema fluid, and blood. Thus, as a final output, the method provides the description of regional volume behavior in time (i.e., regional spiromgrams). An average of 74 ± 42 (SD) tetrahedra were created for each animal. Their volume at TLC [defined as the volume at an airway opening pressure (Pao) of 35 cmH2O before injury] averaged 3.3 ± 0.8 cm3.

Animal preparation and data acquisition. All techniques and procedures were approved by Mayo’s Institutional Animal Care and Use Committee, and the care and handling of the animals were in accordance with National Institutes of Health guidelines. A total of 13 adult beagle dogs of either sex (9.9 ± 1.6 kg) were studied. The animals were anesthetized with pentobarbital sodium (30 mg/kg, with supplemental doses of 10 mg/h), a tracheostomy was performed, and a 9-mm ID glass cannula was inserted into the tracheal lumen. The dogs were mechanically ventilated (Siemens Servo 900C, 9-mm ID glass cannula was inserted into the tracheal lumen. The dogs were mechanically ventilated (Siemens Servo 900C, Solna, Sweden) with a fractional oxygen concentration of 1.0, a tidal volume (VT) of 230–250 ml, a respiratory rate of 20 cycles/min, an inspiratory time fraction of 0.33, and a PEEP set between 3 and 5 cmH2O. Pao was measured at the proximal end of the endotracheal tube (24A1, Honeywell Microswitch, Freeport, IL). Distal esophageal pressure (Pes) was monitored by means of a balloon catheter attached to a pressure transducer (24A1, Honeywell, Microswitch). The optimal position of the catheter was determined fluoroscopically and was verified by use of the balloon occlusion method. Transpulmonary pressure was calculated by subtracting Pes from Pao. Gas flow rates were measured by using a pneumotachograph and transducer (163PC, Honeywell, Microswitch) attached to the Y piece of the ventilator circuit. Flow was integrated to monitor the VT. Gas exchange was assessed by periodic analysis of blood samples drawn from a femoral arterial line (blood gas analyzer IL-1304, Instrumentation Laboratory, Lexington, MA). A pediatric Swan-Ganz pulmonary artery catheter was inserted through the right internal jugular vein to monitor pulmonary artery pressure. Systemic blood pressure was monitored from the femoral arterial line with a pressure transducer (Statham P37A, Oxnard, CA). Three leads attached to the paws provided a single electrocardiographic tracing to monitor the heart rate. Body temperature was monitored rectally (YSI Tele-thermometer 44TF, Yellow Springs, OH) and kept constant at 37°C by using heat lamps. A 16-Fr cannula was placed in a peripheral vein to administer normal saline and anesthetic. Normal saline was administered to maintain hemodynamic stability. Pao, Pes, gas flow, VT, pulmonary artery pressure, systemic blood pressures, electrocardiogram tracing, and notes taken during the experiment were stored in a digital form (LabView, National Instruments, Austin, TX). However, in animals studied in the lateral decubitus posture (groups LD-D and LD-ND; see Table 1), this information was lost because of a software error.

Experimental protocol: Study of PEEP effects. Table 1 provides an overview of the experimental interventions. The effects of PEEP (7.5 and 15 cmH2O) on the regional expansion of OA-injured lungs were characterized in seven supine and two prone dogs. The effects of a change in posture on the regional expansion of OA-injured lungs were examined in four dogs. In two dogs, images of the caudal lobes were obtained before and after turning the animals from the supine to the prone posture. In two other dogs, images of both caudal and upper lobes were obtained before and after turning the animals from one to the other lateral decubitus posture. The resulting change in orientation of upper and caudal lobes within the gravity field are denoted as dependent to nondependent or nondependent to dependent.

Effects of PEEP were examined in seven supine (S-PEEP) and two prone (P-PEEP) animals (Table 1, top). We had reported the zero-PEEP OA injury responses of these nine animals in a previous communication (24). They were paralyzed with pancuronium bromide, 3 mg iv, supplemented with 1 mg iv as needed. The inspiratory capacity was deter-

Table 1. Overview of the experimental interventions

<table>
<thead>
<tr>
<th></th>
<th>Before OA</th>
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<tr>
<td></td>
<td>Study of PEEP effects</td>
<td>Study of posture effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-PEEP (n = 7)</td>
<td>0 PEEP</td>
<td>Supine</td>
<td>→</td>
<td>Prone</td>
</tr>
<tr>
<td>P-PEEP (n = 2)</td>
<td>0 PEEP</td>
<td>Lateral decubitus</td>
<td>→</td>
<td>Lateral decubitus</td>
</tr>
<tr>
<td></td>
<td>7.5 PEEP</td>
<td>Dependent</td>
<td>→</td>
<td>Nondependent</td>
</tr>
<tr>
<td></td>
<td>15 PEEP</td>
<td>Lateral decubitus</td>
<td>→</td>
<td>Lateral decubitus</td>
</tr>
<tr>
<td></td>
<td>7.5 PEEP</td>
<td>Nondependent</td>
<td>→</td>
<td>Dependent</td>
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</table>

*Two dogs with markers in one dependent and one nondependent lobe were studied in the lateral decubitus posture. OA, oleic acid; PEEP, positive end-expiratory pressure (measured in cmH2O); S, supine; P, prone; LD-D, lateral decubitus and dependent; LD-ND, lateral decubitus and nondependent.*
mined by inflating the lungs to an airway pressure of 35 cmH2O. Measurements (including biplane thoracic images) were then taken during closed-circuit sinusoidal oscillations of the respiratory system by use of a locally engineered precision calibrated piston pump. (We forced the lungs with sine waves because, in contrast to clinically used ventilator waveforms, they can be characterized by two constants. This simplifies our analysis, but restricts the range of frequencies, and flow patterns, over which our data are strictly valid.) The pump was set to deliver a VT of 200 ml at 20 cycles/min.

After baseline measurements, all animals were turned prone and injected with 0.09 ml/kg OA in three aliquots via the right atrial port of the pulmonary artery catheter. The prone posture has been shown to minimize topographical gradients in pulmonary blood flow (2). Animals in the supine group were repositioned 5 min after the last OA injection. Starting 90 min after the OA injection, all measurements were repeated, including measurements of whole lung mechanics, gas exchange, and regional volume expansion during which the lungs were sinusoidally oscillated with PEEP set at 0, 7.5, and 15 cmH2O.

At the end of the study, animals were killed with an overdose of pentobarbital sodium. The lungs were excised, weighed, and subjected to a transpulmonary pressure of 25 cmH2O, after which they were weighed again to determine the wet-to-dry ratio and the dry-to-body weight ratio.

Experimental protocol: Study of posture change effects. Effects of posture change were studied in a total of four dogs: two initiated in a supine posture and two in a lateral decubitus posture (Table 1, bottom). The two dogs initiated in the supine posture had beads placed in a single caudal lobe. They were studied supine before and after injury. Measurements were later taken again after the animals were turned prone. In this group, all measurements were performed at PEEP of 5 cmH2O.

The two dogs initiated in a lateral decubitus position had beads placed in a right caudal and left upper lobe. One dog was initiated in a left and the other one in a right lateral decubitus posture. They were studied first before and then after injury. They were later turned into a contralateral decubitus posture and studied again. This way one upper and one lower lobe were initiated in a dependent position; similarly, one upper and one lower lobe were initiated in a nondependent position. In both lateral decubitus dogs, all measurements were taken at 0 cmH2O PEEP. As a rule, images were captured within <5 min after a change in posture. The remainder of the protocol was the same as described for the study of PEEP effects.

RESULTS

Hemodynamics, gas exchange, and wet-to-dry lung tissue ratio. The effects of OA lung injury, different levels of PEEP, and change in posture on hemodynamic and gas exchange parameters are summarized in Table 2. The table contains results from seven supine dogs treated with different levels of PEEP (S-PEEP), two prone dogs treated with PEEP (P-PEEP), and two supine dogs treated with “proning” (S-to-P).

In S-PEEP animals, OA-induced lung injury caused a significant rise in both systolic and diastolic pulmonary arterial pressures and a significant decrease in systemic diastolic blood pressure and heart rate. OA caused a significant worsening in gas exchange as manifested by respiratory and metabolic acidosis, hyperventilation, and a significant increase in respiratory rate as well as tidal volume. The respiratory system was not able to compensate for the increased ventilatory demands, which resulted in a significant increase in the arterial carbon dioxide tension and a significant decrease in the arterial oxygen tension. The wet-to-dry lung tissue ratio also increased significantly as a result of OA-induced lung injury.

Table 2. Effects of OA injury, PEEP, and posture on circulation, gas exchange, and lung water

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before OA</th>
<th>After OA</th>
<th>Before OA</th>
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<th>Before OA</th>
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<tbody>
<tr>
<td>SPAP, mmHg</td>
<td>20 ± 2</td>
<td>28 ± 5*</td>
<td>31 ± 81</td>
<td>29 ± 71</td>
<td>14</td>
<td>27</td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>DPAP, mmHg</td>
<td>12 ± 5</td>
<td>19 ± 6*</td>
<td>23 ± 8*</td>
<td>23 ± 5*</td>
<td>5</td>
<td>11</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>159 ± 23</td>
<td>131 ± 20†</td>
<td>142 ± 22</td>
<td>147 ± 25</td>
<td>142</td>
<td>138</td>
<td>124</td>
<td>126</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>159 ± 13</td>
<td>130 ± 37</td>
<td>126 ± 27†</td>
<td>111 ± 34†</td>
<td>160</td>
<td>148</td>
<td>145</td>
<td>155</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>114 ± 9</td>
<td>83 ± 23†</td>
<td>80 ± 27†</td>
<td>69 ± 29*</td>
<td>105</td>
<td>93</td>
<td>85</td>
<td>95</td>
</tr>
<tr>
<td>pH</td>
<td>7.32 ± 0.06</td>
<td>7.12 ± 0.12</td>
<td>7.01 ± 0.18</td>
<td>6.98 ± 0.19‡</td>
<td>7.34</td>
<td>7.12</td>
<td>7.12</td>
<td>7.06</td>
</tr>
<tr>
<td>PaO2, Torr</td>
<td>37 ± 6</td>
<td>50 ± 10*</td>
<td>59 ± 20*</td>
<td>65 ± 23*</td>
<td>38</td>
<td>48</td>
<td>50</td>
<td>55</td>
</tr>
<tr>
<td>Wet-to-dry ratio, g/g</td>
<td>11.5 ± 2.7</td>
<td></td>
<td></td>
<td></td>
<td>10.7</td>
<td></td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td>Dry-to-body-weight ratio, g/kg</td>
<td>2.12 ± 0.26</td>
<td></td>
<td></td>
<td></td>
<td>2.24</td>
<td></td>
<td>2.49</td>
<td></td>
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</tbody>
</table>

Values are means ± SD. SPAP, systolic pulmonary artery pressure; DPAP, diastolic pulmonary artery pressure; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PaCO2, arterial carbon dioxide tension; PaO2, arterial oxygen tension. *P ≤ 0.01 compared with baseline; †P ≤ 0.05 compared with baseline; §data unavailable; $P ≤ 0.05 compared with PEEP = 0 after OA.
poxemia, and hypercapnia. Application of PEEP did not significantly affect hemodynamic indexes. An increase in PEEP resulted in a significant improvement in blood oxygenation but was associated with worsening acidosis and CO₂ retention.

In P-PEEP dogs, baseline pulmonary artery pressures were lower than in supine animals but increased dramatically after OA and with the application of PEEP. Whereas the limited number of observations precludes a formal statistical analysis, circulation and gas exchange seemed less impaired in the two prone dogs compared with the nine supine dogs. Broccard and colleagues (4) had made similar observations. Proning of supine dogs tended to bring hemodynamic indexes closer to baseline values. With the change in posture, arterial pH, Pco₂, and Po₂ approached preinjury levels.

Consistent with the known effects of OA on vascular permeability and inflammation, both wet-to-dry lung weight ratios and dry lung weight-to-body weight ratios were elevated in all groups of animals.

**Respiratory system mechanics.** The effects of OA-induced lung injury and applied PEEP on the mechanical properties of the respiratory system are illustrated in Fig. 1.

In seven S-PEEP dogs, OA caused a marked increase in both lung elastance and lung resistance (26 ± 10 to 138 ± 50 cmH₂O/l and 3 ± 1 to 20 ± 15 cmH₂O·l⁻¹·s⁻¹, respectively). Application of 7.5 cmH₂O of PEEP caused a significant decrease in both values, whereas a further increase in PEEP to 15 cmH₂O caused no additional change in lung elastance or lung resistance (91 ± 18 and 89 ± 22 cmH₂O/l and 9 ± 4 and 8 ± 5 cmH₂O·l⁻¹·s⁻¹, respectively). The mechanical properties of the chest wall were largely unaffected by injury and PEEP.

In two P-PEEP dogs, OA-induced lung injury was associated with a large increase in both lung elastance and resistance (19 to 104 cmH₂O/l and 2 to 17 cmH₂O·l⁻¹·s⁻¹, respectively). Although the application of 7.5 cmH₂O of PEEP caused a decrease in lung elastance (to 73 cmH₂O/l), further increases in PEEP raised elastance toward postinjury baseline (to 92 cmH₂O/l). Lung resistance, however, declined steadily with rising PEEP (to 11 and 8 cmH₂O·l⁻¹·s⁻¹).

Changes in posture alter the mechanical properties of lung regions apposed to the esophagus, which is likely to bias the Pes output relative to mean pleural pressure oscillations. For that reason, we did not differentiate between lung and chest wall properties when assessing the effects of posture change on respiratory mechanics. OA-induced lung injury caused an increase in both total respiratory system elastance and resistance (from 56 to 82 cmH₂O/l and 6 to 9 cmH₂O·l⁻¹·s⁻¹, respectively). Turning animals prone resulted in a marginal decrease of both elastance and resistance (to 73 cmH₂O/l and 6 cmH₂O·l⁻¹·s⁻¹, respectively).

**Effects of OA injury on lobar FRC and VT.** The effects of OA-induced lung injury on the average LFRC and LVT of the caudal lobe of seven S-PEEP dogs are shown in Fig. 2. Also shown are individual data from dogs injured in the prone (2 caudal lobes) and lateral decubitus positions. Note that, in supine and prone dogs, caudal lobes are in dependent and nondependent locations, respectively. For dogs in the lateral decubitus position, LFRC and LVT represent data from one caudal and one upper lobe, which were imaged in either a dependent (LD-D) or a nondependent (LD-ND) location.

Overall, OA injury caused either no or only small changes in LFR in the postures studied (for S-PEEP, P-PEEP, LD-D, and LD-ND: 0.38 ± 0.06 to 0.39 ± 0.09, 0.54 ± 0.06 to 0.39 ± 0.09, 0.54 to 0.50, 0.34 to 0.31, and 0.47 to 0.48, respectively). In contrast, OA injury invariably decreased LVT of...
dependent lung regions [for S-PEEP and LD-D: 0.14 ± 0.02 to 0.06 ± 0.02 (P < 0.0001) and 0.12 to 0.03, respectively], whereas LVT increased in nondependent segments of the lung (for P-PEEP and LD-ND: 0.16 to 0.19 and 0.14 to 0.18, respectively). The changes in LVT are indicative of an injury-related redistribution of ventilation from dependent to nondependent lung regions.

**Effect of PEEP on lobar volume.** Changes in LFRC and LVT caused by an application of PEEP in seven S-PEEP and two P-PEEP dogs are illustrated in Fig. 3. Overall, the application of PEEP was associated with an increase in LFRC in both supine and prone groups of animals [7.5 and 15 cmH₂O, respectively; for S-PEEP: 0.47 ± 0.09 and 0.68 ± 0.18 (P = 0.59 and 0.008 when compared with 0 PEEP); for P-PEEP: 0.65 and 0.93]. Although PEEP caused a progressive increase in supine animals (0.09 ± 0.04 and 0.13 ± 0.05, for 7.5 and 15 cmH₂O, respectively), it was associated with a decrease in prone dogs (0.12 and 0.13, for 7.5 and 15 cmH₂O, respectively).

**Effect of PEEP on regional volume distribution within lobes.** The existence of PEEP-induced ventilatory recruitment of dependent lung regions in the supine posture is further emphasized in Fig. 4, which illustrates the frequency distribution of rVT at different levels of PEEP in S-PEEP dogs. Before OA injury at 0 cmH₂O PEEP, the median rVT was 0.13, whereas after injury at 0, 7.5, and 15 cmH₂O PEEP, rVT was 0.05, 0.08, and 0.13, respectively. Importantly, there was no significant change in the overall width of the rVT frequency distributions with PEEP.

To investigate topographical differences in regional expansion and PEEP-induced recruitment, we compared the average rVT of dependent regions with that of nondependent regions within caudal lobes in the seven S-PEEP dogs. The results of this analysis are shown in Fig. 5. Under three of four experimental conditions, we found no difference in average rVT between nondependent and dependent regions. However, at a PEEP of 7.5 cmH₂O, the tidal expansion of nondependent regions of the caudal lobe was significantly greater than that of dependent regions (0.10 ± 0.05 vs. 0.08 ± 0.04; P = 0.02).

**Effect of a change in posture on lobar volume.** The effects of a change in posture on LFRC and LVT in supine animals flipped prone (S-to-P) and in lateral decubitus-positioned dogs flipped onto the other side so that dependent lobes became nondependent (LD-D), and vice versa (LD-ND) are illustrated in Fig. 6. Both
LFRC and LVT of lobes moved from a dependent to a nondependent location increased dramatically (for S-to-P dogs, LFRC and LVT increased from 0.41 to 0.66 and from 0.09 to 0.17, respectively; for LD-D lobes, LFRC and LVT rose from 0.31 to 0.49 and from 0.03 to 0.19, respectively). In contrast, for LD-ND lobes made dependent, both LFRC and LVT underwent marked reductions (0.48 to 0.32 and 0.18 to 0.06, respectively).

An analysis of the effect of repositioning that ignores the animals’ initial body posture shows that lobes that moved from a dependent to a nondependent location increased their average LFRC from 0.36 ± 0.09 to 0.57 ± 0.13 (n = 4, P < 0.003), whereas their average LVT increased from 0.06 ± 0.05 to 0.18 ± 0.02 (P < 0.05). The volume response of the two lobes that were moved from a nondependent to a dependent location mirror this effect.

DISCUSSION

The main findings of our study on the mechanics of OA-injured lungs can be summarized as follows: 1) dependent regions maintain normal dimensions at end-expiration irrespective of the animal’s posture; 2) the application of PEEP restores the oscillation amplitude of dependent lung regions (which reflects recruitment) provided that their FRC rises above preinjury levels; 3) the level of PEEP necessary to produce full recruitment of dependent lung might distend nondependent lung regions beyond their normal TLC; and 4) a change in posture is an effective means of recruiting previously dependent and presumably flooded lung units. Before we discuss the mechanistic implications of our findings, we will comment on the choice of experimental model and imaging approach.

Canine OA injury model. The OA injury model is commonly used as an animal model of acute lung injury (36). OA is an unsaturated fatty acid that binds to cell membranes at low concentrations and ultimately produces cell death. The resulting lesion consists of hemorrhagic edema and diffuse alveolar damage with injury to both endothelial and alveolar epithelial cells. When OA is injected into a central vein, it damages the pulmonary microvasculature in a perfusion distribution-dependent manner. In the hope of producing uniform injury, all animals in this study were injected prone because perfusion tends to be most uniform in that posture (2).

Notwithstanding the popularity of the OA model in lung injury research, the relevance of our findings for human disease remains to be established. At least in our hands, OA injection in dogs produces more hemorrhagic edema than is typically seen in patients with ARDS. Puybasset et al. (33) used spiral CT to measure lobar volumes and chest wall dimensions in 21 recumbent patients with acute lung injury and compared their results with data from 10 normal volunteers. In contrast to our findings in OA-injured dogs, these investigators’ results showed average reductions in total thoracic volume (air plus blood, edema, and tissue) of 27%, reflecting volume loss primarily by the lower lobes. The reductions in thoracic volume were accompanied by reductions in anteroposterior and cephalo-caudal chest wall dimensions, a finding that has not been corroborated in other studies on humans or OA-injured dogs (30, 37). Such differences in experimental findings probably reflect differences in the degree of microvascular injury and in the number of patients with primary as opposed to secondary ARDS. The terms primary and secondary ARDS have been introduced byGattinoni and colleagues (10) to emphasize differences in disease mechanisms between primary insults to the lung (e.g., acid aspiration) and secondary impairments in lung function caused by chest wall restriction (e.g., caused by ileus and ascites). Canine OA injury is a prototypical model of primary ARDS in which microvascular injury and edema dominate the lung behavior. In contrast, many surgical patients with abdominal distension have lesser impairments in pulmonary vascular integrity but develop atelectasis and ultimately meet radiographic as well as gas exchange criteria for ARDS.

Parenchymal marker technique. The parenchymal marker technique resolves volume changes of tetrahedra within caudal lobes of 7 S-PEEP dogs. *P = 0.018.
dra (lung regions) on a scale of $\geq 1 \text{ cm}^3$ with a temporal resolution of $\leq 30 \text{ Hz}$. In contrast to CT, the technique is well suited to the measurement of regional parenchymal expansion because it directly provides data that follow the behavior of parenchymal elements as the lung moves. CT images of the thorax are density maps from which the topographical distribution of air per unit tissue volume may be estimated. The images do not define tissue state, and they give no information on tissue extension or strain. It is usually not possible to track a specific structure, such as an alveolus or a small airway bifurcation, across multiple CT images in time. Therefore, it is not possible to measure the amplitudes of regional lung expansion unless one is willing to ignore errors resulting from the misalignment of parenchymal structures across images obtained at different phases of the respiratory cycle.

The parenchymal marker technique has different limitations. The technique is labor intensive, it is often difficult to distribute markers uniformly within a lobe, it is usually not possible to sample more than two lobes per animal, and regional volumes reflect tissue expansion rather than regional air content. The limitation that is most significant in the context of this study is the undersampling of ventral portions of the caudal lobe. The ventral part of the caudal lobe is quite thin, making it nearly impossible to place four markers, from which to form a tetrahedron, exclusively in it. This narrows the vertical spread of the data so that a lack of apparent gravitational gradients must be interpreted with caution.

**Effects of PEEP on regional volume and ventilation of the OA-injured lung.** In a previous publication, we presented data of some of the animals that form the basis of this communication (0-PEEP data of groups S-PEEP and P-PEEP). We concluded that, in supine dogs, dependent lung is derecruited not because it is collapsed, but rather because it is flooded (24). We now extend this observation to the lateral decubitus posture and describe the effects of PEEP and a change in posture on regional lung mechanics. We are struck by the fact that regions of the most injured, dependent lung undergo finite volume oscillations even at 0 PEEP (see Fig. 4). This means either 1) that most tetrahedra contain some alveoli that are still aerated and in communication with patent airways or 2) that flooded tetrahedra are intermittently expanded by edema fluid that moves forth and back between conducting airways and the lung periphery. Although the parenchymal marker technique does not resolve gas from liquid ventilation per se, during inspection of fluoroscopy images we have clearly observed intermittent aeration and flooding of lobar bronchi in injured mechanically ventilated animals. Therefore, it seems to us more appropriate to think about the mechanics of the OA-injured lung as a partial liquid ventilation problem as opposed to a shear stress and airway collapse problem.

Closed airways can exist in two possible configurations. The airway dimensions might be normal, but a liquid bridge spans the lumen, preventing flow. Alternatively, the airway walls and surrounding parenchyma might be collapsed and held in apposition by the cohesive forces of the airway lining fluid (15, 32). Interactions between surface tension, parenchymal tethering forces, airway wall stiffness, luminal fluid volume, and fluid viscosity all determine the local airway geometry (28). Most of the current literature on the regional mechanics of injured lungs has ignored liquid bridging in favor of alveolar compression and dependent lung collapse as the prevailing causes of airway closure. For this very reason, investigators have focused on tissue shear, small-scale heterogeneity, and interdependence phenomena as likely mechanisms responsible for ventilator-induced lung injury (8, 26, 39). Viewed in this context, PEEP is thought to protect the lung from shear injury by maintaining and/or reestablishing normal air space geometry in the face of altered surface tension (6, 9). Consistent with this hypothesis is the extensive experimental evidence that PEEP has beneficial effects on pulmonary gas exchange and on certain markers of lung injury (1, 6, 19, 26, 39). However, the surrogate end points used in these short-term physiological PEEP-response studies do not establish a reduction in tissue shear as the responsible mechanism. Not only will PEEP affect recruitment of an occluded airway irrespective of airway wall dimensions, but there are also numerous alternative mechanisms through which PEEP could modulate tissue inflammation and local wound healing responses. These include cellular mechanoresponses in terms of surfactant secretion (42), cell proliferation (43), matrix deposition and matrix assembly (22), changes in surface tension accompanying the aeration of previously flooded alveoli (23), increases in oxygen tension near “alveolar wounds,” and reductions in local blood flow resulting in decreased edema formation (3).

Two mechanisms dominate the pathobiology of ARDS: 1) surfactant dysfunction raising surface tension and 2) increased capillary permeability. Independence arguments predict that, for an alveolus to collapse in the face of rising surface tension, its transmural pressure must fall by many tens of cmH$_2$O (25). Particularly in the presence of increased microvascular permeability, such stress concentrations are bound to promote flooding, thereby minimizing heterogeneity in air space dimensions. Our experimental data are open to challenge if it is assumed that the scale of the heterogeneity in tissue strain is orders of magnitude smaller than tetrahedra. Although in theory alveolar volumes within a tetrahedron could be nonuniform, we consider this rather unlikely because systematic size differences between aerated and flooded alveoli would require a mechanism that prevents fluid flow along pressure gradients. Given the geometry of the lung and the low viscosity of the edema fluid, however, such a mechanism is hard to envision. Indeed, with the exception of absorption atelectasis during anesthesia or as a complication of an obstructing airway lesion, it is quite unlikely that an increase in local surface tension would produce a local collapse as opposed to flooding. The geometry of the lung unit remains stable and the alveolar ducts patent as long as alveoli can accommo-
date edema fluid. Once fluid starts to accumulate in alveolar ducts, however, the probability of a fluid dynamic instability resulting in liquid bridging rises exponentially with decreasing lung volume and recoil pressure (28).

In keeping with the CT data on the topic, PEEP was able to restore normal oscillation amplitudes in injured regions of the lung, i.e., PEEP caused recruitment (Fig. 4) (9, 27). However, it did so at the “cost” of increasing minimal and mean regional volumes above preinjury levels in all (both dependent and nondependent) regions of the lung. As had been suggested by others, at low levels of PEEP, nondependent and presumably aerated regions initially experienced the greatest increase in regional FRC (9, 40). This reflects the distribution of opening pressures, which must be substantially higher in dependent airways and alveoli with fluid menisci and liquid plugs. To the extent to which there is a vertical gradient in regional lung water within lobes, there ought to be a vertical gradient in regional lung recruitment (9). The subtle but statistically significant difference in oscillation amplitudes between more and less dependent regions of the caudal lobe at a PEEP of 7.5 (Fig. 5) is consistent with this hypothesis. This mechanism does not require a regional gradient in lung volume, only a regional gradient in edema and hence the number of liquid bridges. When PEEP was increased to 15 cmH\textsubscript{2}O, the end-expiratory volume of nondependent regions approached or even exceeded their preinjury volumes at TLC (see Fig. 3, prone data), whereas the most dependent regions of the lobe underwent further recruitment (see Figs. 4 and 5, supine data). This obviously placed nondependent regions at risk for overdistention injury (8), but was necessary for airway pressure to rise sufficiently to clear fluid from dependent airways. The mechanism of recruitment might, thus, be summarized as follows. First, alveolar volume must increase sufficiently to accommodate the edema fluid that heretofore had resided in the conducting airways (38). From there, a substantial volume of edema fluid might get translocated to the interstitial spaces (23). This is because PEEP raises interstitial capacitance and increases the hydrostatic pressure gradient between alveolar spaces and pulmonary interstitium (29). The time scale for translocation of alveolar fluid to the interstitium is minutes, which is squarely within the bounds of our experiment. Therefore, the most likely reason that PEEP lowered regional as well as whole lung impedances relates to airway-alveolar fluid clearance and the accompanying changes in the geometries of air-liquid interfaces. Our data do not support the hypothesis that PEEP “forced open” collapsed air spaces.

Whether peripheral lung units are narrow and collapsed or dilated and flooded is critical when considering the effects of PEEP on lung tissue stress and strain. The pressure necessary to accelerate an air-fluid meniscus and thereby initiate the reopening of an occluded airway is much higher in the presence of collapse than when liquid bridges an airway with normal dimensions. This is because the radii of curvature of the air-liquid interface differ substantially between the two conditions. Furthermore, in the presence of collapse, the yield pressure is dissipated over a narrow area, i.e., at the site at which apposed airway walls peel apart, and can therefore produce a shear stress of sufficient magnitude to injure the underlying epithelium. By reestablishing normal airway dimensions, the net effect of PEEP in this situation is to reduce local tissue shear stress (19, 26, 33, 39, 40). In contrast, in an already dilated but fluid-filled airway, the yield pressure is dissipated over a much larger area and less apt to produce injurious local stress concentrations. In this case, PEEP affects recruitment by increasing the capacity of alveoli to accommodate edema fluid, which helps to reduce the probability of liquid bridge formation in alveolar ducts and conducting airways. Our regional volume data are consistent with this mechanism. The stress distribution associated with this deformation is complex insofar as the displacement of air-liquid interfaces alters orientation and distribution of surface forces on the lung parenchyma (41). Nevertheless, the PEEP-induced distension of lung parenchyma above preinjury FRC increases the likelihood that alveolar walls become stress-bearing elements. Local stress (i.e., transpulmonary pressure) is determined by local geometry (i.e., the dimensions of the tissue relative to its unstressed state). Any intervention, such as PEEP, that raises regional volume, therefore, strains or deforms the tissue relative to its unstressed state. Because the amount of PEEP necessary to promote dependent lung recruitment raised the FRC of all lung regions (dependent and nondependent) relative to their preinjury state, the “price” for recruitment is a universal increase in parenchymal stretch above preinjury levels. Although the PEEP-induced increase in parenchymal stretch is greatest in aerated, nondependent regions (Figs. 2, 3, and 6), it is not confined to this part of the lung. This is interesting insofar as the lungs of patients who succumb to ARDS often reveal the histological fingerprints of barotrauma (i.e., tissue remodeling) in dependent regions of the lung as opposed to nondependent lung regions (35).

Effects of posture on regional volume and ventilation of the OA-injured lung. We show that changes in posture cause significant changes in the topographical distribution of lung volume and ventilation (Fig. 6). Previously dependent regions increased their FRC and tidal expansion regardless of whether animals were repositioned from supine to prone or from one to the other lateral decubitus posture. It follows that changes in posture also increase parenchymal stress of the recruited regions. However, the FRC of the recruited regions (and therefore their parenchymal stress at end-expiration) is either the same or only slightly greater than the FRC predicted before injury in that posture. This is in stark contrast to PEEP-based recruitment strategies, which must increase the FRC (and hence parenchymal stress) of all regions above preinjury levels to be effective. For example, in prone dogs the normal FRC of caudal lobes ranges between...
50 and 60% TLC (16). The change in posture from supine to prone (Fig. 6) raised lobar FRC to ~65% of preinjury TLC. Contrast this to the effect of 15 cm H2O of PEEP in that posture, which raised lobar volume to near 100% TLC (Fig. 3; P-PEEP).

There is much renewed interest in the effects of the prone position on cardiopulmonary function and clinical outcomes in patients with ARDS (5, 7, 21, 31). Albert’s group (14) showed that proning of OA-injured animals had limited effects on the distribution of regional perfusion but markedly improved dorsal lung ventilation. Accordingly, turning prone also improved dorsal lung ventilation-perfusion relationships, with minimal if any compromise of ventral lung ventilation and ventral ventilation-perfusion relationships (20).

On the basis of these observations, these investigators concluded that reversible air space closure occurs in dorsal lung regions when patients with ARDS are supine and that turning prone sufficiently alters dorsal lung transpulmonary pressures to reverse this closure without shifting the air space closure to the ventral regions. Although our observations are consistent with this interpretation, we wish to reemphasize that airway closure must be attributed to flooding and “liquid plugging” as opposed to airway collapse.

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