Maintenance of end-expiratory recruitment with increased respiratory rate after saline-lavage lung injury

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1Department of Clinical Studies, Section of Critical Care, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; 2Department of Anesthesiology, Johannes Gutenberg University, Mainz, Germany; 3Department of Anesthesiology and Critical Care, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; and 4Oscillogy, Folsom, Pennsylvania

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Syring RS, Otto CM, Spivack RE, Markstaller K, Baumgardner JE. Maintenance of end-expiratory recruitment with increased respiratory rate after saline-lavage lung injury. J Appl Physiol 102: 331–339, 2007. First published September 7, 2006; doi:10.1152/japplphysiol.00002.2006.—Cyclical recruitment of atelectasis with each breath is thought to contribute to ventilator-associated lung injury. Extrinsic positive end-expiratory pressure (PEEPe) can maintain alveolar recruitment at end exhalation, but PEEPe depresses cardiac output and increases overdistension. Short exhalation times can also maintain end-expiratory recruitment, but if the mechanism of this recruitment is generation of intrinsic PEEP (PEEPi), there would be little advantage compared with PEEPe. In seven New Zealand White rabbits, we compared recruitment from increased respiratory rate (RR) to recruitment from increased PEEPe after saline lavage. Rabbits were ventilated in pressure control mode with a fraction of inspired O2 (FIO2) of 1.0, inspiratory-to-expiratory ratio of 2:1, and plateau pressure of 28 cmH2O and either 1) high RR (24) and low PEEPe (3.5 or 2) low RR (7) and high PEEPe (14). We assessed cyclical lung recruitment with a fast arterial PO2 probe, and we assessed average recruitment with blood gas data. We measured PEEPi, cardiac output, and mixed venous saturation at each ventilator setting. Recruitment achieved by increased RR and short exhalation time was nearly equivalent to recruitment achieved by increased PEEPe. The short exhalation time at increased RR, however, did not generate PEEPi. Cardiac output was increased on average 13% in the high RR group compared with the high PEEPe group (P < 0.001), and mixed venous saturation was consistently greater in the high RR group (P < 0.001). Prevention of end-expiratory derecruitment without increased end-expiratory pressure suggests that another mechanism, distinct from intrinsic PEEP, plays a role in the dynamic behavior of atelectasis.

acutely injured lung; atelectasis; cyclical recruitment; intrinsic positive end-expiratory pressure; viscoelasticity; arterial oxygen oscillations

In acute lung injury (ALI), and experimental models of ALI, the application of positive end-expiratory pressure (PEEP) is a commonly used strategy to prevent end-expiratory collapse of alveoli. PEEP can maintain alveolar recruitment, which improves arterial oxygen concentrations in some patients (7, 22) and may limit ventilator-associated lung injury by decreasing cyclical recruitment (14, 18, 22, 45, 63, 65, 68, 69). The elevated intrathoracic pressure that results from PEEP, however, impairs venous return and may reduce cardiac output (7, 22, 53). Additionally, increased levels of PEEP are generally associated with higher airway pressures that may aggravate overdistension of alveoli (7, 22).

In surfactant depletion models of lung injury, several investigators have recently explored the use of short exhalation times to prevent end-expiratory collapse despite a low end-expiratory pressure (5, 39, 47). One mechanism proposed to explain this prevention of end-expiratory derecruitment is the generation of intrinsic PEEP. Intrinsic PEEP results from incomplete alveolar emptying during exhalation and can be exacerbated by shortened expiratory times. Both intrinsic PEEP and extrinsic PEEP increase alveolar and intrathoracic pressures (50), and equivalent levels of intrinsic and extrinsic PEEP should have similar hemodynamic consequences. Maintaining recruitment with short expiratory times may, therefore, have no hemodynamic benefit compared with maintaining recruitment with extrinsic PEEP (46, 47). None of the experimental studies in surfactant depletion models that directly evaluated the effects of a short exhalation time on end-expiratory atelectasis, however, have measured intrinsic PEEP (5, 39, 47). Thus the hypothesized role of intrinsic PEEP as the mechanism for the maintenance of recruitment with short exhalation times in saline-lavage injury (33, 47) has not been verified.

In a surfactant depletion model of acute lung injury in rabbits, we compared maintenance of lung recruitment with a slow respiratory rate and high extrinsic PEEP, to maintenance of lung recruitment with a fast respiratory rate and low extrinsic PEEP. Cyclical recruitment was continuously assessed with a fast responding arterial PO2 probe, which measured changes in shunt fraction throughout the respiratory cycle. After adjustment of either extrinsic PEEP or respiratory rate to levels that prevented end-expiratory collapse, we measured intrinsic PEEP, cardiac output, and mixed venous oxygen saturation. Our hypothesis was that the total PEEP (extrinsic plus intrinsic) required to maintain end-expiratory lung recruitment would be identical with both strategies, and depression of cardiac output and mixed venous saturation would be similar between these two ventilator settings.

MATERIALS AND METHODS

Animal preparation. The study protocol was approved by the Institutional Animal Care and Use Committee at the University of Pennsylvania. The animal preparation is similar to a previous report (5) with the following exceptions: general anesthesia was maintained with hydromorphone and midazolam infusions, a cath-

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Oxygen concentrations (FI\textsubscript{O2}) were determined using gas analysis (Stat Profile CCX, NOVA Biomedical) at two inspired levels of 0.21 and 1.0. A tracheostomy was performed under a surgical plane of anesthesia, and a 4.0 mm uncuffed endotracheal tube was sealed in the trachea with umbilical tape. All mechanical ventilation (Servo 900 C, Siemens) was in pressure control mode throughout the experiment. A respiratory monitor (CO\textsubscript{2}SMO-Plus, Novametrix, Wallingford, CT) was attached to the end of the tracheostomy tube to monitor airway pressure at the mouth, end-tidal carbon dioxide (ET\textsubscript{CO2}), and dynamic intrinsic PEEP (PEEP\textsubscript{dyn}).

A 4-Fr. catheter was inserted via an introducer in the right jugular vein and advanced to the level of the right ventricle, as guided by pressure waveform analysis. This catheter was used for mixed venous blood sampling as well as iodine saline injection for transpulmonary thermodilution cardiac output determination. Catheters (4-Fr., 8 cm; Pulsiocath, Pulsion Medical Systems) were inserted via surgical cutdown into both the left and right femoral arteries. The tips of those catheters extended into the distal aorta. One catheter was used for transpulmonary cardiac output, direct arterial blood pressure measurement, and continuous pulse contour cardiac output. The continuous pulse contour cardiac output was calibrated at the beginning of the experiment against transpulmonary thermodilution cardiac output. A fiber-optic fluorescence-quenching oxygen probe (FOXY AL-300, Ocean Optics) displayed the arterial PO\textsubscript{2} in real time at a digital sampling rate of 3.5 Hz.

Immediately prior to induction of lung injury, neuromuscular blockade was established via an intravenous loading dose (0.4 mg/kg) of pancuronium and maintained with a constant rate infusion at 0.2 mg·kg\textsuperscript{-1}·h\textsuperscript{-1} for the duration of the experiment. Surfactant depletion was induced by instilling 26 ml/kg of warm, balanced electrolyte solution (Normosol-R, Abbott Laboratories, Chicago, IL) into the lungs via the endotracheal tube, followed by immediate drainage by gravity. This lavage was performed three times for all rabbits, with 3–5 min between each lavage.

All rabbits had a phenylephrine infusion instituted immediately following saline lavage to maintain hemodynamic stability following lung injury, and the infusion rate was fixed at 0.4 mg/h (the same dose for every rabbit) for the duration of the experiment. In addition, 10–20 ml hydroxyethyl starch boluses were administered, to a maximum cumulative dose of 50 ml, when the systolic blood pressure was <60 mmHg and respiratory variation in blood pressure suggested hypovolemia. Once the study protocol comparing the three ventilatory strategies commenced, additional fluid boluses were prohibited.

Study design. For each of seven rabbits, three different ventilator strategies were investigated following surfactant depletion lung injury. Two settings investigated ventilatory strategies to avoid end-expiratory collapse: either high respiratory rate with low PEEP or low respiratory rate, high PEEP. A third setting, using a low respiratory rate and low PEEP, was used to demonstrate that in the absence of elevations in either respiratory rate or PEEP, end-expiratory collapse would occur as a result of lung injury. All rabbits were ventilated with an FI\textsubscript{O2} of 1.0.

Ventilator settings for each rabbit were determined after lavage according to a defined protocol and then remained fixed for the rest of the experiment in that rabbit. Plateau pressure (Pplat), PEEP, respiratory rate (RR), and inspiratory-to-expiratory (I:E) ratio were selected individually at the beginning of each experiment, with a goal of achieving equivalent levels of lung recruitment in the two main groups despite individual variability in the pressure responsiveness and dynamics of atelectasis. First, Pplat was adjusted during a series of 5–8 s inspiratory pauses to find the region of Pplat, where arterial partial pressure of \textsubscript{O2} (Pa\textsubscript{O2}) indicated nearly maximal lung recruitment but further increases in Pplat produced only small changes in Pa\textsubscript{O2}.

The target Pplat was set to 2–3 cm above that point, up to a maximum limit allowed by protocol of 35 cmH\textsubscript{2}O. Next, PEEP for the high PEEP group was set by a series of end-expiratory pauses, searching for the level of PEEP where derecruitment began and then setting the target high PEEP at 2–3 cmH\textsubscript{2}O above this closing pressure, up to a limit of 15 cmH\textsubscript{2}O. Low PEEP was targeted at 2–4 cmH\textsubscript{2}O for all rabbits. Finally, RR and I:E ratio were adjusted to find a combination of high rate, low PEEP that provided a Pa\textsubscript{O2} similar to the Pa\textsubscript{O2} in the low rate, high PEEP group, while allowing cyclical recruitment in the low rate, low PEEP group (Fig. 1). By protocol, high rate could be increased up to 24 breaths/min, low rate could be decreased to 6 breaths/min, and I:E could be varied over the range 1:2 to 4:1.

![Graph showing maintenance of respiratory rate with increasing respiratory rate and PEEP](image-url)
After ventilator parameters for each rabbit were fixed, the high respiratory rate, low PEEP and low respiratory rate, high PEEP settings were performed in random order, followed by the low rate, low PEEP setting. Each group of three settings was performed in triplicate for each rabbit. Prior to each setting, the rabbits were briefly disconnected from the ventilator to achieve an equivalent lung volume status at zero end-expiratory pressure (ZEEP). During this disconnection, an additional dead space of 32 ml was inserted into the airway, between the Y piece of the ventilator circuit and the CO₂SMO monitor, prior to ventilating with high respiratory rate, and removed prior to ventilating with low respiratory rate. Recruitment maneuvers were not performed prior to any ventilator setting.

Real-time assessment of lung recruitment was determined by average PaO₂ and by the amplitude of PaO₂ oscillations, as measured by the intra-arterial oxygen probe (Fig. 1) for all three ventilator settings. Peak and trough PaO₂ concentrations were recorded from breath-to-breath oscillations, and the amplitude was calculated as the difference between these two values.

Simultaneous mixed venous and arterial blood gas samples were obtained from catheters in the right ventricle and distal aorta, respectively, for the high respiratory rate, low PEEP and low respiratory rate, high PEEP settings. Samples were collected over several respiratory cycles (52) and were analyzed within 5 min of collection. Venous admixture (Qs/Qt) was calculated according to the standard equation: 
\[
Qs/Qt = (CaO₂ - CVO₂)/(CvO₂ - CVO₂), 
\]
where CcO₂ is the end-capillary, CaO₂ is the arterial, and CVO₂ is the mixed venous oxygen content.

At all three ventilator settings, numerous directly monitored and calculated hemodynamic parameters were recorded from the PICCO monitor (Pulsion Medical Systems, Munich, Germany). Cardiac output was transformed by x², systemic vascular resistance by x⁻¹⁹, base excess by x⁻⁵, lactate by x⁻₀·⁵, and PaO₂ oscillation amplitude by (x - 8)⁰·₃³. After transformations, all variables satisfied both normality and equal variance testing before the analysis with two-way ANOVA. Differences in heart rate were not tested for significance because three rabbits had heart rates that exceeded the maximum measurable value of 240 beats/min. Differences between replicate number for the three sets of measurements in each rabbit were not significant for any of the variables.

Cyclical recruitment was assessed by the amplitude of PaO₂ oscillations measured by the fast intra-arterial probe (Fig. 2). The PaO₂ oscillation amplitude in the low rate, low PEEP group was substantially larger than the oscillations in the other two groups (Fig. 2, *P < 0.001). The smaller difference in amplitude between the high rate, low PEEP group and the low rate, high PEEP group was also significant (*P < 0.001), indicating slightly more cyclical recruitment in the high PEEP group.

Equivalence of average lung recruitment between the high rate, low PEEP group and the low rate, high PEEP group was assessed by three measures: 1) PaO₂ from arterial blood gas analysis (Fig. 3 and Table 2); 2) calculation of venous admixture from the arterial and mixed venous blood gas analysis (Table 2); and 3) alveolar dead space fraction (Table 2). The higher average PaO₂ in the high PEEP group (Fig. 3 and Table 2) was not significantly different between the two groups (P =

### Table 1. Ventilator settings

<table>
<thead>
<tr>
<th></th>
<th>High Rate, Low PEEP</th>
<th>Low Rate, High PEEP</th>
<th>Low Rate, Low PEEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR, breaths/min</td>
<td>24 (23, 24)</td>
<td>7 (7, 7)</td>
<td>7 (7, 7)</td>
</tr>
<tr>
<td>E/E</td>
<td>2·1 (2·1, 2·1)</td>
<td>2·1 (2·1, 2·1)</td>
<td>2·1 (2·1, 2·1)</td>
</tr>
<tr>
<td>PEPe, cmH₂O</td>
<td>3·5 (3·3, 3·9)</td>
<td>13·6 (12·4, 14·1)</td>
<td>3·3 (2·8, 3·7)</td>
</tr>
<tr>
<td>Pplat, cmH₂O</td>
<td>28·1 (26·8, 30·1)</td>
<td>28·3 (27·1, 30·4)</td>
<td>28·1 (27·1, 30·3)</td>
</tr>
<tr>
<td>Delta, cmH₂O</td>
<td>25 (23, 26)</td>
<td>16 (15, 17)</td>
<td>26 (24, 27)</td>
</tr>
</tbody>
</table>

Data are reported in the format: median (interquartile range). Data from 7 rabbits, with each setting replicated 3 times per rabbit. *Difference high rate, low PEEP vs low rate, high PEEP; ‡difference high rate, low PEEP vs low rate, low PEEP; †difference low rate, high PEEP vs low rate, low PEEP; P ≤ 0·05, ANOVA.

RESULTS

The postlavage protocol for setting the ventilator resulted in the parameters shown in Table 1. I:E ratio was 2:1 in all rabbits. On average, low respiratory rate was near the minimum of 6 breaths/min and high respiratory rate was near the maximum of 24 breaths/min allowed by protocol. Pplat, and PEEP in the high PEEP group, were both on average substantially less than the maximum pressures allowed by protocol. The similar Pplat and high PEEP among rabbits suggests that the lavage injury on our model was reproducible. The average volume of supplemental hydroxyethyl starch was 41 ± 9 ml (mean ± SD).

All variables satisfied the Levene median equal variance testing without data transformation. Several variables required power transformations to satisfy normality conditions: cardiac output was transformed by x², systemic vascular resistance by x⁻¹⁹, base excess by x⁻⁵, lactate by x⁻₀·⁵, and PaO₂ oscillation amplitude by (x - 8)⁰·₃³. After transformations, all variables satisfied both normality and equal variance testing before the analysis with two-way ANOVA. Differences in heart rate were not tested for significance because three rabbits had heart rates that exceeded the maximum measurable value of 240 beats/min. Differences between replicate number for the three sets of measurements in each rabbit were not significant for any of the variables.

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![Image](http://jap.physiology.org/)

**Fig. 2.** Amplitude of PaO₂ oscillations within each breath, as an index of cyclical recruitment. Rate, respiratory rate. Error bars represent mean ± SD. Data for 7 rabbits, with each setting replicated 3 times per rabbit. *Difference high rate, low PEEP vs low rate, high PEEP; ‡difference high rate, low PEEP vs low rate, low PEEP; †difference low rate, high PEEP vs low rate, low PEEP; P ≤ 0·05, ANOVA.

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Table 2. Cardiovascular, respiratory, and blood gas results.

<table>
<thead>
<tr>
<th>Replicates/Rabbit</th>
<th>Baseline (1)</th>
<th>High Rate, Low PEEP (3)</th>
<th>Low Rate, High PEEP (3)</th>
<th>Low Rate, Low PEEP (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/minute)</td>
<td>160 (155, 200)</td>
<td>187 (181, 234)</td>
<td>195 (188, 222)</td>
<td>197 (186, 231)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>83 (77, 96)</td>
<td>103* (87, 110)</td>
<td>81 (76, 94)</td>
<td>84 (77, 106)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>59 (56, 64)</td>
<td>65* (60, 73)</td>
<td>53 (50, 65)</td>
<td>56 (48, 71)</td>
</tr>
<tr>
<td>CO (ml/min)</td>
<td>495 (466, 518)</td>
<td>591* (567, 625)</td>
<td>527* (474, 560)</td>
<td>577 (535, 586)</td>
</tr>
<tr>
<td>SVR (dyn/cm²)</td>
<td>11,264 (10,813, 12,441)</td>
<td>10,450 (9636, 11,847)</td>
<td>9306 (8789, 11,440)</td>
<td>9900 (8663, 11,743)</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETCO₂ (mmHg)</td>
<td>29 (28, 32)</td>
<td>35* (30, 37)</td>
<td>472 (40, 49)</td>
<td>36 (34, 40)</td>
</tr>
<tr>
<td>PEEP (cmH₂O)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>Vₑ (ml/Kg)</td>
<td>34 (33, 36)</td>
<td>20* (16, 21)</td>
<td>110 (10, 13)</td>
<td>19 (17, 22)</td>
</tr>
<tr>
<td>Pmean (cmH₂O)</td>
<td>9.2 (8.4, 9.3)</td>
<td>20.5* (19.9, 21.9)</td>
<td>25.7* (23.1, 25.9)</td>
<td>21.3 (20.1, 22.7)</td>
</tr>
<tr>
<td>Vₐ/alv/Vₐ/lav</td>
<td>0.19 (0.15, 0.34)</td>
<td>0.11 (0.10, 0.16)</td>
<td>0.14 (0.10, 0.29)</td>
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<tr>
<td><strong>Blood gas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.56 (7.52, 7.56)</td>
<td>7.50* (7.47, 7.54)</td>
<td>7.40 (7.38, 7.46)</td>
<td></td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>542 (526, 554)</td>
<td>458 (421, 509)</td>
<td>486 (459, 523)</td>
<td></td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>35.7 (35.2, 40.1)</td>
<td>39.5* (36.7, 41.0)</td>
<td>58.4 (50.5, 61.2)</td>
<td></td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>99.9 (99.9, 100)</td>
<td>99.8 (99.7, 99.9)</td>
<td>99.8 (99.8, 99.9)</td>
<td></td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>10.5 (10.0, 10.7)</td>
<td>9.2 (8.8, 9.6)</td>
<td>9.3 (8.9, 9.6)</td>
<td></td>
</tr>
<tr>
<td>BE (mmol/l)</td>
<td>9.8 (8.3, 12.2)</td>
<td>6.5* (6.1, 8.5)</td>
<td>9.2 (8.0, 10.8)</td>
<td></td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td>1.6 (1.0, 1.9)</td>
<td>2.4 (1.2, 2.7)</td>
<td>2.1 (1.3, 2.6)</td>
<td></td>
</tr>
<tr>
<td>SvO₂ (%)</td>
<td>81.6* (78.8, 85.4)</td>
<td>77.8 (70.8, 80.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q/Qo (%)</td>
<td>16.3* (10.5, 18.8)</td>
<td>9.7 (7.5, 11.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are in the format: median (interquartile range). Data from 7 rabbits. Baseline values were obtained prior to induction of lung injury. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; CO, cardiac output; SVR, systemic vascular resistance; ETCO₂, end-tidal CO₂; PEEP, intrinsic PEEP; Vₑ, expiratory tidal volume; Pmean, mean airway pressure; Vₐ/alv/Vₐ/lav, estimated alveolar deadspace fraction = (PaCO₂ - ETCO₂)/PaCO₂; SaO₂, arterial oxygen saturation; Hb, hemoglobin; BE, base excess; SvO₂, mixed venous oxygen saturation; Q/Qo, venous admixture. Significant differences (P ≤ 0.05, ANOVA): *high rate, low PEEP vs. low rate, high PEEP; †high rate, low PEEP vs. low rate, low PEEP; ‡low rate, high PEEP vs. low rate low PEEP.
slightly negative slope in this relationship is not significantly different from zero ($P = 0.11$, power = 0.36).

**DISCUSSION**

This study in a surfactant depletion lung injury model in rabbits demonstrated that approximately equivalent reductions in cyclical recruitment could be achieved using either moderate elevations in respiratory rate or application of extrinsic PEEP. The mechanism for maintenance of end-expiratory recruitment using moderately elevated respiratory rates, however, was not related to generation of intrinsic PEEP. In addition, maintenance of recruitment via increased respiratory rates afforded improved cardiac output, mixed venous saturation, and systolic blood pressure, compared with results obtained when PEEP was used to maintain lung recruitment.

*Limitations of the study.* Differences in cardiac output between the paired ventilator settings (high rate, low PEEP vs. low rate, high PEEP) were determined by use of arterial pulse contour analysis. This technique uses a proprietary, and confidential, algorithm to calculate cardiac output from the waveform of the arterial pressure tracing and an assessment of arterial input impedance and aortic compliance (21, 54). The influence of ventilator settings, such as PEEP, on the accuracy of this method has not been reported. Cardiac output via the pulse contour analysis method, however, does compare favorably with thermodilution over a range of doses of a variety of vasoactive drugs (21) that would be expected to change impedance and compliance much more than variations in ventilator settings. Also, measurements of mixed venous saturation provided a supplemental assessment of cardiac output. For cardiac outputs above a critical range, systemic oxygen metabolism ($\text{VO}_2$) becomes independent of systemic oxygen supply ($\text{DO}_2$), and increases of cardiac output above that critical range result in decreased extraction to maintain $\text{VO}_2$ constant (61). In this supply-independent range of $\text{DO}_2$, therefore, decreases in cardiac output are reflected in decreases in mixed venous saturation. The critical oxygen delivery, below which $\text{VO}_2$ becomes supply dependent, has not been reported in rabbits. In multiple species, however, the onset of supply dependence is associated with reductions of mixed venous saturations to the range of 30–50% (1, 8, 36, 60), well below the lowest venous saturation of 64% observed in the current study. The paired differences in $\text{SvO}_2$ between the two groups (high rate, low PEEP vs. low rate, high PEEP), therefore, support the cardiac output data measured by pulse contour analysis. Finally, the finding of increased cardiac output in the high rate, low PEEP group is consistent with the finding of lower end-expiratory pressure in this group, although other mechanisms such as reflex changes in cardiac output cannot be ruled out in this intact animal preparation.

Precisely matching arterial $\text{CO}_2$ tensions over a wide range of ventilator settings is technically quite difficult. We attempted to adjust for the markedly larger minute ventilation in the high rate, low PEEP group by insertion of an additional dead space volume in the airway. Nevertheless, the arterial $\text{CO}_2$ tension in the low rate, high PEEP group was systematically greater than the arterial $\text{CO}_2$ tension in the high rate, low PEEP group. Increased arterial $\text{CO}_2$ levels, however, are associated with increased cardiac output, a result of catecholamine release and systemic vasodilation (51, 55, 67). If any effect would be expected from the difference in $\text{PaCO}_2$, between the
two strategies, it would be to increase the cardiac output in the low rate, high PEEP group. Therefore this difference in PaO2 between the groups probably did not contribute to the higher cardiac output in the high rate, low PEEP group; it actually would be expected to reduce the paired differences in cardiac output.

We measured intrinsic PEEP by the dynamic method (PEEPdyn), as described by Rossi et al. (58) and implemented in the CO2SMO-Plus respiratory monitor. The dynamic method has been shown to underestimate intrinsic PEEP as measured by the static, end-expiratory occlusion method (26). For lungs with homogeneous airways resistances, however, the values measured by PEEPdyn are consistently ~76% of the values obtained by static measurements (26). Even in the worst case scenario of very heterogeneous lungs and a detection threshold of 0.2 cmH2O, the maximum intrinsic PEEP measured by static determinations would be estimated to be <2 cmH2O. Additionally, in a series of pilot studies in our model, we confirmed that a measured PEEPdyn of zero was accompanied by an end-expiratory flow of zero, at respiratory rates of up to 30 breaths/min and I:E ratios of 2:1.

Our study used arterial oxygenation in rabbits breathing 100% oxygen as an index of lung recruitment. At the beginning of each experiment, we adjusted the PEEP in the low rate, high PEEP group and the respiratory rate in the high rate, low PEEP group, with the goal of achieving the same PaO2 in the two groups. During ventilation with 100% oxygen, PaO2 correlates with the percentage of atelectatic lung measured by CT (38, 40, 49) and with true shunt fraction measured by the multiple inert gas elimination technique (46). Matching PaO2 with such different ventilator settings and maintaining this matching with exact precision over the course of the experiment, however, is nearly impossible, even with the real-time information provided by the PaO2 probe. In our study, there was a small and nonsignificant trend for the PaO2 to be greater in the low rate, high PEEP group than in the high rate, low PEEP group (Fig. 3). Additionally, because the different ventilator settings affected cardiac output and venous saturation as well as PaO2, an identical PaO2 did not necessarily reflect identical venous admixture. In our study, the venous admixture was systematically lower in the low rate, high PEEP group (Table 2), indicating better average recruitment in this group. A precise equivalence of average recruitment between the two groups, as assessed by venous admixture, would have resulted in less PEEP in the low rate, high PEEP group, which might have increased cardiac output in this group and made the difference in cardiac output between the groups less marked. However, the data of Fig. 6 argues against a major role of this difference in recruitment in determining the differences in cardiac output between the groups. There was no significant relationship between the magnitude of the differences in shunt fraction between the groups and the magnitude of the differences in cardiac output.

Comparison to previous studies. Several prior studies have suggested that shortened expiratory times can prevent end-expiratory derecruitment. Neumann et al. (47) were the first investigators to explore the potential impact of short exhalation times on end-expiratory collapse. They used dynamic CT to measure time-dependent atelectasis during prolonged expiratory pauses in pigs with saline lavage, oleic acid, or LPS lung injury. Their results suggested that short expiration times (<0.6 s for oleic acid injury) could allow exhalation but maintain end-expiratory recruitment without extrinsic PEEP. In a subsequent study, Neumann et al. (46) investigated the effects of short exhalation times on average lung recruitment during tidal breathing in pigs after oleic acid injury. Exhalation times of 0.5 and 1.0 s with ZEEP reduced shunt fraction compared with control, but did not reduce shunt fraction as much as 20 cmH2O of extrinsic PEEP. Despite providing less average lung recruitment than extrinsic PEEP, the short exhalation times were associated with generation of significant intrinsic PEEP. Reductions in cardiac output, compared with control, were similar in all three study groups. There are several possible reasons for the contrasting results of Neumann’s study and our current study. Most notably, the animal species, lung size, and lung injury models are different between these studies. Mishima et al. (44) presented evidence, for example, that during some phases of oleic acid injury, airway resistance is increased, a phenomenon that would certainly encourage generation of intrinsic PEEP.

Markstaller et al. (39) used dynamic CT to study time-dependent collapse in saline-lavaged pigs. Their results suggested that exhalation times >1 s predispose to end-expiratory collapse. In a following study, Markstaller et al. (40) extended their work with dynamic CT in saline lavaged pigs to examine tidal breathing. Their data demonstrate substantial end-expiratory collapse with an exhalation time of ~1.9 s, confirming that this commonly used exhalation time is associated with cyclical recruitment of atelectasis.

In one of our prior studies (5), we used a rapidly responding PaO2 probe to assess cyclical recruitment in saline-lavaged rabbits. Maintenance of end-expiratory recruitment was strongly influenced by both PEEP and respiratory rate and substantial recruitment could be maintained, during tidal breathing, at an exhalation time of 1.0 s. We did not measure intrinsic PEEP or cardiac output at individual ventilator settings in that study.

In summary, these prior studies of the effects of exhalation time on maintenance of end-expiratory recruitment have suggested that exhalation times in the range of 0.5 to 1.0 s can prevent end-expiratory collapse. Our finding that a mean exhalation time of 0.83 s (range 0.83–0.91 s) prevented end-expiratory collapse is consistent with these prior reports.

Other previous studies have suggested that even shorter expiration times are required to generate intrinsic PEEP in normal rabbit lungs. Cartwright et al. (9) demonstrated a negligible increase in functional residual capacity in normal rabbits ventilated through a 3.0 mm endotracheal tube when the exhalation time was decreased from 1.8 to 0.8 s, indicating that very little gas trapping was induced by the reduced exhalation time. Fujino et al. (16) reported that ventilation of normal rabbits through a 4.0 mm endotracheal tube at a rate of 50 breaths/min and I:E ratio of 2:1 (an exhalation time of 0.4 s) did not generate static intrinsic PEEP. Ludwigs et al. (37) reported intrinsic PEEP ≤5 cmH2O in normal rabbits ventilated through a 3.0 mm endotracheal tube at an exhalation time of 0.4 s (37).

Our results are also consistent with these previous reports of the short exhalation times required to generate intrinsic PEEP in normal rabbit lungs. In our model, nondependent regions of the lung are expected to be nearly normal and dependent regions are expected to have reduced compliance. The relevant
time constant for the generation of intrinsic PEEP, however, is the local RC time constant, i.e., local airways resistance times local compliance (6). Reduction of compliance in the dependent regions would be expected to reduce the RC emptying time constant and make these regions less prone to develop intrinsic PEEP (3, 31), compared with the more normal, non-dependent parts of the lung.

Implications—clinical ventilator management. Our results suggest that in surfactant depletion lung injury, cyclical recruitment of atelectasis can be avoided by judicious choice of exhalation time without generation of intrinsic PEEP. This strategy for maintaining end-expiratory recruitment, compared with maintaining recruitment with extrinsic PEEP, results in significantly improved cardiac output and would have obvious advantages in clinical ventilator management of acute respiratory distress syndrome (ARDS). Several limitations, however, preclude direct translation of our results to clinical ventilator management.

First, there currently is no widely adopted method to directly measure cyclical recruitment at the bedside in routine care, and it is therefore difficult to determine or predict this optimum exhalation time. Static pressure-volume curves have been advocated to predict end-expiratory recruitment by examining the measured end-expiratory pressure in relation to the critical closing pressure on the expiratory limb of the static pressure-volume curve (56, 57) or, alternatively, in relation to the maximal tidal compliance in a decreamental PEEP trial (12, 27, 29). The prediction of dynamic behavior based on static pressure-volume relationships, however, does not take into account the dynamics of end-expiratory collapse. Whether collapse occurs at a particular end-expiratory pressure depends not just on that pressure and the volume history, but also on how long the airway has remained at that pressure (5). Several methods that have the potential to directly assess cyclical recruitment have been applied in recent research studies, including electrical impedance tomography (15, 32, 71), dynamic CT (39, 40, 46, 47, 71), subpleural vital microscopy (24, 65), rapid continuous PaO2 monitoring (5), timed blood gas collection (52), and fast pulse oximetry (66). None of these methods have been used, however, to study the dynamics of end-expiratory collapse in ARDS. It therefore remains unknown if end-expiratory collapse in ALI and ARDS demonstrates dynamic behavior similar to the dynamics observed in our saline lavage model. It is also currently unknown how prevalent cyclical recruitment is with ventilator strategies commonly used in ARDS.

Second, our model of saline lavage lung injury in rabbits is not a complete representation of ARDS. The impacts of species, lung size, lung maturity, and type of lung injury on the dynamics of end-expiratory collapse have not been investigated and we cannot extrapolate the data of our model to predict the dynamics of atelectasis in ARDS. The saline lavage model replicates the surfactant dysfunction of ARDS (34, 70), but other features such as epithelial and endothelial damage and alveolar inflammation take several hours to develop after lavage (41, 59). Our model of mild injury with surfactant depletion in mature lungs is most likely relevant to early stages of injury in patients at risk for development of ARDS and ALI (52, 57, 70).

Third, the ventilator settings in our study were chosen for optimal study of the dynamics of end-expiratory collapse, not to replicate clinically relevant ventilator settings for ARDS. The large tidal volume and low respiratory rate in our low PEEP, low rate group (the group that demonstrated cyclical recruitment) have no counterpart in clinical ventilator management of ARDS. Slow respiratory rates and large tidal volumes are common, however, in the management of patients at risk for ALI, such as operative management of trauma patients.

Implications—dynamics of atelectasis. Most of the recent experimental (37, 46) and clinical (2, 11, 28, 35, 42, 43, 72) studies investigating the effects of a short exhalation time on average lung recruitment, and more specifically on maintenance of end-expiratory recruitment (5, 39, 47), have proposed intrinsic PEEP as the mechanism for prevention of end-expiratory derecruitment. There are, however, other time-dependent phenomena relevant to both recruitment and derecruitment. For example, several investigators have studied the kinetics of surfactant transport and adsorption to a gas-liquid interface (20, 23), which would have a rapidly increasing area during lung recruitment (20). Also, considerable attention has been given to the intrinsic mechanical properties of lung tissue (4, 10, 30, 44, 62, 64). Viscoelastic and plastoelastic models suggest characteristic time constants for expansion and contraction of lung tissue, independent of alveolar pressure-flow relationships. In this regard, it is of interest that time constants estimated on the basis of intrinsic tissue mechanics are generally larger than the RC time constant (airways resistance times regional compliance) relevant to intrinsic PEEP. D’Angelo et al. (10), for example, reported a viscoelastic time constant for normal rabbits of 0.81 s, substantially slower than the time constants of <0.4 s required to generate intrinsic PEEP (16).

Airway closure during exhalation may also be delayed by the time it takes for airway lining fluid to flow, coalesce, and form liquid bridges (48). Because these flows are driven by surface tension instability, increases in surface tension after saline lavage are expected to speed the formation of liquid bridges and airways occlusion (48). Similarly, recruitment of a closed airway could be delayed by the time it takes for an air-liquid meniscus to transit the airway, given finite surface tension and viscosity (19), and a similar phenomenon might introduce time dependence in airway closure. Although airway closure and acinar air trapping per se would not give rise to rapid increases in shunt fraction, similar time-dependent phenomena in the more complex geometry of the alveolar duct might also be rate limited by finite times for fluid flow.

In summary, we demonstrated, in saline-lavaged rabbits, that a respiratory rate of 24 breaths/min and a low PEEP of 3 cmH2O could limit cyclical recruitment as well as a slower rate of 7 breaths/min and a larger PEEP of 14 cmH2O. At a low PEEP of 3 cmH2O, an exhalation time of 0.83 s prevented end-expiratory derecruitment but a longer exhalation time of 2.9 s did not. The mechanism of maintained end-expiratory recruitment with short exhalation times, however, was not intrinsic PEEP. Consistent with this finding, maintaining end-expiratory recruitment with rapid respiratory rates produced better cardiac outputs and mixed venous saturations than maintenance of end-expiratory recruitment with high PEEP. Our results suggest that an optimally chosen expiratory time can prevent end-expiratory collapse but still allow sufficient time for complete exhalation, as implied by the absence of intrinsic PEEP. The finding of negligible intrinsic PEEP in turn suggests that other mechanisms, for example, lung tissue mechanics, kinetics of surfactant transport, or finite time for the flow of
airway lining fluid, were responsible for delaying end-expiratory collapse in this surfactant depletion model of lung injury.

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DISCLOSURES

Dr. Baumgardner is president and sole owner of Oscillogy LLC, a small business that manufactures and sells scientific research equipment. Oscillogy has a long-term strategic commitment to development and commercialization of new technologies that emphasize high temporal resolution for the study of time-dependent phenomena in physiology research. In the short term, however, Oscillogy has only one product available, a system for performing MIGET under the usual steady-state assumptions. Currently the company does not own or license any new technology directed at time-dependent measurements, and Oscillogy has only one product available, a system for performing MIGET.

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