# Predicting the response of the injured lung to the mechanical breath profile

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<sup>1</sup>Vermont Lung Center, University of Vermont College of Medicine, Burlington, Vermont; <sup>2</sup>Department of Surgery, State University of New York Upstate Medical University, Syracuse, New York; and <sup>3</sup>R. Adams Cowley Shock Trauma Center, University of Maryland School of Medicine, Baltimore, Maryland

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Smith BJ, Lundblad LK, Kollisch-Singule M, Satalin J, Nieman G, Habashi N, Bates JH. Predicting the response of the injured lung to the mechanical breath profile. J Appl Physiol 118: 932-940, 2015. First published January 29, 2015; doi:10.1152/japplphysiol.00902.2014.-Mechanical ventilation is a crucial component of the supportive care provided to patients with acute respiratory distress syndrome. Current practice stipulates the use of a low tidal volume (VT) of 6 ml/kg ideal body weight, the presumptive notion being that this limits overdistension of the tissues and thus reduces volutrauma. We have recently found, however, that airway pressure release ventilation (APRV) is efficacious at preventing ventilator-induced lung injury, yet APRV has a very different mechanical breath profile compared with conventional low-VT ventilation. To gain insight into the relative merits of these two ventilation modes, we measured lung mechanics and derecruitability in rats before and following Tween lavage. We fit to these lung mechanics measurements a computational model of the lung that accounts for both the degree of tissue distension of the open lung and the amount of lung derecruitment that takes place as a function of time. Using this model, we predicted how tissue distension, open lung fraction, and intratidal recruitment vary as a function of ventilator settings both for conventional low-VT ventilation and for APRV. Our predictions indicate that APRV is more effective at recruiting the lung than low-VT ventilation, but without causing more overdistension of the tissues. On the other hand, low-VT ventilation generally produces less intratidal recruitment than APRV. Predictions such as these may be useful for deciding on the relative benefits of different ventilation modes and thus may serve as a means for determining how to ventilate a given lung in the least injurious fashion.

ARDS; mechanical ventilation; predictive computational model; lung injury

MECHANICALLY VENTILATING PATIENTS with acute respiratory distress syndrome (ARDS) is a delicate balance between providing sufficient inspired volume with each breath to ensure adequate gas exchange, while at the same time avoiding ventilator induced lung injury (VILI). The damage resulting from VILI is a consequence of the repetitive stresses and strains that are applied to the lung tissues. These stresses and strains are reflected in the way that pressure, flow, and volume manifest at the airway opening throughout each breath, referred to collectively as the mechanical breath profile. Clearly, the mechanical breath profile contains important information, however, requires a quantitative understanding of how the mechanical breath profile translates into stress and strain at the tissue level, and then to tissue damage.

Presently, the link between the mechanical breath profile and VILI is understood only in general terms that are used to guide mechanical ventilation for the overall ARDS patient population. Thus, low tidal volumes (VT) are used to reduce damage caused by tissue overdistension, known as volutrauma, with the goal for all ARDS patients being  $V_T = 6$  ml/kg ideal body weight. Similarly, positive end-expiratory pressure (PEEP) is used to avoid the so-called atelectrauma that results from repetitive closure (derecruitment) and reopening (recruitment) of alveoli and small airways with each breath. It has been recognized for some time that the nature of the pressurevolume (PV) relationship of the lung may contain the information necessary to set the appropriate level of PEEP for a given patient (1, 14, 18, 32, 34, 48), but the precise manner in which PEEP should be set remains controversial (13, 17). Furthermore, almost all studies have neglected the important fact that recruitment and derecruitment are dynamic processes that depend on time as well as pressure (11). Finally, and perhaps most importantly, ventilation strategies that are efficacious for the ARDS patient population as a whole may be far from optimal in any given patient, especially given that ARDS is such a heterogeneous condition.

There is thus a critical need for predictive methods that can link a particular mechanical breath profile to VILI production in a given patient. Toward this end, we used a computational model to link measurements of airway pressure (Paw) and flow to tissue overdistension and repetitive recruitment in a rat model of ARDS. We then used the computational model to investigate how these two VILI mechanisms are modulated by the mechanical breath profile in two clinically established modes of mechanical ventilation.

## METHODS

Animal preparation. All experiments were approved by the Animal Care and Use Committee of SUNY Upstate Medical University and conducted in accordance with National Institutes of Health guidelines. Ten male Sprague-Dawley rats (390-515 g) were anesthetized with 0.1 mg/kg ketamine and 0.011 mg/kg xylazine. A tracheostomy was performed, and a 2.5-mm cannula (Harvard Apparatus, Holliston, MA) was inserted and affixed to a Flexivent small-animal ventilator (SCIREQ, Montreal, QC, Canada). Baseline ventilation (VT = 6 ml/kg, PEEP = 5 cmH<sub>2</sub>O, 55 breaths/min) was applied for 5 min to allow the animals to stabilize. Lung injury was induced by instilling 2.5 ml/kg of 0.2% Tween 20 in normal saline into each lung, as previously described (27, 28). Following instillation, the rats were ventilated (VT = 16 ml/kg, PEEP = 0) for 10 min to induce a modest degree of VILI, resulting in a reduction in alveolar size and increases in alveolar instability (27), conducting airway strain, and alveolar heterogeneity (28). The animals were not paralyzed, as is sometimes done to prevent spontaneous breathing activity from corrupting measurements of lung impedance, but there was no evidence of such

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activity in the present study, and the model fits were all of good quality (see below).

Physiological measurements. All animals began the experiment in the healthy state from which they were subjected to the following protocol, all performed using the Flexivent ventilator. First, to standardize the lung volume (VL) history, the lungs were recruited with a deep inspiration maneuver (DI) consisting of a 7-s pressure ramp from zero PEEP to a peak pressure of 30 cmH<sub>2</sub>O followed by a 7-s hold at peak pressure. We then recorded a dynamic PV loop from zero PEEP at 1 Hz with a ventilator cylinder displacement = 9 ml to gather information about the nonlinear elastic properties of the open lung (see computational model analysis below). A second DI was performed to fully recruit the lung, and this was immediately followed by a derecruitability test, consisting of 5 min of ventilation with  $V_T = 6$ ml/kg and PEEP = 0 that was interrupted at 20-s intervals, starting 6s into the ventilation, by a 2-s multifrequency (0.5–20.5 Hz) volume perturbation (peak-peak ventilator cylinder displacement = 3 ml). The input impedance of the respiratory system was determined from each perturbation, and each impedance was fit with the constant-phase model (22), which provided a value for lung elastance (H). H increased progressively throughout each derecruitability test, which we took to reflect the propensity of the lungs to derecruit over time (3-5, 43, 44). Finally, another DI was performed to gather information about the recruitment characteristics of those lung units that had closed during the preceding derecruitability test.

After the induction of acute lung injury, a DI was first applied to standardize VL history, followed by the recording of a dynamic PV loop at PEEP = 0. We then recorded four measurement sequences, each consisting of a DI followed by a derecruitability test and then a second DI. These sequences were separated by a 20-s period of 6 ml/kg ventilation. The four derecruitability tests were performed sequentially at PEEP levels of 0, 3, 6, and 12 cmH<sub>2</sub>O with the DIs applied above the prescribed PEEP to reach a maximum of 30 cmH<sub>2</sub>O.

*Computational model.* The experimental data were analyzed with the aid of a computational model adapted from our previously reported studies (11, 31, 46, 47). The model is composed of  $N_{\text{Units}} =$  768 parallel respiratory units (RU), each connected to a common airway junction. (This number of units was selected to provide a smooth response during recruitment and derecruitment while maintaining reasonable program execution times.) Each RU consists of a terminal airway connecting to an alveolar compartment. Each alveolar compartment has an identical nonlinear elastance unit (E<sub>Unit</sub>) given by

$$\begin{split} E_{\text{Unit}}(\mathbf{V}_{\text{Unit}}) &= \\ N_{\text{Units}} \begin{cases} E_{\text{Base}}, & \text{if } \mathbf{V}_{\text{Unit}} \leq \mathbf{V}_{\text{Crit}} / N_{\text{Units}} \\ E_{\text{Base}} + E_{\text{Fac}} \{ N_{\text{Units}} [\mathbf{V}_{\text{Unit}} - (\mathbf{V}_{\text{Crit}} / N_{\text{Units}})] \}^2, & \text{if } \mathbf{V}_{\text{Unit}} > \mathbf{V}_{\text{Crit}} / N_{\text{Units}} \end{cases} \end{split}$$

where  $V_{\text{Unit}}$  is the compartment volume,  $V_{\text{Crit}}$  is the volume at which  $E_{\text{Unit}}$  transitions from linear to nonlinear (volume dependent) behavior,  $1.1 \leq E_{\text{Base}} \leq 1.4 \text{ cmH}_2\text{O/ml}$  is the low-volume (linear) elastance equivalent to the value of *H* measured in the healthy animal, and  $E_{\text{Fac}}$  is the rate constant for the volume-dependent elastance increase in the nonlinear regime. The values of the parameters  $V_{\text{Crit}}$ ,  $E_{\text{Unit}}$ , and  $E_{\text{Fac}}$  were determined by fitting the model to experimental data (see below). The elastance of the entire model (EL) thus changes with the number of open units according to

$$E_{L}(t) = \left[\sum \text{ open units}\left(\frac{1}{E_{\text{Unit}}^{i}(V_{\text{Unit}}^{i})}\right)\right]^{-1}$$
(2)

Likewise, the airflow resistance for the entire model (R<sub>mod</sub>) is

$$\mathbf{R}_{\text{mod}}(t) = \mathbf{R}_{\text{unit}} [N_{\text{open}}(t)]^{-1}$$
(3)

with  $R_{\text{Unit}} = N_{\text{Units}} \cdot Raw$ . The airway resistance (Raw)  $0.02 \le Raw \le 0.05 \text{ cmH}_2 \text{O} \cdot \text{s} \cdot \text{ml}^{-1}$  was experimentally determined for each rat by equating it to the Newtonian resistance parameter of the constant phase model that was fit to each respiratory impedance measurement

(22). The magnitude of the airflow ( $\hat{Q}$ ), therefore, depended on the pressure differential between the lung (PL) and ventilator ( $P_{vent}$ ) in the manner first described by Rohrer (39) so that the magnitude of the tracheal flow rate was

$$\left| \dot{Q} \right| = \frac{R_1 - \sqrt{R_1^2 + 4R_2 \left| \mathbf{P}_L - \mathbf{P}_{\text{vent}} \right|}}{2R_2} \tag{4}$$

with  $R_2 = 0.003$  selected to match the peak expiratory flow (PEF) rates measured in Sprague-Dawley rats by Wright et al. (53). The constant  $R_1 = R_{eq} + R_{mod}$  and the resistance of the ventilator tubing ( $R_{eq}$ ) was measured during the ventilator calibration procedure for each rat so that  $0.06 \le R_{eq} \le 0.1 \text{ cmH}_2\text{O} \cdot \text{s} \cdot \text{ml}^{-1}$ .

 $|\dot{Q}|$  is used to calculate the Paw = PL +  $dR_1$   $|\dot{Q}|$ , with d = 1 when PL  $\ge$  P<sub>vent</sub>, and d = -1 when PL < P<sub>vent</sub>. The flow into each open RU is then (Paw - E<sub>Unit</sub> V<sub>Unit</sub>)/R<sub>Unit</sub>. The VL is defined as the sum of the volumes of all open RUs so that PL = EL VL. This formulation allows for gas to be trapped when an RU derecruits, such that the volume of the closed unit is not counted toward the total VL.

When simulating pressure-controlled ventilation, the model was driven with a prescribed pressure waveform. For volume-controlled ventilation, the model was driven with a prescribed volume waveform operating on a shunt gas elastance ( $E_{gas}$ ) of 14 <  $E_{gas}$  < 27 cmH<sub>2</sub>O/ml, representing the compressibility of the air in the Flexivent cylinder.  $E_{gas}$  was determined during the equipment calibration procedure performed before each experiment (43).

To simulate a derecruitability test, it is necessary to take the dynamics of recruitment and derecruitment into account. This is achieved using virtual trajectories, as our laboratory has previously described (11, 30, 31, 47), that provide an empirical representation of the way in which recruitment and derecruitment of lung units depend on both pressure and time. In brief, each RU is associated with a virtual trajectory variable  $0 \le x \le 1$  that increases at a rate  $S_O$  (P<sub>O</sub> – Paw) when Paw is greater than a critical opening pressure (P<sub>O</sub>), where  $S_O$  is the opening velocity constant. Conversely, when Paw is less than the critical closing pressure P<sub>C</sub>, then *x* decreases at a rate given by the closing velocity constant ( $S_C$ ). The recruitment and derecruitment dynamics of the model are governed by the probability distribution functions from which P<sub>C</sub>, P<sub>O</sub>,  $S_C$ , and  $S_O$  are randomly drawn.

Based on a previous study in mice with VILI (47), we employed two groups of RU having different distributions for P<sub>C</sub>, P<sub>O</sub>, *S*<sub>C</sub>, and *S*<sub>O</sub>. One group contained  $(1 - \beta)N_{\text{Units}}$  units, with *S*<sub>C</sub> and *S*<sub>O</sub> drawn from exponential probability density functions given by  $f(x) = e^{x/\Lambda_c}/\lambda_c$ and  $f(x) = e^{x/\Lambda_c}/\lambda_o$ , respectively, where  $\lambda_O = 0.1\lambda_C$  (31).  $\lambda_C$  and  $\lambda_o$  are the scale parameters for the distribution of closing and opening velocities, respectively, and  $\beta$  defines the fraction of the lung in each group of respiratory units that exhibits similar recruitment characteristics. P<sub>C</sub> was drawn from a Gaussian distribution having mean  $\mu_C$ and SD  $\sigma_C$  (11, 12, 23, 38, 47), while P<sub>O</sub> = P<sub>C</sub> +  $\Delta$ P. The parameters  $\lambda_C$ ,  $\mu_C$ ,  $\sigma_C$ , and change in pressure ( $\Delta$ P) were determined for each rat during the model fitting process (see below).

The other population of  $\beta N_{\text{Units}}$  RU had  $\lambda_{\text{C}} = 0.075$  and  $\lambda_{\text{O}} = 0.75$ , with P<sub>C</sub> drawn from a uniform probability density function on the interval (16, 30) to match the long-timescale closure observed in the derecruitment tests and the rapid reopening during DIs. To accommodate recruitment, which was observed during the 14-s DIs and not during 55 breaths/min ventilation, we set P<sub>O</sub> = P<sub>C</sub> and define a latency time parameter for each RU ( $T_s$ ), which is drawn from a Gaussian distribution with a mean  $\mu_T = 0.45$  s and SD  $\sigma_T = 0.05$  s. When Paw  $< P_C$ , the virtual trajectory decreases at a rate  $dx \cdot dt^{-1} = S_C$ , as described above. However, Paw must remain above P<sub>O</sub> for a period  $T_s$  before the virtual trajectory is allowed to increase at a rate  $dx/dt = S_O (P_O - Paw)$ . The model equations were integrated using the forward Euler method at a simulation frequency of 500 Hz.

*Model fitting.* The free model parameters that were evaluated during the model-fitting procedure are listed in Table 1. The model was fit to the experimental data from each rat both before and after Tween instillation using a parallel pattern search (PPS) optimization

Table 1. Initial value, lower and upper bounds, and the initial grid step size for the parameters determined using the numerical optimization algorithm

Parameter	Starting Value	Minimum	Maximum	Initial Grid Step Size
E <sub>Fac</sub> , cmH <sub>2</sub> O/ml <sup>3</sup>	0.04	0.01	0.2	0.015
V <sub>Crit</sub> , ml	8	4	12	1.5
$\Delta P$ , cmH <sub>2</sub> O	6	0	18	2
$\mu_{\rm C}$ , cmH <sub>2</sub> O	5	-1	14	2.5
$\sigma_{\rm C}$ , cmH <sub>2</sub> O	3	0.5	9	2.5
$\lambda_{\rm C}$ , s/cmH <sub>2</sub> O	50	0.01	100	12.5
β	0.2	0	0.8	0.15

See text for definition of terms.

algorithm (24–26, 29, 50) as our laboratory has described previously (46). Briefly, this algorithm seeks to minimize an objective function quantifying the differences between the predicted and measured pressures, volumes, and elastances. At each iteration of the PPS algorithm, this objective function is examined for every one of the 2,187 distinct combinations of the 7 parameters listed in Table 1. The seven-dimensional parameter grid is composed of the current parameter estimates as well the current values, both plus and minus the current grid step size. If the value of the objective function at any of these points is less than its current minimum value, then the center of the multidimensional search grid is relocated to the position of the new minimum. Otherwise, the grid spacing is reduced by 40% for the next iteration. The search for the global minimum of the objective function is terminated when the grid step size has been reduced 10-fold or after 30 iterations.

For each animal, under either baseline conditions or postinjury, the computational model was fit to all physiological data simultaneously by minimizing the composite cost function

$$Y = \mathcal{E}_{\mathrm{DI}} \cdot \left( n t_{\mathrm{DI}} \cdot N_{\mathrm{DI}} \right)^{-1} + \mathcal{E}_{\mathrm{PV}} \cdot \left( n t_{\mathrm{PV}} \cdot N_{\mathrm{PV}} \right)^{-1} + 5 \mathcal{E}_{\mathrm{DTest}} \cdot N_{\mathrm{DTest}}^{-1}$$
(5)

where  $E_{DTest}$  is the root mean square (RMS) error between the measured and calculated elastance values at each simulation point during the derecruitability tests.  $E_{PV}$  is the RMS pressure error during the volume-controlled dynamic PV loops, and  $E_{DI}$  is the RMS error in the delivered volume during the pressure-controlled DI maneuvers.  $N_{DI}$ ,  $N_{PV}$ , and  $N_{DTest}$  are the numbers of DI maneuvers, dynamic PV loops, and the derecruitability test elastance measurements, respectively, that were performed in a given rat. For the healthy rats  $N_{DI} = 2$ ,  $N_{PV} = 1$ , and  $N_{DTest} = 13$ , while for the injured rats  $N_{DI} = 8$ ,  $N_{PV} = 1$ , and  $N_{DTest} = 52$ . The number of time points in each DI maneuver  $nt_{DI} = 6,000$ , and the number of time points in each PV loop  $nt_{PV} = 525$ .

To reduce the computational cost of the simulations, we retain the computed values of Y(Eq. 5) at each step. If an identical parameter combination is used in a subsequent PPS step, the retained Y is used to avoid reevaluating the model. For each animal and treatment condition (healthy or injured), we use a constant value to seed the random number generator that generates the distributions of  $P_{C}$  and  $S_{C}$ throughout the PPS model evaluations and model simulations (described below). This approach improves convergence of the PPS algorithm because Y computed for a given set of parameters remains constant, removing a small amount of random noise from the error surface. Fifty iterations of the model using the best-fit parameters with the random number generator seed based on the wall clock time provided a coefficient of variation in Y of 0.044 for the healthy simulations and 0.13 for the injured cases. The mean of the SD in open fraction at each time point was 0.012 for both the healthy and injured rats.

*Model simulations.* Once the model was fit to each of the rats, we assessed the potential for producing volutrauma and atelectrauma during mechanical ventilation under both baseline and postinjury

conditions. We first performed this investigation for the low-VT ventilation (LTVV) that is now standard of care for ARDS patients, but which was adapted here to be appropriate for the rat. The LTVV had an inspiratory-to-expiratory duration ratio of 1 to 1.5, a rate of 55 breaths/min, and a VT of 6 ml/kg, achieved by applying an inspiratory pressure (PI) ramp beginning at the applied level of PEEP and increasing for 0.05 s at the rate necessary to achieve the desired VT. The PI was determined by iteratively performing recruitment maneuvers and ventilating until the lung open fraction stabilized to achieved the desired VT = 6 ml/kg. Expiration was passive against the prescribed PEEP after ramping down for 0.05 s from the peak PI.

We also simulated airway pressure release ventilation (APRV) which consists of periods of sustained PI of inspiratory time duration, interrupted periodically by brief expiratory phases of duration designed to achieve a desired end-expiratory flow (EEF) as a percentage of PEF. An EEF-to-PEF ratio (EEF/PEF) of 75% is well established as the appropriate clinical setting for APRV (21, 27). We investigated EEF/PEF ranging from 75% (corresponding to a relatively short expiratory duration) to 10% (corresponding to a longer expiratory duration). In a second series of simulations, we investigated the effects of  $5 \le P_I \le 50 \text{ cmH}_2O$  for an EEF/PEF of 75%. In each case, inspiratory time was iteratively adjusted to achieve a minute ventilation of 330 ml·kg<sup>-1</sup>·min<sup>-1</sup>, which was identical to that delivered with LTVV (measured at steady state following a DI). The expiratory pressure (PE) was 0 cmH<sub>2</sub>O in all cases with a ramp of 0.05 s between PI and PE to represent the noninstantaneous transition between these two pressures that is observed experimentally (27, 28). Because of the high expiratory flows occurring early in expiration in APRV, we increased the simulation frequency to 2,000 Hz for all model simulations to improve the accuracy of our calculations.

### RESULTS

Figure 1 shows data and model fits obtained in a representative rat. When the animal was healthy, its compliance decreased above the predicted  $V_{Crit} = 8.6$  ml, presumably due to strain stiffening of the lung tissues at high volumes (Fig. 1*A*). In contrast, after the rat was injured, the slope of the PV curve increased for Paw > 15 cmH<sub>2</sub>O, indicative of ongoing recruitment. The model calculated that the open fraction of the lung in the injured animal increased from 0.28 to 0.96 between Paw = 15 cmH<sub>2</sub>O and 30 cmH<sub>2</sub>O. Figure 1*B* shows the dynamic PV loop for the same animal, after injury, illustrating the marked hysteresis that resulted from the inspiratory recruitment of closed lung units that reclosed during the subsequent expiration. Figure 1*C* shows the corresponding time courses of *H* during each derecruitability test, again after the animal was injured.

Figure 2 shows the derecruitability test data and model fits for seven of the rats we studied. Two of the 10 animals in the experiment were excluded due to incomplete data, and a third animal was excluded because the baseline H measurements were more than 5 SDs above the mean of the remaining 7 animals. These three animals were also excluded from all subsequent analyses. The data in Fig. 2 are similar to those of the single rat shown in Fig. 1C and show that H increased progressively with time during each of the individual derecruitability tests, reflecting progressive closure of lung units (2, 6). There were dramatic increases in both the magnitude and rate of change of H at PEEP = 0 cmH<sub>2</sub>O in the injured rats compared with the healthy animals, indicating a correspondingly increased magnitude and rate of derecruitment. The fits of the computational model to these data provide estimates of the mean open fraction to be 0.67 for the healthy animals with



Fig. 1. Data from a representative rat. A: measured (solid lines) and modeled (dashed lines) relationships between airway pressure (Paw) and lung volume above functional residual capacity (VL) obtained during a deep inspiration recruitment maneuver in the healthy state and after lung injury was induced by Tween lavage. B: measured (solid line) and modeled (dashed line) dynamic pressure-volume loops in the injured animal. C: measured ( $\bullet$ ) and modeled ( $\bigcirc$ ) elastance (H) during derecruitability tests in the injured animal performed at positive end-expiratory pressure (PEEP) levels of 0, 3, 6, and 12 cmH<sub>2</sub>O.

 $PEEP = 0 \text{ cmH}_2O$ . Following injury, the mean open fraction estimates are 0.33, 0.51, 0.66, and 0.80 for PEEP = 0, 3, 6, and 12 cmH<sub>2</sub>O, respectively.

The increased derecruitability of the injured lung is reflected in the best-fit model parameter values (Table 2). A significant difference was found between the healthy and injured rats for  $\lambda_{\rm C}$ , indicating that derecruitment and recruitment both occurred more rapidly in the injured animals. Furthermore, since  $\Delta P$  was also significantly increased, the reopening occurred at higher pressures in the injured animals. Finally, the transition to nonlinear elastance occurred at a lower VL, V<sub>crit</sub>, in the injured animals (Table 2).

Figure 3A shows model predictions of lung distension for both healthy (black) and injured (red) rats during LTVV over a range of PEEP levels from 0 to 25 cmH<sub>2</sub>O. The degree of lung distension is a measure of the extent to which the lung tissues are stretched and is defined here as the ratio of the lung's volume to its open fraction (i.e., distension increases as a given volume is accommodated by a decreasing fraction of



Fig. 2. Mean ( $\pm$ SE) *H* measured during derecruitability tests performed at different PEEP levels in 7 rats ( $\bigcirc$ ), together with the mean of the model fits (solid curves, gray shading is  $\pm$ SE).

the total lung tissue). Figure 3 shows both the maximum value of lung distension achieved at the end of inspiration and the minimum value achieved at the end of expiration. Also shown is the lung distension at which the PV behavior of the lung tissue transitions from linear to nonlinear in the healthy rats (black dotted line). Interestingly, this transition occurs at a lower distension in the injured rats (red dotted line) than in the healthy animals, because injury changed the apparent properties of the tissue so that they became nonlinear at lower volumes (Table 2), likely as a result of alveolar collapse due to surfactant inactivation and air displaced by the instilled Tween. Figure 3*B* shows corresponding plots for the rats ventilated with APRV, with EEF/PEF ranging from 10 to 75%, corresponding to progressively decreasing expiratory durations.

The maximum and minimum values of open fraction predicted by the computational model for both healthy and injured rats are shown for LTVV and APRV in Fig. 4, A and B, respectively. LTVV always avoids significant intratidal recruitment (Fig. 4A), but at the expense of incomplete recruitment, as PEEP decreases below its maximum value of 25 cmH<sub>2</sub>O. In contrast, APRV always achieves full recruitment at end inspiration due to the high prescribed PI, but, as the EEF decreases (i.e., longer expiratory durations), the degree of intratidal derecruitment increases (Fig. 4B). What is particularly striking about these predictions is that, while intratidal recruitment is always rather small in healthy animals (Fig. 4B, black), longer durations of the expiratory phase in the injured rats can result

 Table 2. Best fit parameters for healthy and lung-injured rats

Parameter	Healthy Rats	Injured Rats	
E <sub>Fac</sub> , cmH <sub>2</sub> O/ml <sup>3</sup>	$0.048 \pm 0.012$	$0.047 \pm 0.010$	
V <sub>Crit</sub> , ml	$9.22 \pm 0.78$	$5.81 \pm 0.49*$	
$\Delta P$ , cmH <sub>2</sub> O	$3.62 \pm 1.29$	$12.77 \pm 1.96*$	
$\mu_{\rm C}$ , cmH <sub>2</sub> O	$0.77 \pm 0.13$	$2.65 \pm 0.79$	
$\sigma_{\rm C}$ , cmH <sub>2</sub> O	$2.15 \pm 0.96$	$5.61 \pm 0.59$	
$\lambda_{\rm C}$ , s/cmH <sub>2</sub> O	$8.83 \pm 2.84$	$54.28 \pm 12.64*$	
β	$0.15 \pm 0.055$	$0.08 \pm 0.026$	

Values are means  $\pm$  SE. \*Significant difference between the parameter values following lung injury identified with paired *t*-tests ( $\alpha = 0.05$ ).

Fig. 3. Minimum and maximum of the spatially averaged distension of the open lung tissue (corresponding to end-expiration and end-inspiration, respectively) during low-tidal volume ventilation (LTVV; *A*) and airway pressure release ventilation (APRV) at inspiratory pressure (PI) = 36 cmH<sub>2</sub>O (*B*) predicted from the model fits to 7 rats (means  $\pm$  SE) in healthy animals (black) and after induction of lung injury (red). Also shown (dotted lines) are the threshold volumes at which the lung pressure-volume relationship becomes nonlinear (V<sub>crit</sub>). EEF/PEF, ratio of end-expiratory flow to peak expiratory flow.



in nearly one-half the lung closing and reopening with each breath (Fig. 4*B*, red), highlighting the clinical importance of using APRV with its proper setting of EEF/PEF = 75%. Both modes of ventilation converge on the same recruitment characteristics either as PEEP increases in LTVV (Fig. 4*A*), or as expiratory duration shortens in APRV (Fig. 4*B*).

In Fig. 5, we compare the recruitment and spatially averaged open lung distension characteristics of LTVV as a function of PEEP, as well those of APRV over a range of PI with EEF/PEF = 75%. For a given peak PI, both modes of ventilation produce similar levels of spatially averaged distension of the open lung, but the excursions in distension with APRV are lower than those of LTVV at low PEEP and higher at high PEEP (Fig. 5A). There are also differences in recruitment between the two modes of ventilation (Fig. 5B), the most noticeable being that LTVV produces substantially less open lung at low pressures compared with APRV. At the high PI typically used clinically (>25 cmH<sub>2</sub>O), APRV again maintains more open lung, but only by ~6%, which may not be clinically significant.

#### DISCUSSION

The ARDSnet clinical trials (9) demonstrated improved outcomes in ARDS patients ventilated with a VT of 6 ml/kg ideal body weight, which may be decreased to 4 ml/kg to prevent plateau pressures from exceeding 30 cmH<sub>2</sub>O. The clinical protocol also stipulated that PEEP and inspired O<sub>2</sub> fraction should be set to achieve  $55 \leq$  arterial Po<sub>2</sub>  $\leq$  80 Torr, and that respiratory rate should be adjusted to balance pH. These criteria are based on empirical findings and are not linked directly to the underlying mechanisms that cause VILI, even though they are rationalized by the notion of ventilating the "baby lung" and thus of reducing volutrauma by limiting the injurious effects of over-stretching the healthier lung regions (9). Also, despite the documented survival benefit of the ARDSnet trial, there has been little additional evidence that LTVV coupled with control of other factors, such as PEEP, mean Paw, or ventilator mode, correlates with a reduction in volutrauma as a marker of overdistension (8, 9, 15, 33, 35, 42, 49, 54).

A limitation of the ARDSnet ventilation protocol is the universal application to all ARDS patients, despite the fact that this patient population is highly heterogeneous. The shortcomings of this approach, and the efficacy of personalized ventilation determined via respiratory mechanics, is highlighted in a recent clinical investigation involving H1N1 influenza patients diagnosed with ARDS and refractory hypoxemia and referred for extracorporeal membrane oxygenation (20). In that study, respiratory system elastance was partitioned into lung and

Fig. 4. Minimum and maximum open lung fraction during LTVV (*A*) and APRV at  $PI = 36 \text{ cmH}_2O(B)$  predicted from the model fits to 7 rats (mean  $\pm$  SE) in healthy animals (black) and after induction of lung injury (red).





Fig. 5. Predicted spatially averaged lung tissue distension (*A*) and open lung fraction (*B*) in lung-injured rats. The maximum and minimum values for APRV with a EEF/PEF of 75% and  $5 \le PI \le 50 \text{ cmH}_2\text{O}$  are shown with solid and dashed lines, respectively. Also shown are the maximum ( $\bullet$ ) and minimum ( $\circ$ ) for LTVV with  $0 \le \text{PEEP} \le 24 \text{ cmH}_2\text{O}$ .

chest wall components, and PEEP was titrated to achieve a transpulmonary pressure of ~25 cmH<sub>2</sub>O. In subjects with abnormally high chest wall elastance, this lead to PEEP  $\approx 22$  cmH<sub>2</sub>O and plateau pressures approaching 40 cmH<sub>2</sub>O. These high ventilation pressures resolved the refractory hypoxemia and the need for extracorporeal membrane oxygenation rescue in all of the patients in this subgroup.

Furthermore, the measures described in the ARDSnet protocol are only implemented once ARDS has developed and thus represent a reactionary measure rather than a proactive strategy. It is thus reasonable to suppose that improved approaches to ventilating the injured lung would avoid these limitations by basing decisions on the assessment of the two key mechanisms believed to contribute to VILI, namely overdistension of parenchymal tissues and repetitive recruitment of closed lung units, and by preemptive avoidance of the progressive functional degradation associated with clinical ARDS (45). However, tissue overdistension and repetitive recruitment cannot be monitored directly in the lungs of an ARDS patient. Instead, these injurious processes must be inferred from measureable quantities in which they are reflected. Fortunately, pressure and flow at the airway opening are perfect candidates in both regards. Nevertheless, patterns of overdistension and recruitment can only be extracted from Paw and airway flow via the intermediary of a computational model of lung mechanical function. On the basis of our laboratory's previous studies (10, 44, 46, 47), we identified a suitable model for this purpose and found that it can accurately recapitulate the mechanical behavior of the injured lung during a variety of different maneuvers that collectively reveal its dynamic and nonlinear behavior (Figs. 1 and 2).

To the extent that the mechanisms represented in our computational model correspond to those present in a real lung, we are then able to make predictions about the injurious processes occurring within a given lung during a prescribed regimen of mechanical ventilation. In the present study, we focus on two particular ventilation modes. The LTVV mode now widely serves as a standard of care due to the success of the ARDSnet trial (9). APRV is often considered a rescue mode for patients with established ARDS rather than a primary mode of ventilation (7, 16, 21), but it has been investigated as a primary mode and has been shown with early application to significantly reduce ARDS incidence and mortality (7). In the present study, we made predictions concerning these two modes of ventilation in rats because the model was fitted to data measured in rats, but there is no reason in principle why the same approach could not be used in human patients once the necessary dynamic lung function data are in hand.

First, we compared the degree of tissue distension occurring with LTVV vs. APRV (Fig. 3) and identified some immediately obvious differences. Most importantly, while distension is roughly proportional to PEEP with LTVV and does not achieve high levels until PEEP is correspondingly high (Fig. 3A), distension is always relatively high with APRV (Fig. 3B) because we maintain  $P_1 = 36 \text{ cmH}_2\text{O}$ . At corresponding plateau pressures, LTVV and APRV demonstrate an equivalent level of spatially averaged distension as shown in Fig. 5. Furthermore, the excursion in tissue distension during a breath (i.e., from end-expiration to end-inspiration) is relatively unaffected by PEEP in LTVV because of the fixed VT. In contrast, the range of tissue distension is highly dependent on the duration of the expiratory phase in APRV, where VT is dependent on the targeted EEF/PEF, and this applies to both normal and injured lungs. For example EEF/PEF of 75 and 10%, respectively, provide average VT values of 10.7 and 26.5 ml/kg in the injured animals for  $P_I = 36 \text{ cmH}_2\text{O}$ . However, when the EEF/PEF is held at 75%, the distension range remains roughly constant at higher values of PI, but is decreased at low PI due to the reduced VT values (Fig. 5A). LTVV and APRV also differ somewhat in their recruitment characteristics (Fig. 5B), although these differences are not particularly large, except perhaps at low minimum pressures where LTVV allow for substantially more derecruitment than APRV (Fig. 5B).

On the other hand, APRV with an extended duration of  $P_I = 36 \text{ cmH}_2\text{O}$  is generally better than LTVV at keeping the lungs recruited, as shown in Fig. 4, *B* and *A*, respectively. Because of both the pressure and time dependence of recruitment, APRV in the healthy lung maintains full recruitment during the plateau phase with very little derecruitment at all levels of EEF (Fig. 4*B*). Inspiratory recruitment during expiration increases rapidly with increasing expiratory duration. This demonstrates why it is so important to use APRV with the proper setting of EEF/PEF = 75%; when EEF/PEF is set improperly at 10%, the model predicts a substantial amount of intratidal recruitment

and derecruitment that could be very damaging to the lung tissues. In contrast, LTVV predicts minimal intratidal recruitment and derecruitment, but at the expense of a substantial residual level of derecruitment at end-inspiration until PEEP reaches at least 15 cmH<sub>2</sub>O (Fig. 4A). Since there is no benefit to longer expiratory times with APRV, we simulated the effects of varied PI with the PEF/EEF fixed at 75%, consistent with previously published guidelines (21). To facilitate direct comparison with the LTVV simulations, we plot the predicted spatially averaged distension and open fraction for the injured rats against the prescribed PI in Fig. 5, which shows that maximum of the mean open lung distension is directly related to PI, regardless of the mode of ventilation. For PI > 25cmH<sub>2</sub>O, where such injured lung would likely be ventilated clinically, our predictions indicate that, for a given level of distension, APRV provides greater recruitment than LTVV, but without increasing overdistension.

These predictions thus show that LTVV and APRV have complementary strengths and weaknesses, which are strongly dependent on the functional state of the lung and the applied mechanical breath profile. When directly comparing the two modes at comparable levels of maximum tissue distension in the injured lung (Fig. 5), we predict APRV will improve recruitment in the range of PI values that would be applied to the injured lung. However, the range of distension and open fraction are less with LTVV. Precisely how these various factors translate into clinical outcomes remains to be determined, because we do not yet have a way of equating the rate of generation of VILI to some function of overdistension, intratidal recruitment and distension, and maximum amount of open lung. Nevertheless, the modeling methodology we have employed here establishes a basis on which an injury cost function for VILI might be developed. This supposition, however, must be viewed relative to a number of important limitations of our study.

Perhaps the most important limitation is the fact that we have based our analysis of the relative merits of LTVV and APRV on a computational model that contains a number of critical assumptions. We assume, for example, that overdistension applies equally to all regions of open lung because we assume that these regions all experience essentially the same distending pressure due to homogeneous resistance, and that each alveoli has an identical stress-strain relationship (e.g., equal V<sub>Crit</sub> and E<sub>Base</sub>). There are numerous factors that this ignores, including gravity-dependent differences in pleural pressure that play an important role in clinical ARDS and variations in the local stress-strain behavior of the parenchyma resulting from ventilation inhomogeneity. In addition, our model predictions are representative of a passively ventilated patient and, therefore, do not account for the effects of spontaneous breathing, which has been shown during APRV to improve recruitment (52), end-expiratory VL (51), and ventilation of the dependent lung (36). Thus there may be additional benefits to APRV in patients exhibiting spontaneous inspiratory efforts that are not included in our predictions. Trying to account for these effects would greatly complicate the model and model fitting, and it is unclear that the gains would be worth the effort. Perhaps even more critical is our assumption of a mechanism for the time dependence of recruitment and derecruitment based on the use of virtual trajectories (10, 31). The behavior of these virtual trajectories bears distinct resemblance to processes involved in airway collapse and reopening that have been studied extensively in the laboratory (19, 37), which perhaps lends some credibility to their use in the present application. Nevertheless, they remain an essentially empirical mechanism.

Another potential and important limitation of our study concerns is translatability to the human patient. For example, we have neglected gravitational gradients in the present study, because these are essentially unimportant in the small lung of the rat, but they are significant in a human lung. Also, finding model parameter values that accurately embody recruitment and derecruitment dynamics requires perturbing the lung experimentally under a rather wide amplitude range of pressure, flow, and volume (Figs. 1 and 2). It remains to be seen whether it is possible to safely obtain a rich enough data set for this purpose in human patients, particularly those with injured lungs. One promising approach might be to use Paw and airway flow data collected during variable VT ventilation, a new approach to mechanical ventilation that has been shown to have certain physiological advantages over conventional ventilation and that we have recently shown allows the dynamics of recruitment and derecruitment to be identified (46).

In summary, we have shown in rats that measuring Paw and airway flows during a sufficiently rich set of dynamic perturbations allows the identification of a computational model embodying the injurious mechanisms of both tissue overdistension and repetitive recruitment. We then used the model to simulate lung distension and recruitment during LTVV with a range of PEEP levels and during APRV with a range of expiratory durations and PI values. These simulations indicate that LTVV produces somewhat less intratidal recruitment than APRV. However, when APRV is properly set with EEF/PEF = 75% at clinically relevant pressures in the injured lung, it achieves a higher level of open lung than LTVV and does not result in additional tissue distension. Our model thus demonstrates that both the timing and magnitude of the pressures applied during mechanical ventilation play a role in recruitment, while the spatially averaged maximum tissue distension is a function of PI. Taken together with our porcine model of ARDS, which exhibited improved oxygenation and lung compliance when ventilated with APRV compared with LTVV (40, 41), and a recent meta-analysis that suggests that properly set APRV appears to reduce ARDS incidence and in-hospital mortality (7), our simulations suggest that the protective benefits of recruitment may outweigh the damage caused by tissue overdistension.

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#### DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

#### AUTHOR CONTRIBUTIONS

Author contributions: B.J.S., G.F.N., N.H., and J.H.B. conception and design of research; B.J.S., L.K.L., M.K.-S., J.S., and G.F.N. performed experiments; B.J.S. and G.F.N. analyzed data; B.J.S., L.K.L., M.K.-S., J.S., G.F.N., N.H., and J.H.B. interpreted results of experiments; B.J.S. and J.H.B.

prepared figures; B.J.S. drafted manuscript; B.J.S., L.K.L., M.K.-S., J.S., G.F.N., N.H., and J.H.B. edited and revised manuscript; B.J.S., L.K.L., M.K.-S., J.S., G.F.N., N.H., and J.H.B. approved final version of manuscript.

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