Predicting ventilator-induced lung injury using a lung injury cost function

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Hamlington KL, Smith BJ, Allen GB, Bates JH. Predicting ventilator-induced lung injury using a lung injury cost function. J Appl Physiol 121: 106–114, 2016. First published May 12, 2016; doi:10.1152/japplphysiol.00096.2016.—Managing patients with acute respiratory distress syndrome (ARDS) requires mechanical ventilation that balances the competing goals of sustaining life while avoiding ventilator-induced lung injury (VILI). In particular, it is reasonable to suppose that for any given ARDS patient, there must exist an optimum pair of values for tidal volume ($V_T$) and positive end-expiratory pressure (PEEP) that together minimize the risk for VILI. To find these optimum values, and thus develop a personalized approach to mechanical ventilation in ARDS, we need to be able to predict how injurious a given ventilation regimen will be in any given patient so that the minimally injurious regimen for that patient can be determined. Our goal in the present study was therefore to develop a simple computational model of the mechanical behavior of the injured lung in order to calculate potential injury cost functions to serve as predictors of VILI. We set the model parameters to represent normal, mildly injured, and severely injured lungs and estimated the amount of volutrauma and atelectrauma caused by ventilating these lungs with a range of $V_T$ and PEEP. We estimated total VILI in two ways: 1) as the sum of the contributions from volutrauma and atelectrauma and 2) as the product of their contributions. We found the product provided the minimally injurious regimen for that patient can be determined. The above considerations suggest that there should exist, for any given ARDS patient, an optimum combination of $V_T$ and PEEP that minimizes risk for the development of VILI. Utilizing such patient-specific optimum values for $V_T$ and PEEP would constitute a personalized approach to mechanical ventilation in ARDS and would represent a significant advance over the current “one-size-fits-all” approach that employs the same $V_T$ (in ml/kg ideal body wt) for every patient. To realize this advance, however, we need to be able to predict how injurious a given ventilation regimen will be in any given patient so that the minimally injurious regimen for that patient can be determined.

The complexity of predicting VILI in a patient-specific manner is likely best suited to a computational model that is able to link the stresses and strains imposed by mechanical ventilation to the production of both volutrauma and atelectrauma. We have successfully developed such models and matched their predictions to data obtained from mice and rats with lung injury (20, 31, 32). Although these models are able to accurately reproduce the dynamic mechanical behavior of injured rodent lungs, they require extensive experimental data sets and substantial computational time to provide unique fits. Data arrays of recorded airway pressure, flow, and volume signals from a ventilated patient in the intensive care unit are typically limited in both dynamic range and frequency content, safety considerations being paramount. In addition, the simulations must be executed quickly to provide information in a timely manner. Accordingly, a practical and clinically useful model must be as simple as possible, with the fewest degrees of freedom and a limited number of free parameters. Our goal in the present study was therefore to develop an efficient mathematical model for the mechanical behavior of the injured lung and to use this model to explore injury cost functions that could one day serve as predictors of VILI in a closed-loop

NEW & NOTEWORTHY

This article describes a new computational model of lung mechanics that includes mechanisms for predicting the development of ventilator-induced lung injury (VILI) via the mechanisms of both volutrauma and atelectrauma. The model uses these predictions in two novel injury cost functions that potentially could be used to guide patient-specific mechanical ventilation in acute respiratory distress syndrome so that VILI is minimized.

THE ONLY CURRENT TREATMENT option for acute respiratory distress syndrome (ARDS) is supportive care based around mechanical ventilation, which balances the competing goals of sustaining life against avoiding further mechanical damage to the already injured parenchymal and microvascular tissues (13, 21, 29). There are two guiding principles to the avoidance of ventilator-induced lung injury (VILI). One is to minimize damage caused by overdistension (i.e., volutrauma). This is achieved by limiting lung inflation and is the principle behind the current standard of care for ARDS that mandates the use of a low tidal volume ($V_T$) of 6 ml/kg ideal body wt (1). The other guiding principle is to minimize the damage caused by repetitive reopening of closed airways (i.e., atelectrauma). This typically occurs at low lung volumes and is avoided by applying positive end-expiratory pressure (PEEP) (14). However, small $V_T$ does not necessarily eliminate tissue overdistension, particularly if a significant enough fraction of the lung is consolidated such that the remaining fraction has to accommodate all of the imposed ventilation (33). Similarly, PEEP will not eliminate repetitive recruitment if some units only recruit at high pressures (1a, 12, 18). Furthermore, PEEP increases end-expiratory lung volume and therefore works against the distension-reducing benefits of a small $V_T$ at peak inflation. Any particular choice of $V_T$ and PEEP therefore represents a trade-off between the avoidance of volutrauma and the avoidance of atelectrauma within the constraints imposed by the requirements for sufficient oxygenation and ventilation. This trade-off is patient-specific because not every ARDS patient responds favorably to the addition of PEEP (17), and thus the risk of volutrauma and atelectrauma is highly variable.
personalized mechanical ventilation regimen in patients with ARDS.

**Glossary**

- \( E \): Elastic coefficient for parenchymal stiffness
- \( K \): Exponential coefficient determining nonlinear parenchymal stiffness
- \( P \): Applied pressure at airway opening
- \( P_A \): Alveolar pressure
- \( P_{1/2} \): Pressure at which half the recruitable lung units are open during inflation
- \( \Delta P \): Average amount by which closing pressures are less than opening pressures
- **PEEP**: Positive end-expiratory pressure
- \( R_{aw} \): Airway resistance
- \( t \): Time
- \( T \): Time interval over which injury is computed
- \( V \): Time integral of \( V \)
- \( V_a \): Volume of alveolar compartment
- \( V_T \): Tidal volume
- \( x \): Vertical expansion component representing inflation of open lung units
- \( x_{adj} \): Degree of tissue distension above which volutrauma begins to occur
- \( y \): Horizontal expansion component representing recruitment of closed lung units
- \( \alpha \): Fraction of lung units permanently open
- \( \beta \): Fraction of lung units permanently open at zero alveolar pressure
- \( \gamma \): Maximum possible fraction of open lung units
- \( \lambda \): Weight that \( \Omega_{vol} \) contributes to additive injury
- \( \tau \): Rate at which lung units become recruited with increasing pressure
- \( \Omega_{at} \): Injury due to atelectrauma
- \( \Omega_{prod} \): Injury due to product of \( \Omega_{at} \) and \( \Omega_{vol} \)
- \( \Omega_{sum} \): Injury due to sum of \( \Omega_{at} \) and \( \Omega_{vol} \)
- \( \Omega_{vol} \): Injury due to volutrauma

**METHODS**

**Modeling simultaneous lung inflation and recruitment.** Figure 1 shows what we believe to be the simplest model structure capable of usefully mimicking the mechanical events by which volutrauma and atelectrauma develop in the lung. The lung is represented as a uniformly ventilated alveolar compartment served by a single airway. In contrast to conventional single-compartment lung models, this alveolar compartment can change volume with two independent degrees of freedom. One degree of freedom is vertical expansion quantified by the variable \( x(t) \) (Fig. 1), which represents inflation (i.e., distention) of open lung units and in extreme cases (i.e., overdistension) leads to volutrauma. The other degree of freedom is horizontal expansion quantified by the variable \( y(t) \) (Fig. 1), which represents recruitment (opening) of closed lung units (30) that if repeated often enough, will lead to atelectrauma in those units cycling between open and closed states.

The elastic properties of the parenchymal tissues are represented by a spring that controls the vertical expansion of the alveolar compartment as a function of the alveolar pressure, \( P_A \). Because overdistension of the parenchymal tissues is a critical feature of ARDS, particularly when derecruitment is severe, it is crucial to account for their nonlinear elastic properties. Accordingly, we give the spring a nonlinear stress-strain behavior, such that \( P_A \) and \( x \) are related by the classic Salazar-Knowles relationship (27) modified so that \( x = 0 \) corresponds to functional residual capacity. That is,

\[
x = E(1 - e^{-KPA})
\]

where \( E \) and \( K \) are parameters that control the scale and curvature of the relationship, respectively, giving

\[
P_A = \frac{1}{K} \ln \left( \frac{E}{E - x} \right)
\]

\( P_A \) itself is determined by the applied pressure, \( P \), at the airway opening and the pressure drop across the resistance, \( R_{aw} \), of the airways according to

\[
P(t) - P_A(t) = R_{aw} \dot{V}(t)
\]

where \( \dot{V}(t) \) is airway flow.

When a lung is fully deflated, a significant fraction of its alveolar units collapse to become derecruited, especially when the lung is injured (11, 30). When the lung is then reinflated, these derecruited units progressively recruit in a time- and pressure-dependent fashion. For simplicity, we neglect here any time dependence of the recruitment process (2, 3, 5) and assume that the closed lung units open purely as a function of the pressure, \( P_A \), to which they are exposed. The recruitment behavior of the model is thus governed by a second spring that controls the horizontal dimension of the alveolar units, \( y(t) \) (Fig. 1), again under the influence of \( P_A \). The force-length behavior of this spring is highly nonlinear because although recruitment and derecruitment during a breath likely take place over extended ranges of pressure (18), they do not occur uniformly throughout inspiration and expiration (12). In particular, there may be limited recruitment and derecruitment taking place at low \( P_A \) once the regions of the lung that are going to close have done so. Similarly, regions that are going to open at high \( P_A \) will remain open even as \( P_A \) increases further. Recruitable lung units will thus transition between open and closed states mainly within an intermediate range of \( P_A \). Such behavior has been previously expressed in terms of Gaussian probability distributions of critical opening and closing pressures (11). Accordingly, we

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**Figure 1.** Schematic representation of the computational model. The variable \( x \) represents tissue distension, with the threshold value \( x_{adj} \) demarcating the level above which volutrauma starts to occur. The variable \( 0 < y \leq 1 \) represents lung recruitment. \( E \) is the stiffness of the spring that controls tissue distension. \( P_a \), alveolar pressure; \( V_a \), alveolar compartment volume; \( R_{aw} \), airway resistance; \( V \), tracheal flow, \( V \), time-integral of \( V \); \( P \), airway pressure.
expect the cumulative recruitment and derecruitment of lung units to be represented as a sigmoidal function of pressure resulting from the integration of a peaked probability distribution function.

To account for this behavior, we give the length, y, of this spring a sigmoidal dependence on $P_A$ during lengthening according to the function

$$y = \alpha + (\gamma - \alpha) \left[ 1 + e^{\left( \frac{P_A - P_A^0}{\tau} \right)} \right]^{-1}$$

(4)

where $P_{1/2}$ is the value of $P_A$ at which half of the recruitable lung units are open during inflation, while $\tau$ determines how sharply the sigmoidal transition to full recruitment occurs as a function of $P_A$; $\alpha$ is the fraction of lung units that always remain open regardless of the applied pressure, and the difference $\gamma - \alpha$ is the total fraction of recruitable units during inflation. For $\gamma = 1$ all remaining lung units are recruitable, whereas for $\gamma < 1$ a fraction of the units are not recruitable and are always closed. Ventilated lungs are not typically subjected to negative airway pressures, so instead of choosing a value for $\alpha$, we set a baseline fraction, $y = \beta$, of lung that remains recruited at $P_A = 0$. Solving Eq. 4 for $\alpha$ under this condition gives

$$\alpha = \frac{1}{1 + e^{\left( \frac{P_A^0 - P_A}{\tau} \right)}} \beta - \gamma$$

(5)

where $0 \leq \beta < 1$. Equations 4 and 5 thus specify how lung units are recruited as the lung is inflated from a pressure of zero to a pressure corresponding to total lung capacity. Recruitment occurs most rapidly when $P_A = P_{1/2}$, with most recruitment events taking place over the range $(P_{1/2} - \tau) < P_A < (P_{1/2} + \tau)$.

The derecruitment of open lung units during the deflation of an initially fully inflated lung is essentially the reverse of the recruitment pattern just described except that the pressures at which they close are typically lower than those at which they open (1a). If we assume that this pressure difference is $\Delta P$ on average, then

$$y = \alpha + (\gamma - \alpha) \left[ 1 + e^{\left( \frac{P_A^0 - P_A}{\tau} \right)} \right]^{-1}$$

during expiration. The model is driven by a specified flow during inspiration, and expiration occurs passively. Thus, at each time step during inspiration, the volume, $V_A$, of the alveolar compartment is known, while during expiration it is determined by integrating $V$ determined from Eq. 3. In either case,

$$V_A(t) = x(t)y(t)$$

(7)

and $V_A$ is referenced to functional residual capacity. From Eqs. 1, 2, 4, and 7 we then have

$$P_A = \frac{1}{K} \ln \left( \frac{E}{E - V_A} \right) = P_{1/2} + \tau \ln \left( \frac{\gamma - \alpha}{\gamma} \right)$$

(8)

Similarly, during expiration we have from Eqs. 1, 2, 6, and 7 that

$$P_A = \frac{1}{K} \ln \left( \frac{E}{E - V_A} \right) = P_{1/2} - \Delta P + \tau \ln \left( \frac{\gamma - \alpha}{\gamma} \right)$$

(9)

The value of $\gamma$ for each value of $V_A$ was determined iteratively using Eqs. 8 and 9 for inspiration and expiration, respectively. The GLOSSARY lists the model parameters and acronyms used in the model.

The equations were solved for a given $V_T$ and PEEP over a time duration of 1 min using first-order Euler integration with the model being driven by constant flow at the airway opening $(V)$ during inspiration and by alveolar pressure $(P_A)$ during expiration. For all $V_T$ values, the breath frequency was adjusted to maintain a constant minute ventilation of 40 ml/min, which approximates that used in our mouse studies (30, 31).

Simulating lung injury. We assume that lung injury manifests primarily as an increase in the propensity for lung units to derecruit and that open units retain normal function. This neglects, for example, any effects of altered surfactant function on the intrinsic compliance of the parenchyma, but it appears to be a reasonable first-order approximation to the situation we observe in the laboratory (20). Accordingly, we represent lung injury in the model by altering how the model derecruits as a function of $P_A$. This is achieved by decreasing the fraction of always open and recruitable lung units (i.e., the values of $\beta$ and $\gamma$) and increasing the values of $P_{1/2}$ and $\tau$ in Eqs. 4–6. Derecruitment presumably takes place in the healthy lung only when $P_A$ is low, and those few units that are closed are soon recruited as $P_A$ increases above zero. We achieve this in the model by assigning $\beta$ a value close to 1 with small values of $P_{1/2}$ and $\tau$. In this case, all lungs are recruitable, so $\gamma = 1$. Increasing degrees of lung injury severity are then represented by a greater fraction of the lung being derecruited at high $P_A$ (decreasing $\beta$, the fraction always open) with less of the lung available to be recruited (decreasing $\gamma$), lung recruitment taking place over a wider range of $P_A$ (increasing $\tau$), and recruitment occurring at higher values of $P_A$ (increasing $P_{1/2}$). We presume that the difference between recruitment and derecruitment pressures ($\Delta P$) also increases with severity of injury (32). Table 1 lists the parameter values we chose to represent healthy, moderately injured, and severely injured lungs. These values are typical of those we have observed in previous mouse and rat studies (3, 4, 30–32).

Quantifying VIII. The model in Fig. 1 allows $x(t)$ and $y(t)$ to be evaluated from $P$, $V$, and $V$ measured at the airway opening, thereby linking the stresses and strains applied by mechanical ventilation to lung tissue distension and recruitment. The variable $x(t)$ quantifies the degree of stretch to which the tissues are subjected, suggesting that volutrauma should be quantifiable according to some function of $x(t)$. Similarly, changes in $y(t)$ represent recruitment and derecruitment, suggesting that atelectrauma ought to be quantifiable in terms of some function of $y(t)$. Determining functions of $x(t)$ and $y(t)$ that provide measures of volutrauma and atelectrauma, respectively, thus constitutes the central challenge in using the model in Fig. 1 as the basis for personalized mechanical ventilation. Here we propose two simple functions that might serve this purpose.

First, we note that volutrauma is a consequence only of excessive tissue distension and that normal levels of distension are noninjurious, at least in a normal lung. This suggests that injury only occurs when $x$ exceeds a threshold value $x_{inj}$. Indeed, recent experimental evidence from our laboratory (28, 31, 32) and others (15, 35) supports the existence of an injury threshold volume above which the epithelial and endothelial barriers in the lungs are breached. Volutrauma presumably involves damage to the epithelial and endothelial barriers that allows plasma fluid and proteins to leak into the air spaces, interfering with surfactant function and adversely affecting lung mechanics. One would therefore expect injury due to volutrauma, $\Omega_{vol}$, to accumulate over time such that the rate of development of $\Omega_{vol}$ increases as $x(t)$ increases above $x_{inj}$. A simple functional relationship satisfying these conditions over the duration $T$ is

Table 1. Model parameter values used to simulate healthy and injured lung conditions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy</th>
<th>Moderate Injury</th>
<th>Severe Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_{rev}$</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>$E$</td>
<td>1.2</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>$K$</td>
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<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>$\beta$</td>
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<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>$\gamma$</td>
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<td>0.9</td>
<td>0.85</td>
</tr>
<tr>
<td>$P_{1/2}$</td>
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<td>8</td>
<td>25</td>
</tr>
<tr>
<td>$\tau$</td>
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<td>7</td>
<td>15</td>
</tr>
<tr>
<td>$\Delta P$</td>
<td>2.0</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>$x_{inj}$</td>
<td>0.63</td>
<td>0.63</td>
<td>0.63</td>
</tr>
</tbody>
</table>

See GLOSSARY for parameter definitions.
The total degree of injury is presumably some function of $\Omega_{\text{vol}}$ and $\Omega_{\text{all}}$, but exactly what this function might be is presently not clear. We consider two possibilities. One is that volutrauma and atelectrauma contribute independently and additively to total injury as a weighted sum, $\Omega_{\text{sum}}$, such that

$$\Omega_{\text{sum}} = \lambda \Omega_{\text{vol}} + (1 - \lambda) \Omega_{\text{all}}$$

where $0 < \lambda < 1$. We have no data to indicate what value $\lambda$ should have, so for the time being we will assume $\lambda = 0.5$, giving volutrauma and atelectrauma equal weight in determining VILI. The other possibility is that volutrauma and atelectrauma act synergistically with both having to be present to cause injury, in which case their product provides a measure of total injury, $\Omega_{\text{prod}}$, thus:

$$\Omega_{\text{prod}} = \Omega_{\text{vol}} \cdot \Omega_{\text{all}}$$

Of course, reality is likely to be more complicated than either of these two scenarios, but for the purposes of the present study we focus on Eqs. 12 and 13 as the two nontrivial canonical possibilities.

To the extent that the model in Fig. 1 captures the link between lung mechanics and VILI and that either Eq. 12 or Eq. 13 constitutes a valid injury cost function, personalized mechanical ventilation can now be given a precise definition: ventilate the lungs in such a way to minimize either $\Omega_{\text{sum}}$ or $\Omega_{\text{prod}}$ while maintaining a specified minimum value of minute ventilation.

**RESULTS**

Figure 2A shows what the pressure-volume relationship of our simulated lung would be if it were to be fully recruited at all times (i.e., $y = 1$). This relationship exhibits the well-known strain-stiffening behavior captured by Eq. 1 and represents the intrinsic elastic behavior of lung tissue without any influence from recruitment and derecruitment. Note that this curve is different from typical experimental pressure-volume curves that include both intrinsic elasticity and ongoing recruitment and derecruitment. However, even normal lungs are never fully recruited at every volume over the vital capacity range and thus are expected to exhibit some degree of air space closure at sufficiently low pressures. Accordingly, we assigned our simulated normal lung the relationships of recruitment and derecruitment vs. pressure shown in Fig. 2B, which confine all recruitment and derecruitment events to pressures only slightly above zero. The corresponding relationships for a moderately injured lung and a severely injured lung are shown in Fig. 2, C and D, respectively. The pressures at which recruitment and derecruitment occur increase as injury develops and become more widely separated and spread out over wider pressure ranges, as would be expected with developing surfactant dysfunction (10, 20, 25). These distributions of recruitment and derecruitment pressures approximate the dynamics observed during progressive VILI in mice (31) and surfactant inactivation in rats (32) (see Table 1 for parameter values).
Figures 3 and 4 show normalized injury surfaces for $\Omega_{at}$ (Eq. 11), $\Omega_{vol}$ (Eq. 10), $\Omega_{sum}$ (Eq. 12), and $\Omega_{prod}$ (Eq. 13) predicted by the model over $0.2 \leq V_T \leq 1$ and $0 \leq$ PEEP $\leq 15$. The injury is normalized relative to the maximum $\Omega$ in each case as indicated in each plot, with the color gradient blue to red corresponding to $0$ each case as indicated in each plot, with the color gradient in injured ($\Omega_{at}$) or severe injured ($\Omega_{prod}$) predicted by the model over $0.2 \leq V_T \leq 1$ and $0 \leq$ PEEP $\leq 15$. The injury is normalized relative to the maximum $\Omega$ in each case as indicated in each plot, with the color gradient blue to red corresponding to $0 \leq \Omega \leq 1$. PEEP-$V_T$ combinations generating pressures $>45$ cmH$_2$O are assumed to have resulted in pneumothorax and are not plotted. The size of the pneumothorax (maximum barotrauma) region increases for the simulated lungs with a higher level of preexisting injury.

Figure 3 shows that all combinations of PEEP and $V_T$ result in $\Omega_{at} > 0$ in the moderately (Fig. 3B) and severely injured lungs (Fig. 3C). In contrast, only low values of PEEP produce a small degree of atelectrauma in the healthy lung (Fig. 3A) at all levels of $V_T$. In Fig. 3, D–F, the size of the region with $\Omega_{vol} = 0$, occurring at lower PEEP and $V_T$, decreases for the moderately (Fig. 3E) and severely injured (Fig. 3F) cases compared with the healthy lung (Fig. 3D). The magnitude of $\Omega_{vol}$ is greatest for high $V_T$ and high PEEP when lung volumes are large. Figure 4 shows the patterns of VILI resulting from the combination of $\Omega_{at}$ and $\Omega_{vol}$, which differ according to the assumptions that VILI is either an additive ($\Omega_{sum}$) or synergistic ($\Omega_{prod}$) process. In the healthy lung, $\Omega_{sum}$ predicts that VILI occurs at low PEEP and is dominated by $\Omega_{at}$, while $\Omega_{prod}$ predicts that VILI occurs only at high $V_T$ when both $\Omega_{at}$ and $\Omega_{vol}$ are present. In the moderately and severely injured lungs, $\Omega_{sum}$ is characteristically similar to $\Omega_{at}$ with less, but still substantial, VILI at low $V_T$ and higher levels of PEEP. The $V_T$-PEEP dependence of $\Omega_{prod}$ in the injured lung is similar to that of $\Omega_{vol}$, with the least VILI occurring with low-$V_T$ and -PEEP combinations.

Also shown in Fig. 4 are the locations of PEEP-$V_T$ combinations that we have previously found to be either noninjurious or injurious in initially healthy mice (28, 31). These various PEEP-$V_T$ combinations correspond to injury levels predicted by $\Omega_{prod}$ (Fig. 4D) that are much more reminiscent of our prior experimental findings than are the

![Fig. 3. Normalized lung injury prediction surfaces for range of positive-end expiratory pressure (PEEP) and tidal volume ($V_T$) values. Atelectrauma, $\Omega_{at}$, is shown for a healthy (A), moderately injured (B), and severely injured (C) lung, and volutrauma, $\Omega_{vol}$, is shown for a healthy (D), moderately injured (E), and severely injured (F) lung. The surfaces are normalized to the maximum value indicated in each plot.](image-url)
injury levels predicted by $\Omega_{\text{sum}}$ (Fig. 4A). Specifically, our studies of VILI in overventilated mice (28) have shown that 4 h of mechanical ventilation does not cause lung injury when $V_T = 0.2$ ml with PEEP = 3 or 0 cmH$_2$O or when $V_T = 0.8$ ml with PEEP = 3 cmH$_2$O (injury being assessed in terms of lung derecruitability and bronchoalveolar lavage protein levels). On the other hand, we showed that substantial injury results when $V_T = 0.8$ ml and PEEP = 0 (28). We have also shown that the rate of VILI development accelerates progressively as $V_T$ is increased from 0.8 to 1.0 ml, but again only provided PEEP = 0 (31). The predictions of $\Omega_{\text{prod}}$ (Fig. 4D) are also compatible with the notion we advanced in a previous study (28) of there being a “safe region” within the PEEP-$V_T$ plane for which a normal lung will not sustain damage due to VILI (indicated by the white outlined region in Fig. 4D). This safe region shrinks as VILI develops (Fig. 4, E and F), making it progressively more difficult to avoid VILI (28).

**DISCUSSION**

Evidence-based management of the ARDS patient is currently performed in a largely open-loop fashion in which $V_T$ is set according to an algorithm based on the patient’s height and calculated ideal body weight (7). Some attempts to close the loop with regard to the setting of PEEP have been proposed based on the characteristics of the pressure-volume relationship of the lung (1a, 6, 23), but as of yet there is no universally accepted algorithm by which this is done. Most practitioners set PEEP according to heuristic rules based solely on the patient’s inspired oxygenation requirements (9, 22) that do not account for the effect of changes in $V_T$ and PEEP on other biophysical properties of the lungs and the resultant risk of imposing further VILI. It therefore remains a compelling notion that a more personalized approach to mechanical ventilation in ARDS represents a promising approach to reducing its high mortality rate of 27–45% (7).
Any system that delivers a personalized approach to mechanical ventilation must be able to implement three distinct procedural steps: 1) assess the injury status of the lung in any given patient, 2) predict how a given regimen of mechanical ventilation will cause further injury in that particular lung, and 3) implement the minimally injurious regimen. In addition, since lung injury is something that waxes and wanes over time as the patient progresses toward their final outcome, these three steps must be dynamic enough to meet the patient’s changing needs. We currently have a reasonable capacity to implement steps 1 and 3. The severity of ARDS is believed to be most reliably assessed in terms of oxygenation (PaO2/Fio2 ratio), PEEP requirement, extent of air space disease, and mechanical lung function, the latter most specifically assessed in terms of compliance (24, 26). Modern mechanical ventilators typically have the capacity to apply a wide variety of ventilation modes that can be adjusted to meet most patient needs. The problem lies in knowing what these needs are because our current capacity to predict the long-term effects of a given ventilator regimen at the bedside (step 2 above) is still essentially nonexistent. This is the problem we sought to address in the present study.

The quantitative prediction of VILI requires a mathematical model capable of relating the stresses and strains of mechanical ventilation to the resultant lung tissue injury. This requires fitting an appropriate mathematical model of the lung to measurements of airway pressure and flow, quantities that are both readily accessible at the bedside and are directly related to lung parenchymal tissue stress and strain. To obtain a unique and well-constrained set of best-fit parameter values, however, it is crucial that the model contain as few parameters as possible. As the number of parameters that need to be adjusted during the model-fitting process increases, the confidence in the estimated values of these parameters degrades until they become unconstrained by the data and thus convey essentially no useful information about the quantities they purport to represent. The key challenge, therefore, is to devise a model that contains only those features that are essential for providing a useful prediction of VILI while avoiding the unnecessary complexity caused by inclusion of features of secondary importance. It is thus inevitable that such a model will have to make some rather sweeping assumptions, as is the case with our proposed model shown in Fig. 1. The numerous limitations of this model can be enumerated in the features that are known to exist in the injured lung but which the model lacks. These include a representation of regional mechanical heterogeneity (19, 36), the temporal dynamics of recruitment and derecruitment (2, 3, 5, 20), and the viscoelastic properties of the lung tissues (8, 16). We cannot say for sure at this point if any of these features are crucial for usefully predicting VILI, so our model in Fig. 1 should be viewed as an initial step toward the predictive capacity required for the closed-loop control of mechanical ventilation in ARDS.

Nevertheless, the simple model in Fig. 1 does capture what are widely held to be the two key injurious mechanisms in VILI, namely overdistension and repetitive/cyclical recruitment (21, 29). Furthermore, this model captures these phenomena in what we suggest is the simplest possible manner. That is, we cannot leave anything out of this model without destroying its ability to represent both volutrauma and atelectrauma. As such, we propose that this model is a reasonable starting point upon which to embark on the search for a VILI injury cost function. Of course, we still do not have a complete understanding of how overdistension and repetitive/cyclical recruitment lead to volutrauma and atelectrauma, respectively. On the other hand, it seems intuitively obvious that volutrauma will accrue while the lung tissues remain in an overdistended state. Similarly, it seems clear that atelectrauma will accrue with accumulating cycles of recruitment and derecruitment. Accordingly, we propose in Eqs. 10 and 11 what seem to be the simplest expressions that embody these concepts by incorporating the experimentally supported (15, 35) and intuitively reasonable notion that volutrauma only begins to occur once the tissues are stretched above an injury threshold. Again, it may well turn out, as further experimental evidence arrives, that these expressions for volutrauma and atelectrauma may need to be modified, but for the time being they represent what we believe are reasonable starting points.

The model parameter values listed in Table 1, and their corresponding mechanical manifestations shown in Fig. 2, are designed to capture the essential features of normal and injured lungs. Note that we assume the intrinsic properties of the lung tissue, embodied in the parameters E and K (Eq. 2), are not affected by lung injury. The only consequence of injury is thus an increased propensity for lung units to derecruit. This negates any effect of altered surfactant function on units that remain open. However, our previous studies in mice with acid instillation lung injury (20) and VILI (31) and in rats with surfactant deactivation due to Tween-20 instillation (32) suggest that the dominant consequence of injury is a shift in the distributions of opening and closing pressures throughout the lung toward higher pressures. Accordingly, this was the mechanism we chose to implement, in a graded fashion, to represent injury in our present model (Fig. 2, B–D).

When the injury cost functions \( \Omega_{\text{sum}} \) (Eq. 12) or \( \Omega_{\text{prod}} \) (Eq. 13) are evaluated over a range of \( V_T \) and PEEP, they produce injury surfaces. Figure 4 shows these surfaces for the healthy and injured lung parameter sets listed in Table 1. These surfaces provide a visual means of determining how to minimize VILI for any given target minute ventilation. We chose to represent VILI as either \( \Omega_{\text{sum}} \) or \( \Omega_{\text{prod}} \) because they embody the notions that volutrauma and atelectrauma contribute to VILI either additively or synergistically, respectively. Note that \( \Omega_{\text{at}} \) accumulates over the entire ventilation period while \( \Omega_{\text{vol}} \) accumulates only after a threshold has been reached and that \( \Omega_{\text{at}} \) is nonzero for all \( V_T \)-PEEP combinations that cause lung injury. This results in the qualitative similarities we observed between \( \Omega_{\text{at}} \) and \( \Omega_{\text{sum}} \) and between \( \Omega_{\text{vol}} \) and \( \Omega_{\text{prod}} \) (Figs. 3, A–C, and 4, A–C, and Figs. 3, E and F, and 4, E and F, respectively). It should also be noted that the larger absolute values of \( \Omega_{\text{at}} \) compared with \( \Omega_{\text{vol}} \) are not meaningful because we currently do not know whether the cost function should be scaled in some way to characterize the interaction between atelectrauma and volutrauma. Rather, the potential clinical importance of the \( \Omega_{\text{at}} \) and \( \Omega_{\text{vol}} \) surfaces lies in the location of their respective minima in the \( V_T \)-PEEP plane and in the way that they change as one moves away from these minima. These surfaces also allow us to postulate a level of predicted injury below which VILI will not actually occur, as illustrated by the white polygonal regions in Fig. 4, D–F. Thus a safe region can be defined in the \( V_T \)-PEEP plane within which mechanical ventilation may be pursued without causing injury, and this
region is expected to shrink in size as injury develops, as we previously postulated (28).

Furthermore, the surfaces for $\Omega_{\text{sum}}$ and $\Omega_{\text{prod}}$ are very different from each other in the normal (Fig. 4, A and D), moderately injured (Fig. 4, B and E), and severely injured (Fig. 4, C and F) lungs. This means that the prediction of a minimally injurious mode of ventilation is very dependent on the cost function used, which underscores the need to determine the correct representative cost function. Our research to date in mice suggests that of the two cost functions $\Omega_{\text{sum}}$ and $\Omega_{\text{prod}}$ we have considered here, $\Omega_{\text{prod}}$ appears to be the most representative of reality because initially uninjured mice develop VILI only when they are mechanically ventilated with both a high $V_T$ and a very low PEEP (3). Whether this applies to all ARDS patients or in other animal models of VILI remains undetermined, but it is clear that until an appropriate VILI prediction tool can be formulated, a closed-loop personalized control of mechanical ventilation in ARDS will fail to find its way into clinical practice.

In summary, we have developed a minimally complex computational model of the lung embodying what are believed to be the two principle mechanisms underlying VILI, tissue overdistension and repetitive recruitment of closed lung units. The model recapitulates realistic pressure-volume relationships during mechanical ventilation and provides promise for one day quantifying the degrees of volutrauma and atelectrauma incurred during a given ventilatory regimen by offering a tool with which clinicians could potentially personalize delivery of mechanical ventilation to patients in danger of sustaining VILI. We propose two formulae for the total amount of VILI that is incurred from volutrauma and atelectrauma for any given combination of $V_T$ and PEEP. One assumes that the relative contributions of these two mechanisms are independent of one other and thus additive, and the other assumes that they are multiplicative and thus synergistic. Comparison of our predictions with the results of previous experimental studies suggests that the synergistic formulation may be the more realistic of the two, but it remains to be determined whether this holds true for ARDS in general or whether a modified formula is needed for human subjects. This model thus serves as a formal statement of the prediction problem in the closed-loop delivery of mechanical ventilation in ARDS and provides a foundation upon which future experimental studies can build as we strive toward the goal of optimizing support for patients with ARDS by minimizing VILI.

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JASON H.T. BATES IS A MEMBER OF THE ADVISORY BOARD OF AND OWNS SHARES IN OSCILLAVENT, INC.

AUTHOR CONTRIBUTIONS

REFERENCES


