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Linking Physiological Biomarkers of Ventilator-Induced Lung Injury to a Rich-Get-Richer Mechanism of Injury Progression

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Abstract

Mechanical ventilation is a crucial tool in the management of acute respiratory distress syndrome (ARDS), yet it may itself also further damage the lung in a phenomenon known as ventilator-induced lung injury (VILI). We have previously shown in mice that volutrauma and atelectrauma act synergistically to cause VILI. We have also postulated that this synergy arises because of a rich-get-richer mechanism in which repetitive lung recruitment generates initial small holes in the blood-gas barrier which are then expanded by over-distension in a manner that favors large holes over small ones. In order to understand the causal link between this process and the derangements in lung mechanics associated with VILI, we developed a mathematical model that incorporates both atelectrauma and volutrauma to predict how the propensity of the lung to derecruit depends on the accumulation of plasma-derived fluid and proteins in the airspaces. We found that the model accurately predicts derecruitment in mice with experimentally induced VILI.

Keywords

acute respiratory distress syndrome; mechanical ventilation; lung mechanics; mouse model

Introduction

Mechanical ventilation is a crucial tool in the management of acute respiratory distress syndrome (ARDS) ^{1,2}, yet it may itself also further damage the lung in a phenomenon known as ventilator-induced lung injury (VILI) ^{3,4}. There are two key biophysical mechanisms thought to contribute to VILI. One is distention of the parenchyma to the point of mechanical failure, which causes volutrauma. The other is repetitive reopening of lung

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units that close during expiration, which causes atelectrauma. Exactly how these two mechanisms conspire to cause VILI remains a matter of investigation, but their net result is to cause holes to form in the blood-gas barrier through which plasma fluid and proteins flow into the pulmonary airspaces. This plasma-derived material then interferes with the surface-tension lowering properties of pulmonary surfactant, which further increases the stresses of mechanical ventilation and leads to greater perforation of the blood-gas barrier. These mutually reinforcing events result in an accelerating progression of VILI that is difficult to reverse.

We have shown that progressive VILI can be produced in initially normal anesthetized mice during the first 4 hours of mechanical ventilation if they receive a large tidal volume superimposed on a positive end-expiratory pressure (PEEP) of zero⁵⁻⁷. Either condition on its own appears to be well tolerated, suggesting that volutrauma and atelectrauma act synergistically. We recently postulated that the basis of this synergy may be related to the sizes of the holes in the blood-gas barrier that are created by VILI⁸. Our previous experimental observations suggest that, at any point during VILI progression, the number of holes with area (A) follows a distribution function of the form A^{-k} where k is a small constant. A power-law distribution function of this type can potentially be attributed to a preferential attachment, or “rich-get-richer”, mechanism such as has been invoked to explain the distribution of site notoriety on the internet^{9,10}. In the case of VILI, we have hypothesized⁸ that atelectrauma is responsible for generating the initial small holes that form in the blood-gas barrier, and then volutrauma expands these barrier holes in a way that favors large holes.

There is thus a causal link between the manner and rate at which volutrauma and atelectrauma cause holes to appear in the blood-gas barrier and the rate at which derangements in lung mechanical function develop. A quantitative understanding of this link could be crucial for the rational design of ventilation regimes that minimize VILI, something that remains a central focus of ARDS management. Accordingly, in the present study we develop a mathematical model that incorporates this mechanism to predict how lung mechanics change over time as a function of injurious mechanical ventilation. We validate the model against measurements of lung function from a previous study of mice subjected to various injurious regimens of mechanical ventilation.

Materials and Methods

Model Development

Our previous study⁸ supports the notion that holes form in the blood-gas barrier during the development of VILI according to a rich-get-richer mechanism on account of the fact that their size distribution appears to be a power law function of area, which leads to the hypothesis that atelectrauma is responsible for initial hole formation while volutrauma subsequently expands these holes with a preference for holes that are already large. The leak of plasma-derived material into the alveolar spaces through these holes over time then leads to the progressive derangements in lung function that constitute the principle VILI phenotype. We created a model that expresses these various processes in mathematical terms as follows.

Let λ be the number of injurious events acting on the blood-gas barrier per unit time. A fraction $0 < \beta < 1$ of these events cause existing holes in the barrier to become expanded by a fixed area A_0 . The remaining fraction $1 - \beta$ of injurious events cause the creation of new holes each having initial area A_0 . The rate of change of total hole area due to hole expansion is, thus $A_0\beta\lambda$, while the total hole area at time t is $A_0\lambda t$ if hole creation begins at $t = 0$. The expansion events are applied randomly to existing holes according to a rich-get-richer mechanism whereby, on average, bigger holes expand more rapidly than smaller holes. We implemented this mechanism by making the probability of choosing a given hole for expansion by A_0 at each step be proportional to its current area. Another reasonable way to implement the rich-get-richer mechanism would be to have the probability of selection for expansion be the same for all holes, but have the amount of area increase with each event be proportional to hole area. We are not aware of any evidence for choosing one process over the other

The probability that an expansion event is assigned to a given hole of area A_i is $A_i/(A_0\lambda t)$. The product of $A_i/(A_0\lambda t)$ and the rate of change of total hole area ($A_0\beta\lambda$) then gives the expected rate of change of area per unit time for this particular hole, which is

$$\frac{dA_i(t)}{dt} = A_0\beta\lambda \frac{A_i(t)}{A_0\lambda t} = \frac{\beta A_i(t)}{t}. \quad (1)$$

Not all holes having area A_i at the current time were created at the same time point in the past because some holes win in the rich-get-richer stakes while others do not. Nevertheless, because of the stationary nature of the hole creation statistics in this model, the time at which a hole of current area $A_i(t)$ was created has a statistically expected value. Let this time of creation be $t_i < t$. When this hole was created it had, by assumption, an area of A_0 , so we can solve Eq. 1 with the initial condition $A_i(t_i) = A_0$ to obtain the expected value of $A_i(t)$ as

$$A_i(t) = A_0 \left(\frac{t}{t_i} \right)^\beta \quad (2)$$

which rearranges to give

$$t_i = \left(\frac{A_0}{A_i(t)} \right)^{\frac{1}{\beta}} t. \quad (3)$$

Consider a hole that is randomly selected at time t without regard to its size. Since holes are created at the constant rate of $\lambda(1 - \beta)$ per unit time, the probability that this randomly selected hole was generated prior to time t_i is simply t_i/t . The complementary probability that the hole was created between t_i and the current t is then $1 - t_i/t$. Now take size into account and consider the probability that this randomly selected hole has an area less than

some value A , which means by Eq. 3 that its expected time of creation was at some point after $\left(\frac{A_0}{A}\right)^{\frac{1}{\beta}} t$, the probability of which is $1 - \left(\frac{A_0}{A}\right)^{\frac{1}{\beta}}$. In other words,

$$P[A_i(t) < A] = \alpha(t) \left[1 - \left(\frac{A_0}{A}\right)^{\frac{1}{\beta}} \right]. \quad (4)$$

where $\alpha(t)$ is a time-dependent normalization factor.

When the total number of holes is large we can consider A to be a continuous variable taking values A_0 . The probability density function for A over this range can then be calculated as the derivative with respect to A of the cumulative probability function given by Eq. 4, which gives

$$p(A, t) = \frac{\alpha(t)}{\beta} A_0^{\frac{1}{\beta}} A^{-1 - \frac{1}{\beta}} = \alpha_1(t) A^{-1 - \frac{1}{\beta}}. \quad (5)$$

where $\alpha_1(t) = \frac{\alpha(t)}{\beta} A_0^{\frac{1}{\beta}}$ ensures the area under the probability distribution is unity. That is,

$$\int_{A_0}^{A_{max}} \alpha_1(t) A^{-k} dA = 1 \quad (6)$$

where A_{max} is the largest possible hole that could exist at time t , which we see from Eq. 2 is given by

$$A_{max} = A_0 \frac{t^\beta}{t_0^\beta}. \quad (7)$$

The time t_0 in Eq. 7 is the time at which the first hole was created; t_0 is assumed to be a very small relative to t . Evaluating the integral in Eq. 6 gives

$$\alpha_1(t) \frac{A_0^{-k+1}}{-k+1} \left(t_0^{\beta(k-1)} t^{\beta(1-k)} - 1 \right) = 1 \quad (8)$$

Since $k = 1 + \frac{1}{\beta}$, Eq. 8 gives:

$$\alpha_1(t)\beta A_0^{-1/\beta} \frac{t-t_0}{t} = 1 \quad (9)$$

Equation 5 can then be rewritten as

$$p(A, t) = \frac{A_0^{1/\beta}}{\beta} \frac{t}{t-t_0} A^{-k} \quad (10)$$

which converges in the limit of large t to

$$p(A) = \frac{A_0^{1/\beta}}{\beta} A^{-k} \quad (11)$$

When $\beta = 0.5$, Eq. 11 leads to $k = 3$, which is approximately the power-law exponent found experimentally by Hamlington *et al.*⁸ for the modeled scale-free network. This suggests that the injurious processes associated with VILI in mice generate new holes in the blood-gas barrier and expand existing holes with roughly equal probability.

The cumulative histogram for the number of holes, $n(A, t)$, is found by scaling the expression for $p(A)$ described in Eq. 10 by the total number of holes, which is $\lambda(1 - \beta)t$. Setting $\beta = 0.5$ and $k = 3$ gives

$$n(A, t) = \lambda(1 - \beta)t \cdot \frac{1}{\beta} A_0^{1/\beta} A^{-1-1/\beta} = A_0^2 \lambda t A^{-3}. \quad (12)$$

We have previously studied lung derecruitability in mouse models of lung injury by measuring how the elastic parameter (H) of the constant-phase model of lung impedance¹¹ changes with time following a recruitment maneuver.¹² We found that the first H measurement (H_1) increases progressively with degree of lung injury, as does its subsequent mean rate of change with time. Both H_1 and its rate of change appear to be strongly linked to the surface tension of the lining fluid within the lungs^{7,8,13} and thus are presumably influenced by inhibition of surfactant function by the airspace accumulation of plasma proteins, albeit to different degrees. In particular, H_1 would seem to reflect alveoli containing enough plasma-derived material that either they collapse immediately or are completely flooded with fluid to the point that they are never recruited at all. The rate at which H changes with time, on the other hand, would seem to reflect the much slower collapse of lung regions in which surfactant function is less severely deranged. Accordingly, we assume for the purposes of the present model that increases in H_1 above baseline are proportional to the volume of accumulated fluid that has leaked into the airspaces through holes in the blood-gas barrier^{1,6,14,15}.

To calculate this volume of accumulated fluid we need to know how the flow of fluid through the holes depends on the total number of holes and their respective areas. The resistance of flow of fluid through a single circular hole is appropriately modeled as inversely proportional to the area of the hole raised to an exponent close to 2 depending on the flow regime involved (i.e., laminar versus turbulent). Since the holes involved here are tiny, and flow velocities probably also very small, turbulence seems highly unlikely. Regardless of the flow regime, however, movement of material takes place through a large number of holes in parallel, and the relative abundance of hole area remains constant according to Eq. 5. As a result, the only factor determining how flow increases with time is the rate at which hole number increases with time because this is the same for all hole areas. The total flow of material through all holes at any point in time is thus simply proportional to the number of holes and thus the total hole area at that time.

However, even healthy animals exhibit small disruptions to the blood-gas barrier without obvious compromise in lung function⁸. Such minor ongoing injury might result, for example, from repetitive recruitment of closed lung units that potentially occurs in healthy lungs, particularly during sleep when functional residual capacity is reduced¹⁶. There is evidence that this damage (i.e., small holes of area A_0) are usually repaired in less than a minute¹⁷ before they can grow to become problematic. Furthermore, any material that leaks into the airspaces through these small holes is rapidly cleared¹⁸. Thus, while some rate of ongoing leak of material into the alveolar spaces is likely a normal process, in a healthy lung this material is cleared at the same rate so that it does not accumulate progressively. In contrast, larger wounds in an epithelial cell, such as are caused by volutrauma acting in concert with atelectrauma, may result in the death and removal of the cell¹⁹. The result is a gap in the epithelial barrier that can only be healed through the spreading, migration and differentiation of neighbor cells. This is a process that takes place over a time scale of hours to days²⁰, especially if it involves alveolar Type-II cells²¹. In the meantime, plasma-derived material leaks through these larger holes faster than it can be cleared with the result that the material builds up over time in the alveolar spaces.

For the purposes of modeling data collected in mice over the first 4 hrs of injurious ventilation we will neglect the longer term dynamics of hole repair and focus solely on the dynamics of hole generation and expansion. In addition, we will assume that the value of H is adversely affected only by the increased flow of plasma-derived material through holes that have become expanded by volutrauma. In terms of the continuous model of hole area developed above, we will assume that holes are innocuous if they have areas less than $2A_0$, and it is only the accumulated material that flows through holes having areas greater than $2A_0$ that displaces an equivalent volume of alveolar to cause aberrations in lung mechanics. When this accumulation occurs, all airflow entering the lungs must be accommodated by the remaining unflooded lung regions. In addition, the accumulation of proteinaceous edema leads to progressive alveolar collapse so that H increases with the inverse of the ratio of flooded to total lung volumes.

From Eq. 12 we see that the number of holes having area less than $2A_0$ is

$$\int_{A_0}^{2A_0} An(A, t) dA = \int_{A_0}^{2A_0} A_0^2 \lambda t A^{-2} dA = \frac{1}{2} \lambda t A_0. \quad (13)$$

Since the total hole area is $\lambda t A_0$, the combined area of all holes of area greater than A_0 is $\frac{1}{2} \lambda t A_0$. Since the collective rate of fluid flow, $\dot{V}$, through these holes is proportional to their total area as discussed above, and inversely proportional a characteristic resistance, R_0 , the amount of fluid, V_{fluid} , that has accumulated in the airspace since the beginning of injury is

$$V_{fluid}(t) = k \int_0^t \frac{1}{2R_0} \lambda t A_0 \Delta P dt = \frac{A_0 \Delta P \lambda t^2}{4R_0} \quad (14)$$

where P is the pressure gradient driving fluid flow through the holes in the blood gas barrier.

Since we assume that an increase in H_1 above its baseline uninjured value, H_0 , is proportional to the volume of lung that has been rapidly or permanently derecruited after the recruitment maneuver, and this volume is itself proportional to $V_{fluid}(t)$, we have

$$H_1(t) = H_0 \frac{V_L}{V_L - b V_{fluid}(t)} = \frac{H_0}{1 - \frac{b A_0 \Delta P}{4R_0} t^2} = \frac{H_0}{1 - a_1 t^2} \quad (15)$$

where

$$a_1 = \frac{b A_0 \Delta P \lambda}{4R_0} \quad (16)$$

and b is a constant of proportionality.

Experimental Data

We validated the above model against experimental data collected in a previously published study in mice ⁶ These data were collected in adherence with the Guide in the Care and Use of Laboratory Animals established by the U.S. National Academy of Sciences, and the protocol was approved by the Institutional Animal Care and Use Committee of the University of Vermont. The details of the protocol are given in our previous publication ⁶. Briefly, initially healthy animals were subjected to up to 4 hrs of injurious mechanical ventilation at zero PEEP. The animals were divided into 4 groups, with each group receiving a different very high tidal volume (1.0 mL, n=6; 1.1 mL, n=6; 1.2 mL, n=5; 1.3 mL, n=6). After every 16.5 min of injurious ventilation, a derecruitability test was performed by decreasing tidal volume to 0.25 ml for a period of 4.5 min during which H was measured

every 20 seconds using the forced oscillation technique. Each test began with a deep inflation to 30 cmH₂O to recruit the lungs followed by 4.5 min of low tidal volume ventilation. The first measurement of H made in each derecruitability test, H_1 was obtained 20s after each recruitment maneuver. We have shown in a number of prior publications^{5,6,13,22} that the rate at which H increases after the recruitment maneuver is a sensitive indicator of the rate at which the injured lung derecruits, which itself is closely linked to the degree of lung injury.

Model Fitting

The Levenberg-Marquardt algorithm (MATLAB 2015b, The Mathworks, Natick, MA, USA) was used to fit Eq. 15 to experimental measurements of $H_1(t)$ from Smith *et al.*⁶ by minimizing the cost function

$$\Phi = \sum_{k=1}^N [H_1(t_k) - \hat{H}_1(t_k)]^2 \quad (17)$$

where N is the number of data points, and $\hat{H}_1$ is the value of H_1 estimated by Eq. 15.

Ninety-five % joint confidence regions around the best-fit values of the parameters in Eq. 15, $\hat{H}_0$ and $\hat{a}_1$ respectively, were calculated based on Lutchen and Jackson²³ as follows. If θ is the vector of best-fit parameter values, variations about this vector for a given increase in the minimum value of Φ is approximately

$$\delta\Phi \delta\theta^T \frac{H_{ij}}{2} \delta\theta \quad (18)$$

where H_{ij} is the Hessian matrix defined by

$$H_{ij} = \frac{\partial^2 \Phi(\theta)}{\partial \theta_i \partial \theta_j}; \quad i, j = 1, 2. \quad (19)$$

Provided the residuals of the model fit are normally distributed we can write²⁴

$$\delta\Phi = 2\sigma^2 F_{0.05}(2, N-2) \quad (20)$$

where $F_{0.05}$ defines the 5% probability value of the F-distribution with 2 and $N-2$ degrees of freedom, and σ^2 is the variance of the noise in the data which is estimated as

$$\sigma^2 = \frac{\Phi}{N-P} \quad (21)$$

The 95% joint confidence region for $\hat{H}_0$ and $\hat{a}_1$ is then given by the ellipsoid

$$\left| \delta\theta^T H_{ij} \delta\theta \right| \leq 2\delta\Phi \quad (22)$$

Results

The fit of Eq. 15 to the means of four groups mice ventilated at zero PEEP and high tidal volume are presented in Fig. 1. The normality of the residuals was assessed using the Shapiro-Wilk test and the null-hypothesis was not rejected within a significance level of 0.05 for all groups of mice.

Figure 2 shows mean $\pm$ 2 SEM of the two model parameters in Eq. 15 for the four groups of mice. There are significant differences in $\hat{H}_0$ between two of the study groups, but the overall impression is that this parameter is not strongly dependent on tidal volume (Fig 2.A). In contrast, $\hat{a}_1$ increases markedly with tidal volume with statistically significant differences observed between almost all groups (Fig. 2.B).

The joint 2-dimensional 95% confidence regions for $\hat{H}_0$ and $\hat{a}_1$ for the 4 groups of ventilated mice are shown in Fig. 3A convey a similar message; the different groups are clearly distinguished by variations in $\hat{a}_1$ but not in $\hat{H}_0$. The relative uncertainties in $\hat{H}_0$ and $\hat{a}_1$ are shown in Fig. 3B, indicating that, for the most part, their uncertainties grow at similar rates with increasing levels of VILI.

Discussion

VILI has been extensively studied for decades but the nature of its temporal exacerbation as a function of ventilation parameters remains unclear. Motivated by our recent study⁸ suggesting a “rich-get-richer” mechanism for enhancement of holes in the blood-gas barrier, we revisited some of our previous data⁶ with the goal of defining a quantitative link between alveolar leak of plasma-derived material and derangements in lung mechanical function. Specifically, we have attempted to account for the accelerating rise in the parameter H_1 observed shortly following a recruitment maneuver during periods of mechanical ventilation using high tidal volumes with zero PEEP in mice that were initially normal. We propose this first post-inflation measure of lung elastance to be a biomarker of VILI that reflects very rapid (or permanent) derecruitment of lung units by accumulated fluid that disrupts surfactant function. The resulting increase in surface tension leads to a decrease in the radius of curvature of the alveoli and ultimately alveolar collapse^{1,3,6}. This being the case, our model provides the opportunity to calculate how fluid accumulates in the alveolar airspace over time. These calculations provide a very good fit to the data of H_1 versus time as VILI progresses (Fig 1), which supports a mechanistic link between damage to the blood-gas barrier and physiologic function. Equation 16 shows, however, that we cannot tell if the increase in total hole area in each of the groups is driven by differences in

A_0 or λ or both because we do not know how the quantity $\frac{b\Delta P}{R_0}$ varies between animals. In the present study we simply assume it to be the same for all groups of mice.

The rate of VILI progression increases with increasing tidal volume as evidenced by the corresponding increases in H_1 with time (Fig. 1) determined in our previous study⁶. This effect is strongly reflected in the model parameter a_1 (Fig. 2B) presumably because its factors include the rate at which injury occurs to the blood-gas barrier (λ in Eq. 16). In contrast, the parameter H_0 , which reflects the stiffness of the open lung, is much less strongly determined by the applied ventilation (Fig. 2B). It is possible, therefore, that the intrinsic stiffness of the lung tissues remained relatively unchanged as VILI progressed, while the amount of short-timescale derecruitment following a recruitment maneuver increased substantially. This is compatible with the notion that the rapid derecruitment events reflected in H_1 are due, at least in part, to high levels of surface tension causing partially flooded lung units to collapse at relatively low pressures. When collapse occurs, some of the accumulated fluid can be squeezed out so that it then flows into adjacent units, potentially then contributing to their tendency to collapse²⁵. This may be a mechanism whereby increases in H_1 are linked to increases in D_{rate} . The joint 95% confidence regions for the two model parameters, which are roughly $\pm 20\%$ of the best-fit values, also support a discriminatory role for a_1 but not H_0 since these regions are separated along the a_1 axis but not the H_0 axis (Fig. 3A). Increasing tidal volume increased the 95% confidence regions for both parameters (Fig. 3B), probably because of the increased inter-animal variability associated with increased rates of VILI.

A limitation of our study is that we have validated our model on experimental data derived from a short-term VILI model lasting only 4 hrs. Accordingly, we did not consider the dynamics of hole repair in the model on the grounds that there would not have been enough time for the reparative spreading, migration, and differentiation of alveolar Type-II cells²⁰ to manifest. In human patients, VILI typically develops over a time scale of days during which self-repair may start to occur. In fact, a significant fraction of ARDS patients go on to survive the condition²⁶ as a result of the body's own healing capacity that includes an ability to clear fluid from the alveolar space¹⁸ and repair wounds to the parenchymal tissue^{17,19,20}. We can thus expect that a longer time-course of VILI would be significantly impacted by such repair mechanisms even in mice. Repair dynamics of this kind might be modeled, for example, as a first-order process that is activated after a time-delay corresponding to the time required to transcribe new proteins in response to the cellular detection of injury. Another important limitation of our study is the assumption that the pressure gradient driving plasma fluid from the vasculature to the alveolar space remains constant (P in Eq. 14). We do not know if and how this pressure gradient changes over time, but it is reasonable to suppose that it could be affected by alterations in hemodynamics such as can accompany severe systemic pathologies like ARDS²⁷.

In summary, we have developed a model for the time-evolution of VILI during its early formative stages that is based on the rich-get-richer mechanism proposed by Hamlington *et al.*⁸. The model assumes that lung tissue damage manifests as holes in the blood-gas barrier through which plasma-derived fluid and proteins flow at a rate proportional to total hole

area, and that accumulation of this material in the alveoli is responsible for the very rapid phase of lung derecruitment observed in mice at 20 s following a recruitment maneuver. This model helps to establish a mechanistic understanding of VILI development by linking it to the dynamics of altered lung function.

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Figure 1.

Average H_1 ($\pm$ SEM) from the 4 groups of mice (symbols and error bars). The groups were ventilated with different tidal volumes: black =1.0 mL, red =1.1 mL, green =1.2 mL, blue =1.3 mL. The solid lines show the fits of Eq. (15) to the data from each group; the colors of the lines match the colors of the data.

Figure 2.

Mean $\pm$ 2 SEM for the estimates $\hat{H}_0$ and $\hat{a}_1$ of the two model parameters in Eq. 15 versus the tidal volume applied to each of the four groups of mice. Statistically significant differences are indicated by * ($p < 0.05$).

Figure 3.

A) Joint 95% confidence regions for the estimates $\hat{H}_0$ and $\hat{a}_1$ of the two model parameters in Eq. 15 for the 4 groups of mice that were ventilated with different tidal volumes: black =1.0 mL, red =1.1 mL, green =1.2 mL, blue =1.3 mL. B) Corresponding relative 95% confidence region for the two parameters.