

SUPPLEMENTAL DIGITAL CONTENT**Atelectrauma versus Volutrauma: A Tale of Two Time-Constants**

Jason H.T. Bates, PHD, DSc, ATSF¹, Donald P. Gaver, PhD², Nader M. Habashi, MD³

and Gary F. Nieman, BA⁴

¹Department of Medicine, University of Vermont, Burlington VT

²Department of Biomedical Engineering, Tulane University, New Orleans LA

³R Adams Cowley Shock Trauma Center, University of Maryland, Baltimore MD

⁴Department of Surgery, Upstate Medical University, Syracuse NY

We represent the lung as a single alveolar compartment that can expand in two orthogonal directions, as illustrated in Fig. S-1. Vertical expansion corresponds to distension of the open lung, measured by $h(t)$, while horizontal expansion corresponds to an increase in the open lung fraction (i.e., recruitment of closed lung units), measured by $F(t)$.

The intrinsic mechanical properties of the respiratory system tissues are represented by a spring with stiffness E_{rs} representing the elastance of the respiratory system when the lung is fully recruited. As the lung derecruits (represented by a decrease in the lateral dimension of the alveolar unit in the model illustrated in Fig. S-1), respiratory elastance increases above E_{rs} in inverse proportion to the fraction of lung that remains open. The alveolar compartment is served by a conduit representing respiratory system resistance R_{rs} . This resistance contains a component from the lung and chest wall tissues as well as the airways themselves (1), but in a mechanically ventilated patient the effective value of R_{rs} includes significant contributions from the

endotracheal tube and the ventilator circuit, which are not affected by recruitment and derecruitment. Accordingly, we assume in our model that R_{rs} remains fixed regardless of the state of the lung. The time-constant of the respiratory system that governs how rapidly it empties during passive expiration is given by $\tau_{rs} = R_{rs}/E_{rs}$, which shows that the time required for lung deflation decreases if either R_{rs} decreases or E_{rs} increases.

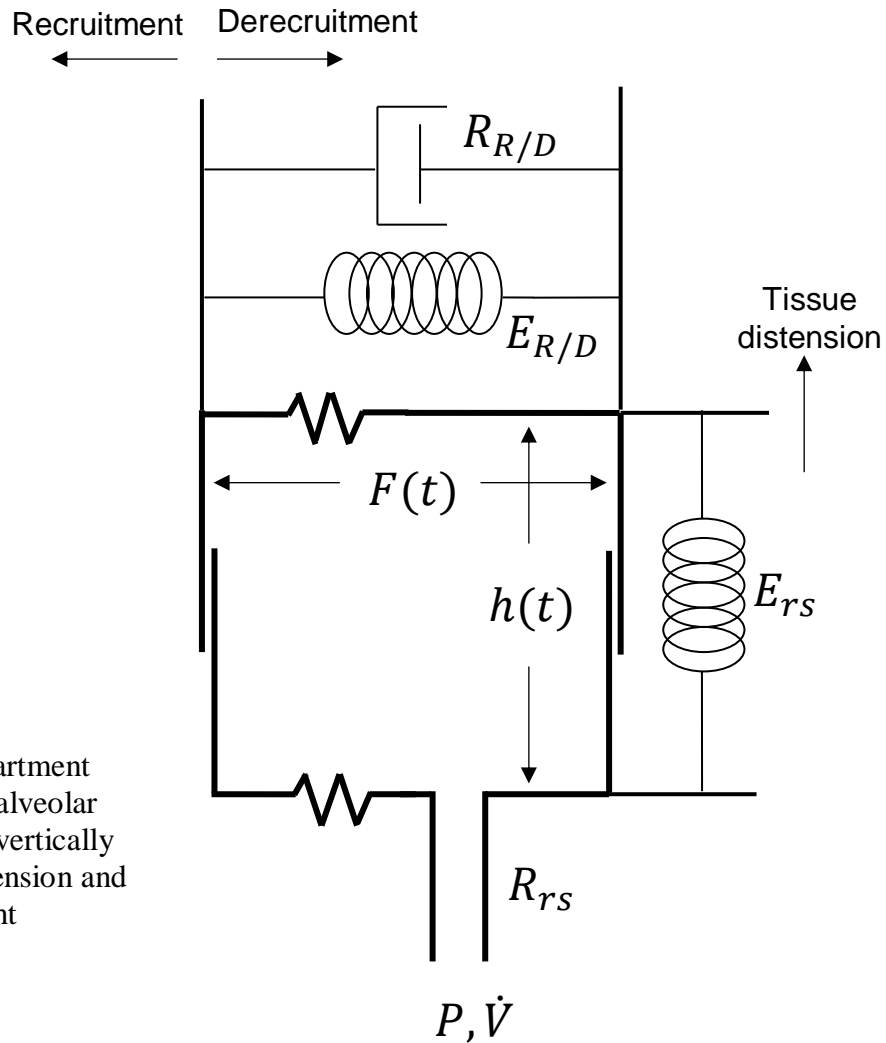


Figure 1: Single-compartment model of the lung; the alveolar compartment expands vertically to represent tissue distension and horizontally to represent recruitment.

The rate at which the model recruits and derecruits is governed by the two parameters $E_{R/D}$ and $R_{R/D}$ that together determine a time-constant of recruitment and derecruitment, $\tau_{R/D} =$

$R_{R/D}/E_{R/D}$. If alveolar pressure is held constant, the fraction of open lung will eventually approximate a steady-state value determined by the stiffness $E_{R/D}$ of the horizontal spring in Fig. 1. The horizontal dashpot with resistance $R_{R/D}$ in Fig. S-1 prevents the steady-state open fraction from being attained immediately following a change in alveolar pressure, and is related to the resistance provided by the motion of a plug of airway fluid or the peeling open of a collapsed airway that is required for airflow (2). Instead, the steady-state value is approached asymptotically as the dashpot slides under the force exerted by the spring. $E_{R/D}$ and $R_{R/D}$ together thus imbue the model with dynamic recruitment/derecruitment behavior whereby the fraction of open lung at any point in time is determined by prior excursions in alveolar pressure, in addition to its current value.

At any point in time (t) the parenchymal tissue is assumed to comprise two populations of lung units – those that are open and distended by alveolar pressure (P_A), and those that are closed. A critical opening/closing pressure (P_{crit}) is associated with each unit. At steady state (i.e., when a given P_A is maintained indefinitely) those units for which $P_A > P_{crit}$ will be open and those for which $P_A \leq P_{crit}$ will be closed. We assume that the critical opening and closing pressures for a given unit are the same, so there is only one value of P_{crit} for each unit regardless of whether it is subject to recruitment or derecruitment.

Following our previous work and that of others (3, 4), we assume in the present study that P_{crit} is a Gaussian function of P_A , with mean μ and standard deviation σ . This means that the steady-state open fraction, F_{stat} , is the cumulative Gaussian function

$$F_{stat}(P_A) = \int_{-\infty}^{P_A} \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(P-\mu)^2}{2\sigma^2}} dP \quad (\text{S.1})$$

Computational model fitting to experimental data in mice suggests that μ increases monotonically with surface tension at the air-liquid interface (i.e., with the increasing surfactant dysfunction that accompanies VILI), while σ remains fixed (3). Accordingly, we assume that the progression of VILI is defined entirely by the function $\mu(t)$.

The consequence of P_A acting on the intrinsic tissue elastance of the respiratory system, E_{rs} , is given by

$$P_A(t) = h(t)E_{rs} \quad (\text{S.2})$$

The volume, $V(t)$, of the lung is then given by

$$V(t) = h(t)F(t) \quad (\text{S.3})$$

The stiffness of the spring $E_{R/D}$ in the model (Fig. S-1) is thus a nonlinear function defined by the ratio of P_A to F_{stat} as defined by Eq. S.1.

Importantly, changes in F do not take place as soon as P_A changes; rather, the lung opens transiently when pressures are suddenly raised, and closes transiently when pressures are suddenly lowered. The dynamics of these transients are assumed to be first-order. That is, if the lung is held at a fixed value of P_A , F approaches $F_{stat}(P_A)$ asymptotically at a rate that depends only on the difference between F and $F_{stat}(P_A)$. These dynamics are created in the model by having a dashpot with resistance $R_{R/D}$ connected in parallel with spring $E_{R/D}$. The value of $R_{R/D}$ is a fixed fraction of $E_{R/D}$ so that the ratio $\frac{R_{R/D}}{E_{R/D}} = \tau$ defines a fixed time-constant that governs how quickly F relaxes toward F_{stat} . This is motivated by experimental derecruitability tests showing that, following a

recruitment maneuver, decruitment of the lung at a fixed inflation pressure is quasi-exponential (5-8). These dynamics are thus governed by the equation

$$\dot{F}(t) = \frac{1}{\tau} [F_{stat}(P_A(t)) - F(t)] \quad (\text{S.4})$$

The simulation of pressure-controlled mechanical ventilation requires a parameter corresponding to airway resistance, R_{aw} , so that the lung empties with a realistic time-constant. If the ventilator applies an airway opening pressure waveform $P_{ao}(t)$ to the trachea then the flow, $\dot{V}(t)$, into the lungs is

$$\dot{V}(t) = \frac{P_{ao}(t) - P_A(t)}{R_{aw}} = h(t)\dot{F}(t) + \dot{h}(t)F(t) \quad (\text{S.5})$$

which gives

$$\dot{h}(t) = \frac{\dot{V}(t) - h(t)\dot{F}(t)}{F(t)} \quad (\text{S.6})$$

For a lung in a fixed state of injury, this model has only 5 free parameters - E_{rs} , R_{aw} , σ , τ , and μ . Equations S.1 to S.6 define how the model behaves in response to any prescribed ventilator pressure or volume waveform. Figure 1B in the manuscript shows example airway pressure and flow during two consecutive breaths simulated by the model under baseline conditions. The model was ventilated using two modes of mechanical ventilation. Pressure-controlled low-Vt ventilation was administered by having airway pressure increase linearly from a PEEP of 10 cmH₂O to a peak pressure of 20 cmH₂O over a 2 s inspiration, and then return to PEEP for a 4 s expiration. APRV with the same breath duration and peak pressure was simulated using the parameters $T_{high} = 5.5$ s, $T_{low} = 0.5$ s, $P_{high} = 20$ cmH₂O, and $P_{low} = 0$.

To establish that our model is able to represent dynamic recruitment and derecruitment behavior in a realistic manner we tested its ability to mimic experimental data from our previous modeling study in mice treated with intra-tracheal hydrochloric acid to simulate aspiration lung injury (3). We concluded in that study that worsening injury did not affect the value of σ significantly, but did cause progressive elevations in μ that we interpreted as reflecting increasing surface tension in the air-liquid interface in the lung (9, 10). Accordingly, on the basis of trial and error, but guided by our previous study (3), we fixed $\sigma = 6$ cmH₂O, with healthy and severely injured lungs having $\mu = 2$ and 7.5 cmH₂O, respectively. With these parameter values, and the time-constant of recruitment and derecruitment (τ_{RD}) set to 10 s, the model behaved similar to experimental observations. Figure 2A in the manuscript shows the first 120 s of experimental elastance profiles for control and severely injured mice measured during mechanical ventilation at PEEP levels of 1, 3 and 6 cmH₂O from our previous study (3). Figure 2B in the manuscript shows the corresponding elastance profiles obtained from the model by initializing it to be 100% recruited, setting PEEP to either 1, 3 or 6 cmH₂O, and then ventilating at 120 breaths per min (similar to mice) using a linearly increasing airway pressure during inspiration that terminated at 10 cmH₂O above PEEP. Elastance was taken as inversely proportional to the open lung fraction (that is, E_{rs} divided by the open fraction). The simulated elastance profiles (Fig. 2B) exhibit similar dependencies on time and PEEP as the experimental data (Fig. 2A).

REFERENCES

1. Bates JH, Brown KA, Kochi T. Respiratory mechanics in the normal dog determined by expiratory flow interruption. *J Appl Physiol* (1985) 1989;67(6):2276-2285.
2. Fujioka H, Takayama S, Grotberg JB. Unsteady propagation of a liquid plug in a liquid-lined straight tube. *Phys Fluids* (1994) 2008;20(6):62104.
3. Massa CB, Allen GB, Bates JH. Modeling the dynamics of recruitment and derecruitment in mice with acute lung injury. *J Appl Physiol* (1985) 2008;105(6):1813-1821.
4. Crotti S, Mascheroni D, Caironi P, et al. Recruitment and derecruitment during acute respiratory failure: a clinical study. *Am J Respir Crit Care Med* 2001;164(1):131-140.
5. Albert SP, DiRocco J, Allen GB, et al. The role of time and pressure on alveolar recruitment. *J Appl Physiol* (1985) 2009;106(3):757-765.
6. Allen G, Bates JH. Dynamic mechanical consequences of deep inflation in mice depend on type and degree of lung injury. *J Appl Physiol* (1985) 2004;96(1):293-300.
7. Mellenthin MM, Seong SA, Roy GS, et al. Using Injury Cost Functions from a Predictive Single Compartment Model to Assess the Severity of Mechanical Ventilator Induced Lung Injuries. *J Appl Physiol* (1985) 2019.
8. Seah AS, Grant KA, Aliyeva M, et al. Quantifying the roles of tidal volume and PEEP in the pathogenesis of ventilator-induced lung injury. *Ann Biomed Eng* 2011;39(5):1505-1516.
9. Cassidy KJ, Halpern D, Ressler BG, et al. Surfactant effects in model airway closure experiments. *J Appl Physiol* (1985) 1999;87(1):415-427.
10. Gaver DP, 3rd, Samsel RW, Solway J. Effects of surface tension and viscosity on airway reopening. *J Appl Physiol* (1985) 1990;69(1):74-85.