Viewpoint: Turning the Air Blue

Mechanical Power and Ventilator-Induced Lung Injury: What Does Physics Have to Say?

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Ventilator-induced lung injury (VILI) is a potential threat to anyone receiving supportive mechanical ventilation for acute respiratory failure. Despite decades of research, however, the safest way to ventilate any given patient remains controversial. This makes fertile ground for novel concepts, and one that has arisen recently concerns the idea that a ventilator imparts potentially damaging mechanical energy to the lungs (1, 2). The motivation for this concept is clear: energy transfer is involved when any structure becomes physically damaged. It may be intuitive, then, that the *rate* at which energy is delivered to the lungs by a ventilator, namely *mechanical power*, should be associated with VILI. Nevertheless, understanding the relationship between mechanical power and VILI requires clarity on the difference between stored versus dissipated energy regardless of whether ventilation is caused by positive pressure at the airway opening or negative pressure in the pleural space (3).

When a ventilator inflates the lung, some of the applied work is stored in the lung tissues as *elastic potential energy*. This type of energy is what physicists call conservative, meaning it is completely recoverable. This can only be the case if those tissues that become distorted during inspiration are returned precisely to their pre-inflation configurations upon expiration. The net result to the tissues is equivalent to the energy never having been delivered in the first place.

Tissue damage, on the other hand, involves irreversible alterations to tissue structure. Any energy involved in such damage is not recovered – it is dissipated within the tissues as heat. However, not all energy dissipated during mechanical ventilation results in harm. Damage is most likely to occur when energy is dissipated rapidly within a small volume of tissue, resulting in a high *dissipation power intensity*.

The total energy dissipation in the respiratory system of a ventilator-dependent patient can be readily measured at the bedside as the area enclosed by the airway pressure-volume (PV) loop.

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Even a perfectly healthy lung produces a PV loop enclosing a measurable area, as demonstrated by the model-simulated loops shown in Fig. 1. The energy dissipation predicted by this simple model (see Online Supplement) is due purely to flow of gas along airways. Barring effects due to shear stresses at the airway epithelium, energy dissipation by this mechanism plays no role in clinically significant lung injury because of its low power intensity within the tissues.

Energy dissipation also takes place within the lung tissues, because they are *viscoelastic*. During inspiration, the tissues dissipate energy by a variety of mechanisms, including friction between adjacent collagen and elastin fibers, extrusion of ground substance through membrane pores (4), and breakage of molecular bonds at the air-liquid interface (5). Inclusion of a viscoelastic mechanism in the model (see Online Supplement) results in a modest shift in the position of the PV loop (Fig. 1). There is little change in its area with pressure-controlled ventilation because the extra energy dissipated in the tissues reduces airflow and thus reduces the energy dissipated in the airways. Viscoelastic processes are distributed throughout the parenchyma and so, as with airflow, normally have low power intensity and thus play no appreciable role in VILI.

There is a form of potentially injurious energy dissipation, however, that is not present to a significant degree in a normal lung, but which may be important in the inflamed or injured lung. This form of dissipation manifests during each inspiration due to the *recruitment* of alveoli and/or small airways that close during the prior expiration. Forcing contacted epithelial surfaces apart requires significant energy, particularly when impaired surfactant function causes high surface tension at the air-liquid interface (6). The energy dissipated in the lung by this mechanism is reflected in a substantial widening of the PV loop at lower lung volumes where derecruitment is prominent and, if persistent, causes the well-established VILI mechanism known as *atelectrauma*. The extra work dissipated by recruitment is likely less than that due to the other aforementioned

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mechanisms, even in an injured lung as illustrated in Fig. 1. (The Online Supplement explains how Fig. 1 relates to a commonly used formula for the components of mechanical power). Nevertheless, when a closed alveolus or airway is recruited, it transitions between closed and open state very rapidly, resulting in high levels of local dissipative power transmission to the tissues. This power intensity is increased in already injured lungs. For example, impaired surfactant function elevates in surface tension and thus injurious stresses.

The above discussion makes the case for cyclic recruitment as being the primary mechanism by which supportive mechanical ventilation contributes to VILI. Why, then, do other measures of mechanical power, particular those attributed to the elastic work done during inspiration (1), seem to be associated with VILI? The answer, surely, is that elastic work correlates with the actual culprit, namely over-distension. Work is given by the integral of recoil pressure with respect to volume, so the more the lung is inflated, the greater will be the elastic work.

When the lung is inflated beyond a certain volume, its tissues will sustain the kind of irreversible damage that is known as *volutrauma*, just as sufficient straining of any structure will cause it to fail mechanically. Furthermore, tissues that are already damaged in injured lungs are more at risk for this type of injury than normal tissues. Reducing parenchymal strain reduces damage (7-9), so it is not surprising that this is reflected in reduced inspiratory work. Of course, the actual damaging events themselves are not elastic but dissipative, because they involve the irreversible breakage of tissue structures. These events are distributed throughout the lung and occur gradually over extended periods of time. Although they necessarily must add to the PV loop area, these additions may be difficult to detect. Excessive strain may also induce inflammatory events via stimulation of mechanical stretch receptors (10), or perhaps even transiently stretch the endo/epithelia and thus reduce barrier function, permitting surfactant deactivating components to enter the airspaces and

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increase the stresses of recruitment. Both effects however, are consequences of over-distension, not energy *per se*.

In conclusion, physical first principles dictate that purely elastic work delivered during inspiration has no impact on tissue damage, except insofar as it might enjoy a correlation with injurious levels of over-distension. Mechanical power does have direct relevance to VILI, but this relevance pertains only to the rate and intensity of energy dissipation in the lung tissues, and even then, only to a fraction of it. Exactly how to quantify *injurious* dissipated energy in the lung from airway pressure-volume relationships measured at the bedside is a matter for future research.

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Figure Legend

Figure 1: Simulated PV loops. The solid line shows the PV loop generated by a model that includes only tissue elasticity. The dashed line shows how the loop changes when tissue viscoelasticity is included in the model. The dotted line shows the further changes that occur when recruitment and derecruitment corresponding to a severely injured lung are included. (See Online Supplement for model details.)

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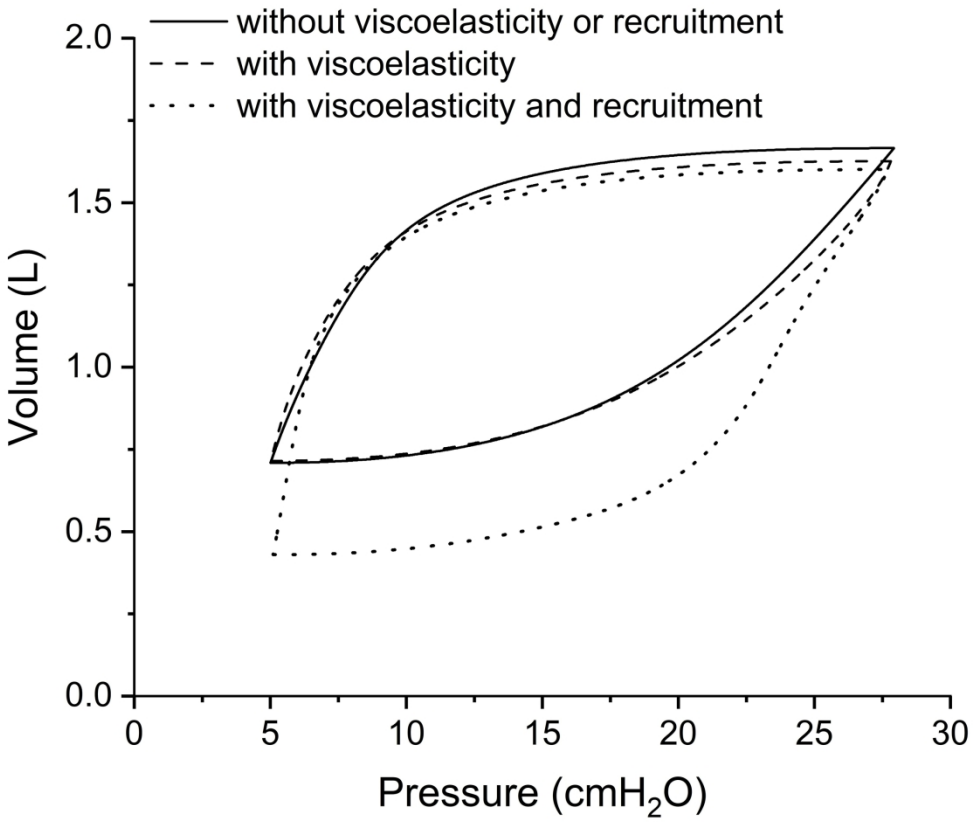

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ONLINE DATA SUPPLEMENT

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Analysis of Mechanical Power Delivered to the Lung During Mechanical Ventilation

Energy, U, is defined as the integral of a force acting over a distance. In respiratory terms, this translates to a pressure, P, applied to the airway opening by a mechanical ventilator and the volume change, V, that results in the lungs. The is written mathematically as

$$U = \int_{V_{init}}^{V_{init}+V_{Tot}} PdV = \int_{0}^{T} P(t)\dot{V}(t)dt \tag{S-1}$$

where V_{init} is the initial volume, V_{Tot} is the total volume change, T is the time over which this volume change occurs, and $\dot{V}$ is flow (the time-derivative of volume). The final expression on the right acknowledges that P and $\dot{V}$ are both functions of time, t. This equation is a precise statement of the energy delivered to the lungs by a mechanical ventilator over the duration T, but it makes no presumptions about whether the energy is conserved or dissipated.

Equation S-1 applies to any V_{Tot} and its corresponding T. In particular, it applies to a single entire breath of duration T_{tot} for which V_{Tot} has returned back to zero. A plot of $V(t)$ versus $P(t)$ in this case forms a closed loop – the so-called PV loop – because both $V(t)$ and $P(t)$ return precisely to their starting points. The fact that the PV loop encloses a finite area means, by definition, that there has been a net transfer of energy from the mechanical ventilator to the lungs. In other words, not all the energy that is put into the lungs during inspiration is returned to the environment during expiration. Due to conservation of energy, an amount of energy equal to the PV loop area is dissipated in the lungs in the form of heat.

So far, nothing has been said about how this non-returning energy is dissipated. Inferences can be made about its dissipation by considering the physical processes known to be involved in the inflation and deflation of the lungs – flow of viscous gas along airways, stretching of elastic structures in the parenchymal tissue, breakage of temporary bonds formed at the air-liquid interface, and such like – but these require experimental confirmation.

A convenient way to estimate how the delivered energy is apportioned among the various structures that comprise the lung is to consider a mathematical model of the mechanical behavior of the lungs. All models are approximations to reality, so any analysis based on a model must itself be considered approximate. A model that has been used recently in this regard is the standard single-compartment model that considers the lung to behave like a single elastic compartment served by a single flow-resistive airway. The equation of motion of this model is

$$P(t) = EV(t) + R\dot{V}(t) + P_0 \tag{S-2}$$

where E is the elastance of the compartment, R is the resistance of the conduit, and P_0 is positive end-expiratory pressure.

Substituting Eq. S-2 into Eq. S-1 for a single complete breath gives

$$U = \int_{0}^{T_{tot}} \left[EV(t) + R\dot{V}(t) + P_0\right]\dot{V}(t)dt \tag{S-3}$$

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$$= \left[\frac{EV^2(t)}{2}\right]_0^{T_{tot}} + \int_0^{T_{tot}} R\dot{V}^2(t)dt + [P_0V(t)]_0^{T_{tot}}$$

Because $V(t) = V(T_{tot})$, the first and third terms above are zero. The only term that is non-zero is the middle term containing R. In other words, no energy is dissipated in the lungs from either elastic recoil or PEEP. It is only the component of energy due to resistance that remains in the lung at the end of a complete breath, so it is only resistance that results energy dissipation.

The above mathematical analysis of energy dissipation in the lung applied specifically during inspiration shares some similarities with recent graphical representations that are based on the linear single-compartment model of the lung inflated with constant inspiratory flow (1, 2). The following equation (using the terminology in this Supplement) for the work done on the lung inspiration based on the same assumptions has also been proposed (3):

$$U = \frac{{V_T}^2 E}{2} + RV_T\dot{V} + V_T P_0 \quad \text{(S-4)}$$

However, when expiration follows inspiration, the first and third terms in Eq. S-4 cancel to zero leaving only a term in R. In other words, what Eq. S-3 above demonstrates is that even if sizeable amounts of elastic energy are stored in the lungs during inspiration, this energy is recovered during expiration.

Modeling Methods

Following Hamlington et al. (4), we represent the lung as a single alveolar compartment that can expand in two orthogonal directions, as illustrated in Fig. S1. Vertical expansion corresponds to distension of the open lung, while horizontal expansion corresponds to an increase in the open lung fraction (i.e., recruitment of closed lung units).

The viscoelastic properties of the respiratory tissues are represented by a nonlinear Kelvin body consisting of two springs and a dashpot that collectively change length in the vertical direction (Fig. S1). To account for the strain stiffening of lung tissue, the stiffness of the spring representing static tissue elastance depends linearly on its extension, y. Similarly, the stiffness of the second spring depends linearly on its extension, x. The resistance of the dashpot also has the same dependence on x as the spring to which it is connected so that the spring-dashpot pair mimic stress relaxation with a fixed time-constant. In addition, the constitutive properties of the three elements in the Kelvin body vary inversely with the fraction $0 < w \leq 1$ of the lung that is recruited (Fig. S1). The stiffnesses of the two springs and the resistance of the dashpot are thus, respectively,

$$\hat{E}_1 = E_1 y/w \quad \text{(S-5)}$$

$$\hat{E}_2 = E_2 x/w \quad \text{(S-6)}$$

$$\hat{R}_t = R_t x/w \quad \text{(S-7)}$$

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The forces across the two springs contribute in parallel to the pressure, P_A, in the alveolar compartment, giving

$$P_A(t) = \hat{E}_1 y(t) + \hat{E}_2 x(t) + P_0 \tag{S-8}$$

where P_0 is the pressure across the lung at functional residual capacity. At the same time, the force across the dashpot equals the force across the spring to which it is connected, giving

$$\hat{E}_2 x(t) = [\dot{y}(t) - \dot{x}(t)]\hat{R}_t. \tag{S-9}$$

The single alveolar compartment is served by a conduit representing airway resistance R_{aw} that includes the resistance of the endotracheal tube. Pressure and flow at the airway opening (P_{ao} and $\dot{V}$, respectively) thus satisfy

$$P_{ao}(t) = R_{aw}\dot{V}(t) + P_A(t). \tag{S-10}$$

where $\dot{V}(t) = dV(t)/dt$ is the rate of change of lung volume, $V(t)$.

$\dot{V}(t)$ is determined by both the rate of extension of the already open tissue ($\dot{y}(t) = dy(t)/dt$) and the rate of lung recruitment ($\dot{w}(t) = dw(t)/dt$). That is,

$$\dot{V}(t) = \frac{d[y(t)w(t)]}{dt} = y(t)\dot{w}(t) + \dot{y}(t)w(t). \tag{S-11}$$

However, $w(t)$ and $\dot{w}(t)$ are governed by $P_A(t)$ acting on the horizontal spring and dashpot in Fig. S1 that together account for the dynamics of recruitment and derecruitment. Thus, although this model is represented in Fig. S1 as having a single alveolar compartment, it effectively contains a distribution of compartments each with a critical pressure, P_{crit}, above which the compartment opens and below which it closes (the remainder of the lung is open all the time). The values of P_{crit} for the recruitable units are distributed according to a Gaussian function of P_A having mean μ and standard deviation σ (5). Thus, if P_A is held constant, the horizontal spring will eventually achieve a steady-state extension corresponding to the fraction of open lung represented by all those units for which $P_{crit} \geq P_A$. Since the fraction of open lung is a nonlinear function of P_A, the value of E_{RD} depends on w such that it has a relatively small value when w is in the vicinity of μ because changes in P_A cause significant changes in the fraction of open lung. As w moves further away from μ in either direction, the value of E_{RD} grows accordingly.

Changes in w do not occur instantaneously with a change in P_A, however, because the horizontal dashpot prevents the steady-state extension of the horizontal spring from being attained

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immediately. In order to give this transient behavior a well-defined time constant ($\tau_{R/D}$), we assign R_{RD} the same dependence on w as given to E_{RD} so that their ratio is a constant. The equation governing the dynamics of w is

$$P_A(t) = R_{RD}(w)\dot{w}(t) + E_{RD}(w)w(t) \quad \text{(S-12)}$$

We simulated mechanical ventilation by driving the model with a prescribed airway pressure profile, $P(t)$, producing a calculated airway flow profile, $\dot{V}(t)$. The pressure profile consisted of a constant inspiratory pressure of P_{insp} applied for a duration T_{insp} followed by a constant positive end-pressure $PEEP$ during expiration applied for a duration of T_{exp}. The PV loops shown in Fig. 1 were generated with $P_{insp} = 28$ cmH_2O, $PEEP = 5$ cmH_2O, $T_{insp} = 3$ s, and $T_{exp} = 7$ s. The initial conditions of the model were $V_0 = \dot{V}_0 = x_0 = \dot{x}_0 = 0$. The model was run for 4 complete breaths in order to achieve steady state; the PV loops in Fig. 1 are from the final breath.

The complete model including both tissue viscoelasticity and recruitment/derecruitment was simulated with the parameter values: $R_{aw} = 12$ $cmH_2O.s.L^{-1}$, $E_1 = 10$ $cmH_2O.L^{-1}$, $E_2 = 4$ $cmH_2O.L^{-1}$, $R_t = 4$ $cmH_2O.L^{-1}$, $\mu = 12$ cmH_2O, $\sigma = 2$ cmH_2O, $f_{RD} = 0.7$. The baseline model with neither viscoelasticity nor recruitment/derecruitment was simulated using the same parameter values except R_t and f_{RD} were both set to zero. The model with only viscoelasticity present was simulated by setting only f_{RD} to zero.

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Figure Caption

Figure S1: Model of the respiratory system consisting of a single alveolar compartment that expands both vertically (representing tissue distension) and horizontally (representing tissue recruitment).

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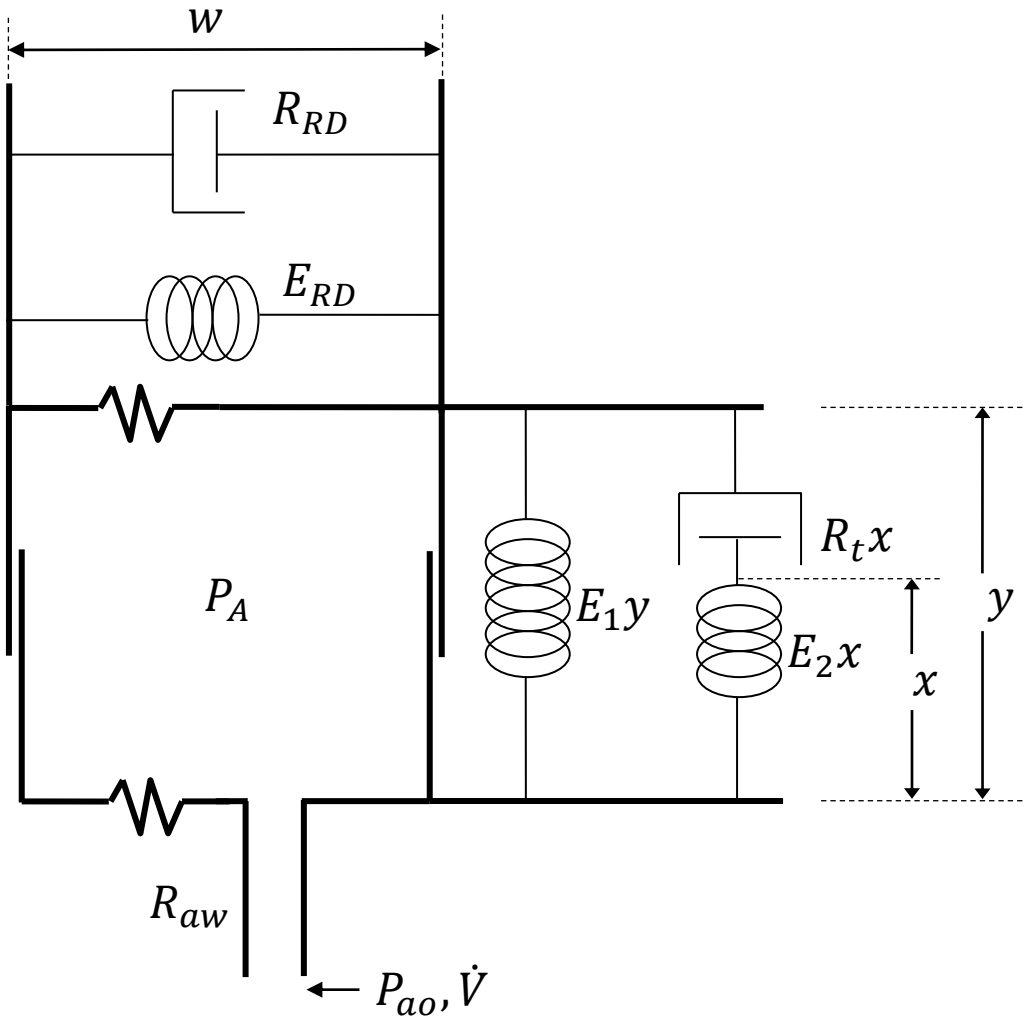

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