

Static and Dynamic Contributors to Ventilator-induced Lung Injury in Clinical Practice

Pressure, Energy, and Power

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Abstract

Ventilation is inherently a dynamic process. The present-day clinical practice of concentrating on the static inflation characteristics of the individual tidal cycle (plateau pressure, positive end-expiratory pressure, and their difference [driving pressure, the ratio of V_T to compliance]) does not take into account key factors shown experimentally to influence ventilator-induced lung injury (VILI). These include rate of airway pressure change (influenced by flow amplitude, inspiratory time fraction, and inspiratory inflation contour) and cycling frequency. Energy must be expended to cause injury, and the product of applied stress and resulting strain determines the energy delivered to the lungs per breathing cycle. Understanding the principles of VILI energetics may provide

valuable insights and guidance to intensivists for safer clinical practice. In this interpretive review, we highlight that the injuring potential of the inflation pattern depends upon tissue vulnerability, the number of intolerable high-energy cycles applied in unit time (mechanical power), and the duration of that exposure. Yet, as attractive as this energy/power hypothesis for encapsulating the drivers of VILI may be for clinical applications, we acknowledge that even these all-inclusive and measurable ergonomic parameters (energy per cycle and power) are still too bluntly defined to pinpoint the precise biophysical link between ventilation strategy and tissue injury.

Keywords: ventilator-induced lung injury; energy; power; acute respiratory distress syndrome; lung protective ventilation

Promoting the healing of lung injury is a primary objective of critical care. Over the past 2 decades, a solid base of experimental evidence (1), complemented by supportive data from randomized clinical trials (2, 3), has demonstrated that modifications of the tidal inflation pattern and ventilating frequency may raise or lower the risk of ventilator-induced lung injury (VILI). Dating from the practice-

altering evidence provided by the ARDSnet randomized clinical trial that compared traditional to lower V_T s (12 ml/kg vs. 6 ml/kg) (2), the clinician's perception of which machine settings need to be carefully regulated has gradually changed. This progression has proceeded from applying a "low" V_T and targeting a "fully open" lung to emphasizing prone positioning (4) and regulating

transpulmonary end-inspiratory and driving pressures (3, 5).

Although the majority of clinical guidelines and practices are certainly defensible on the basis of experimental models, it must be pointed out that no clinical study has yet directly demonstrated that VILI itself is the causal link between ventilation strategy and mortality risk. In addition, we do not know what proportion

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of any mortality risk is directly attributable to mechanical ventilation itself. Moreover, ventilation is inherently a dynamic, not static, process. The present-day clinical practice of concentrating on the static inflation characteristics of the individual tidal cycle (plateau pressure, positive end-expiratory pressure [PEEP], and their difference [driving pressure, the ratio of V_T to compliance (V_T/C)]) does not take into account key factors shown experimentally to be important to injury causation. These include rate of airway pressure change (6–8) (influenced by flow amplitude, inspiratory time fraction, and inspiratory inflation contour) and cycling frequency (9, 10). More fundamentally, although there is general agreement that intolerable tidal stresses and strains repeatedly applied to susceptible lung tissues initiate the VILI process, questions persist as to exactly how these forces develop and injure. The following discussion addresses the still incompletely answered questions regarding those causative links.

Energetics of Damage

At some very basic level, energy must be involved in VILI generation; an input of energy is needed to inflate, overstretch, deform, and potentially damage tissue structures (11). Preclinical data have indicated that isolated excesses within the ventilating prescription, such as PEEP, plateau pressure, driving pressure, and frequency, can inflict lung damage (1, 12). Each of these helps to comprise the delivered energy of repeated tidal cycling (13). Despite their prominence in current bedside practice, static pressures, such as plateau and PEEP, may maintain distortion but cannot of themselves cause physical microwounding injury.

To cause damage, a pressure must be paired with a volume change. More specifically, the damaging factor is the pressure applied directly to the lung (i.e., transpulmonary pressure [P_{tm}]; stress) coupled to the associated change of lung volume relative to resting volume (strain) (14). This coupling of applied stress to resulting strain defines and requires energy delivery. Because the extent of damage depends upon stress/strain development in the individual microstructural elements of the lung, the distribution of stress/strain

is a key determinant of regional VILI hazard.

The critical straining consequences of changing P_{tm} help explain why the distribution of VILI may be highly regional, with most investigations indicating that mechanically heterogeneous zones are most at risk to injury first and with greatest severity in response to a hazardous ventilating pattern (15–17). Unfortunately, no externally measured combination of global ventilating parameters (i.e., circuit pressures, flows, and volumes) can completely characterize the strain actually encountered regionally at the micro level.

Power is defined as the amount of energy per unit of time and may vary within the span of an individual inflation or deflation half cycle by altering the flow profile (Table 1). Mechanical power, as currently applied in the clinical setting, is defined as the product of the total inflation energy per cycle and the cycling frequency ($J/cycle \times cycles/min$) (18). Defined in this way, duration of such power exposure is also fundamentally important to the extent of damage manifested at any given time (19).

Specific power (SP), defined here as power per ventilated lung unit, should also be considered. A given increase of mechanical power without changes in the ventilated lungs inevitably results in higher

SP, whereas if both power and ventilated lungs increase simultaneously, the SP may remain constant or even fall. As discussed subsequently, this principle relating power to aerating (volume expandable) capacity assumes special importance for the “baby lung” of acute respiratory distress syndrome (ARDS), for which the energy applied per unit time is concentrated onto a smaller volume (20).

From the clinical perspective of practitioner-modifiable machine settings, these concepts of per-breath power delivery (analogous to electrical watts [defined as the product of potential difference (voltage) and flow (amperage)] and cumulative inspiratory energy applied to the lungs over multiple breathing cycles (analogous to the electrical kilowatt-hour) have drawn intense recent interest, as these ergonomic characteristics integrate most known clinician-selected and measurable contributors to VILI, while suggesting a plausible biophysical coupling mechanism through which they all channel (18, 20–22). Yet, as attractive as the energy/power hypothesis for VILI may be, there are strong reasons to believe that these all-inclusive and measurable ergonomic parameters (energy and power, expressed as machine-delivered energy/min) are still too bluntly defined to pinpoint the precise biophysical link.

Table 1. Definitions of Ventilator-induced Lung Injury Energetics

Stress	Forces tending to cause (and oppose) extension from resting state
Strain	Amount of elongation in the direction of applied force, relative to initial length
Energy per cycle	The entity that performs work of inflation Integral of pressure and inspiratory flow: $\int P \Delta V dt$ Force \times length product: pressure (force/area) \times volume (area \times length)
Power	Energy expended per unit time Product of inflation energy \times ventilating frequency
Threshold	Stress-strain level at which tidal damage is initiated
Cumulative energy load and cumulative strain	Total number of energy or strain cycles delivered over a given period
Specific power	Power/volume on which it acts
Unaccounted (absorbed) energy	Inflation energy that is neither stored as potential energy nor dissipated in driving airflow

Determinants and Consequences of Inflation Energy

Forms of tidal mechanical energy. It is an unassailable thermodynamic principle that energy needed to perform work or to inflict tissue damage can neither be created nor destroyed—only transformed, as exemplified by the Bernoulli principle that governs gas velocity and pressure (23). Energy operating within biologic systems can be classified into three basic categories: chemical, thermal (heat), and mechanical. The mechanical energy imparted by the ventilator exists primarily in potential and kinetic forms, and, during the respiratory cycle, transforms between them. Those transitions occur with limited efficiency; kinetic inflation energy applied by the ventilator to the passive respiratory system may (in part) dissipate as heat against the resistance of airways and the energy cost of reshaping lung parenchyma (tissue resistance). Another portion of kinetic energy (eventually discharged in expiration) converts to stored elastic tension within the lung and chest wall by temporarily deforming and straining tissue microelements. This imperfectly efficient conversion to storage, which involves unfolding, expanding surface film and structural alteration, simultaneously dissipates energy.

Measurable components of delivered inflation energy. At the bedside, we are limited to global measurements of pressure, flow, and volume. The pressure relevant to the lung (as opposed to the entire respiratory system) is the P_{tm} , clinically approximated by the difference between airway and pleural (esophageal balloon) pressures (24). In the discussion that follows, the principles relating pressure to energy apply in identical fashion to the relevant pressure (airway pressure or P_{tm}) for the structure in question (respiratory system or lung, respectively). For simplicity, airway pressure will be used to illustrate.

The total (absolute) pressure that acts in conjunction with the associated volume change to determine the “per-breath” inflation energy can be broken down into three major elements: flow resistive, tidal elastic, and end-expiratory (Figure 1). Although their contributions to VILI risk quantitatively differ and depend on their relative amplitudes and interactions with the other pressure components, each of these three energy elements has been demonstrated experimentally to have the potential to contribute to lung damage when frequency and/or minute ventilation are held constant (18).

Plateau, PEEP, and driving pressure. Plateau pressure and PEEP are static variables that quantify the force per unit area applied at the alveolar level at the extremes of one tidal cycle but do not directly reflect the associated volume change, rate of volume expansion, or resulting strain. Consequently, even their difference (driving pressure) gives limited insight for assessing VILI risk. For instance, an impressive driving pressure excursion can generate a high peak pressure without expanding, straining, or damaging an unyielding structure (e.g., a glass bottle or closed rigid box; here, the applied pressure difference causes no energy expenditure). Enthusiasm for using the conveniently measured driving pressure as a VILI risk indicator, therefore, should be tempered by the understanding that it is the energy-requiring process of imposing excessive strain (the incremental change of linear dimension)—not high pressure itself nor even differences of static pressures (e.g., driving pressure)—that inflicts damage. Although externally measured compliance may correlate better with number of aerated lung units than with the average flexibility of the individual micro-units of the baby lung, that correlation is far from perfect and is likely to weaken further with

duration and severity of disease. It follows that, for the same high values of plateau and driving pressures, the poorly compliant lung unit may be relatively protected from injuring strain when compared with a relatively compliant one embedded in a different region of the same damaged lung (Figure 2).

Flow-resistive pressure. Because different elements in the lung parenchyma vary in their reluctance to expand, high rates of change of volume (and associated static pressures) accentuate local “dragging” forces that alter the distribution and amplitude of the micro-stresses applied to biologic tissues (25). During buildup of the driving pressure, these viscoelastic properties of the inflating and deforming structure focus stress and affect the efficiency with which the applied energy is stored as elastic tension (see AMPLIFIERS OF DAMAGING ENERGY AND POWER). Because rapid expansion limits the extent to which accommodation to varying expansion rates can occur (25–27), increments of energy that are applied quickly are more likely to inflict tissue damage (26, 27).

Upon unrestrained decompression, the entirety of the driving pressure (and the stored potential elastic energy it represents) is released, both to disperse as heat (in the airways, parenchyma, circuitry, and atmosphere) and to recover the initial tissue conformation (e.g., by refolding collapse and reorganization of extracellular matrix components). The way this transition happens may be important; by analogy, consider the stepwise discharge of the gravitational potential energy of a fragile cup that is carried down a staircase from an upper landing to the floor below in comparison to its sudden drop from the same height. The first is safely accomplished, whereas the second may cause the container to shatter (see Figure E1

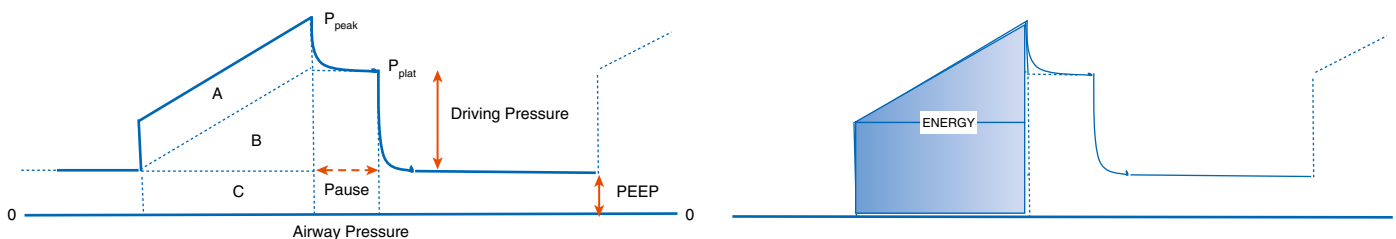


Figure 1. Left panel: airway pressure profile during inflation with constant flow. Under these conditions, time and inspired volume are linearly scaled. Total positive end-expiratory pressure (PEEP) is comprised of the set PEEP and auto-PEEP. Areas A, B, and C correspond to the flow-resistive, tidal-elastic, and PEEP-related energy components. Right panel: the shaded area is the pressure–volume area that defines the mechanical work performed by the ventilator during passive inflation, equivalent to the energy it delivers to the respiratory system. P_{peak} = peak dynamic pressure; P_{plat} = static (“plateau”) pressure.

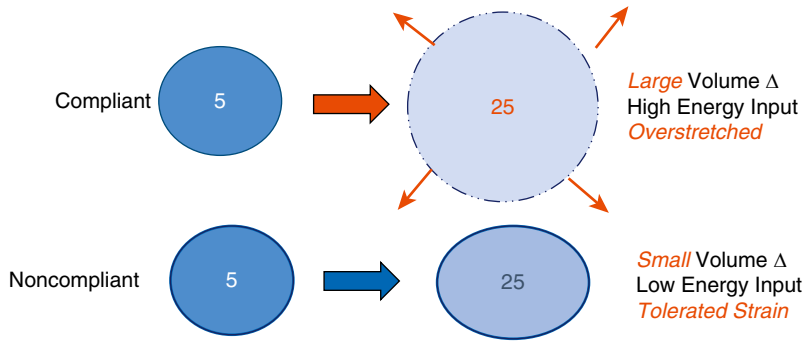


Figure 2. Potential importance of compliance to consequences of driving pressure on injuring strain. Damage from a given driving pressure depends jointly on associated lung unit compliance and delivered energy. In this example, the same driving pressure of 20 cm H₂O overstretches the compliant alveolus (top), whereas the less-compliant alveolus (bottom) undergoes less volume change and tolerates the associated strain. Open units of varying specific compliance are embedded in different zones within the same injured “baby lung.”

in the online supplement). Both events dissipate the entirety of the potential energy of the landing-to-floor “driving pressure,” but only the latter delivers a potentially damaging transitional impulse of energy. Such considerations of driving pressure release have special relevance to the deflation phase (*see following*). A similar, but inverse, principle applies to the rate of energy storage during the transition from PEEP to plateau during the tidal cycle. In other words, the *rates* of expansion and contraction of the lung—strain rates—strongly influence energy transitions and the possibility to damage (6–8, 26).

PEEP. PEEP applied at a constant V_T may simultaneously alter overall lung

compliance as it boosts total baseline pressure (28, 29). As it rises from low levels, the relationship of PEEP to strain and VILI risk assumes a nonlinear U shape, and the histology of damage trends progressively toward ductal dilation and emphysema, rather than inflammation (30). Generally speaking, low levels of PEEP favor an energy-offsetting improvement of compliance and driving pressure (V_T/C), whereas higher levels simply increase the need for energy input and elevate the static strain baseline. From this higher strain platform, a given driving pressure may lift plateau pressure and ventilating stress across a threshold into a range that could damage highly jeopardized regions of the lung’s micro-architecture (30) (Figure 3) (*see*

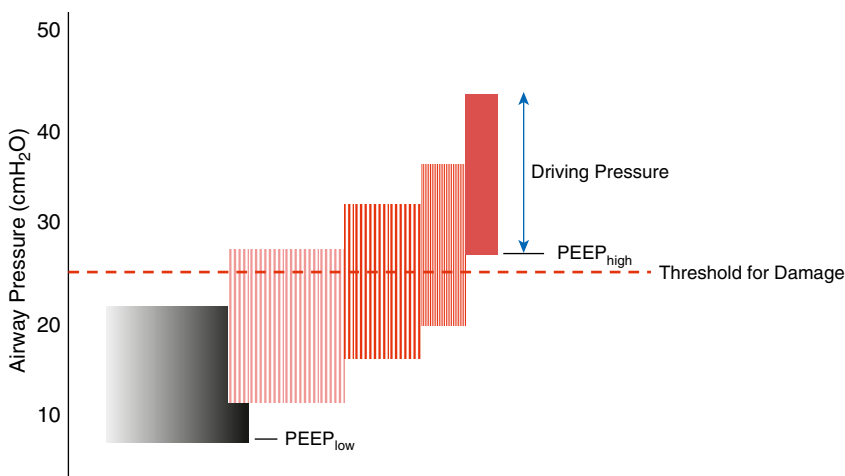


Figure 3. Influence of positive end-expiratory pressure (PEEP) on lung tissue strain for the same driving pressure (bidirectional arrow). Dashed red line represents the threshold pressure at which ventilator-induced lung injury begins. The width of each rectangle indicates the number of high-risk junctional interfaces between open and closed lung units. PEEP may reduce number of junctional interfaces but increases strain on those remaining unrecruited, as indicated by the deepening hues.

PARENCHYMAL STRAIN THRESHOLD). We should note that the process of recruiting an injured lung is not always beneficial. Previously resting lung units reopened by the PEEP increment may present new sites of stress focusing and local power amplification (31).

Amplifiers of damaging energy and power. By the thermodynamic principle of energy conservation, energy accounted for in its noninjuring forms (stored potential or dissipated frictional heat) cannot simultaneously have been spent in deforming tissue or inflicting damage. Very small amounts of mechanical energy are delivered during inflation, and even smaller amounts remain unrecovered or unaccounted at the end of the breathing cycle (13). Arguably, however, it is this unaccounted fraction of input energy, which likely rises disproportionately with V_T and driving pressure (32), that relates most directly to damage. With these determinants and thermodynamic principles in mind, one might wonder how such small amounts of unaccounted (absorbed) energy could initiate tissue damage.

The answer likely lies within the following four considerations of micromechanics. First, the baby lung of ARDS has much less capacity to accept gas than its healthy counterpart, so that given amounts of ventilating energy and power concentrate within a “container” with innately smaller capacity to accept it (20, 33). This spatial concentration amplifies both the magnitude and velocity of the stretching forces of the tidal breath. Thus, the same amount of externally measured power that severely injures the baby lung would have negligible biologic impact when applied to the lungs of a healthy adult; the SP of the former (power/capacity) far exceeds the latter.

Second, the mechanically heterogeneous environment of acutely injured tissue amplifies stresses at the junctions of mechanically dissimilar tissues (e.g., closed and open units) (34, 35), and, in that process, initiates strong forces at the boundary between pliable and nonpliable parenchymal elements (36, 37).

Third, as already noted, not all parenchymal structures expand at the same rate in response to an applied stress. These viscoelastic “drag” properties of acutely injured tissues impede effective stress distribution, further augmenting the local forces and strain incurred during expansion at junctional interfaces in rough proportion to the rate of volume change and strain (25–27). The observation of *pendelluft*,

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