CONCISE CLINICAL REVIEW

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_Ts (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

(Received in original form August 8, 2019; accepted in final form October 30, 2019)

Supported, in part, by grants awarded by the Conselho Nacional de Desenvolvimento Científico e Tecnológico.

Author Contributions: J.J.M., P.R.M.R., and L.G. conceived and wrote the manuscript. All authors reviewed and discussed the manuscript during preparation.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

CME will be available for this article at www.atsjournals.org.

Am J Respir Crit Care Med Vol 201, Iss 7, pp 767–774, Apr 1, 2020

Originally Published in Press as DOI: 10.1164/rccm.201908-1545CI on October 30, 2019
Internet address: www.atsjournals.org

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 [Ptm]; 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 Ptm 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 × 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: $\int P\Delta Vdt$ Force × length product: pressure (force/area) × volume (area × length)
Power	Energy expended per unit time Product of inflation energy × 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 Ptm, 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 Ptm) 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

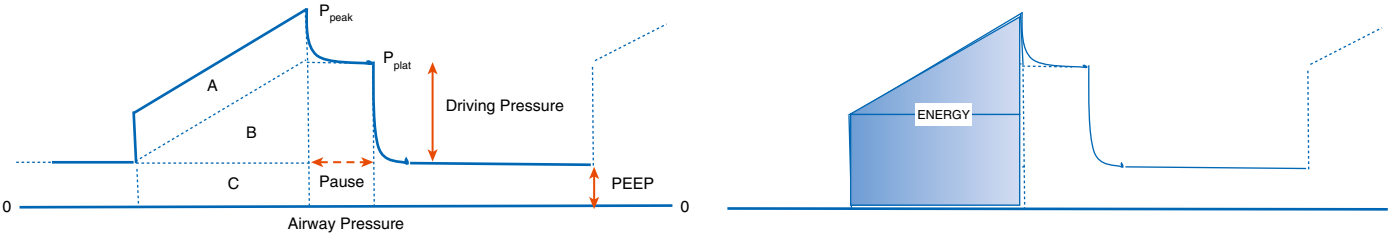

Figure 1. Left panel: airway pressure profile during inflation with constant flow. Under these conditions, time and inspired volume are linearly scaled. Total positive end-expiratory pressure (PEEP) is comprised of the set PEEP and auto-PEEP. Areas A, B, and C correspond to the flow-resistive, tidal-elastic, 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.

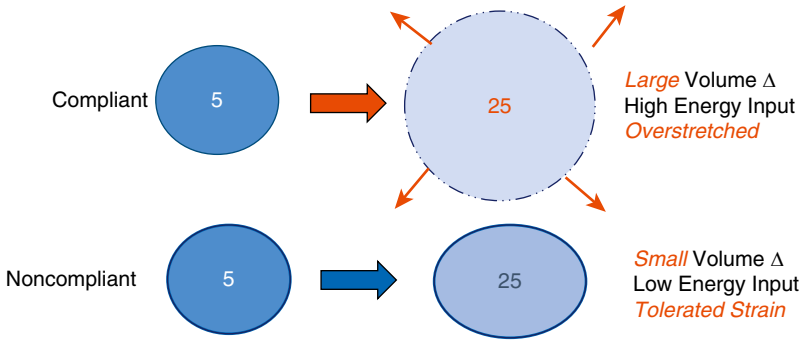

Figure 2. Potential importance of compliance to consequences of driving pressure on injuring strain. Damage from a given driving pressure depends jointly on associated lung unit compliance and delivered energy. In this example, the same driving pressure of 20 cm H_2O overstretches the compliant alveolus (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 VT 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 (VT/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* 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).

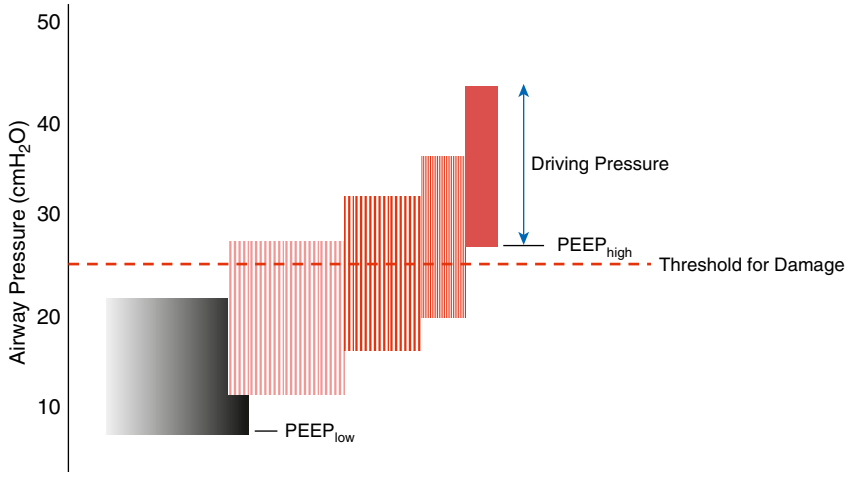

Figure 3. Influence of positive end-expiratory pressure (PEEP) on lung tissue strain for the same driving pressure (bidirectional arrow). Dashed red line represents the threshold pressure at which ventilator-induced lung injury begins. The width of each rectangle indicates the number of high-risk junctional 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.

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 VT 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*,

though quite detectable in acute lung injury, may simply be an expression of differential rates of regional expansion, with associated inflation patterns otherwise bearing an unclear relationship to VILI. In this context, it should be borne in mind that the baby lung expands faster than its healthy counterpart, simply because there are fewer air channels and lung units to accept the incoming gas charge. For the same V_T, the applied flow waveform conditions the velocity of expansion and the lung volume at which parenchymal pressure change is maximized.

Fourth, and very importantly, the pulmonary stress-bearing element is not a single (unified) supporting structure, but a network of extracellular fibrils that, arranged in parallel, cooperate to share the imposed strain and stress (38–40). This parallel interdependence is roughly analogous to the multiple strands that comprise a fraying rope (Figure E2). As weaker strands break in response to an imposed load, the remaining ones must take up the burden. Such parallel interdependence and progressive overloading of still-intact filamentous interstitial elements by "sequential dropout" helps explain the catastrophic breakdown and sudden alveolar flooding in response to an unchanging ventilation pattern that are observed experimentally after an initially quiescent period of maintained barrier integrity (Figure 4) (40, 41). Moreover, repeated high levels of traction on these junctional cell membranes may eventually overwhelm the energy-dependent adaptive process of internal lipid trafficking (42, 43). In summary, the small externally measured amount of unaccounted "absorbed" energy during the tidal cycle is concentrated and expended on a very limited number of vulnerable elements. These stresses to the complex interstitial structure increase in magnitude and accumulate as the duration of exposure proceeds (19).

Parenchymal strain threshold. It remains unclear whether all combinations of frequency, V_T, and pressure (flow-resistive pressure, driving pressure, and PEEP) that sum to the same power value are equally dangerous. It does stand to reason, however, that, as a precondition, a tidal strain *threshold* for damage initiation, however indistinct, must first be crossed at the site of potential injury (21, 44). Such threshold levels would almost certainly vary among species, being lower for small than for large animals (19). Furthermore, preventilation inflammation ("first hit") likely predisposes to VILI and lowers the level of Ptm that corresponds to the thresholds for damaging strain and/or energy delivery ("second hit") (40, 45, 46). Those thresholds may relate inversely to the increasing severity of lung disease. Consequently, any threshold for further injury is destined to fall as VILI progresses in the same animal or patient.

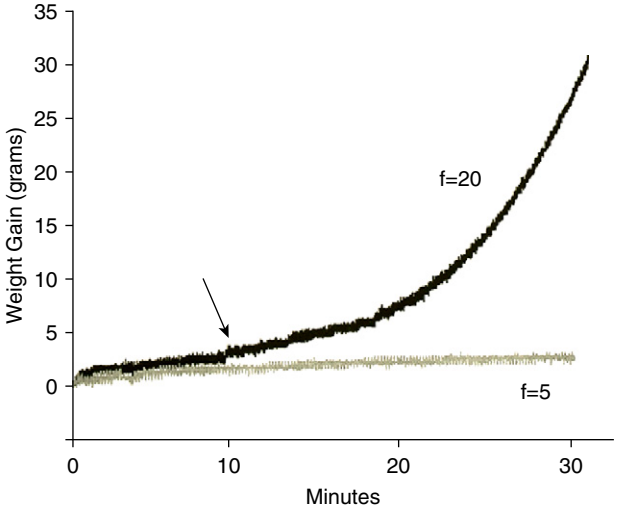

Figure 4. Catastrophic breakdown of the alveolar–capillary barrier. In this isolated, ventilated, and perfused rabbit lung, weight gain rapidly accelerates (arrow) after the first 10 minutes of ventilation at the higher ventilating frequency (f = 20 vs. 5 tidal cycles/min). Stress amplitude intensifies at the higher frequency with the alveolar dropout that occurs as alveoli progressively flood.

Implications for the ventilatory prescription. Returning to a practical level, the individual ventilatory parameters we currently select and/or monitor in practice each help comprise the total energy and stress imparted to the respiratory system. Certain key variables, such as V_T, PEEP, end-inspiratory plateau pressure, and driving pressure, have received well-deserved attention. Individually, however, these inherently *static* variables do not address dynamic strain, imparted energy, power, or unaccounted energy. Inescapably, *ergonomics* must be involved in the actual process of inflicting tissue damage, and energy expenditure requires joint consideration of both volume change and pressure (how these multiple, diverse mechanical contributors might theoretically interact to produce VILI, as well as the limits of ergonomics for explaining VILI risk, are proposed in the online supplement).

Bedside Measurement of Inflation Ergonomics

Geometrically, the energy trapezoid generated during constant flow inflation can be partitioned into three work-defining sectors: flow resistive (parallelogram), dynamic elastic (triangular), and static elastic (rectangular) (Figure 1) (31, 47). At end inspiration, the corresponding components of inflation pressure can be expressed as: $P_{tot} = \dot{V} \times R + V_T/C + PEEP_{tot}$. Some portion of the $\dot{V} \times R$–related energy is expended in viscoelastic pressure amplification, the V_T/C driving pressure expands the lung against elastance, and $PEEP_{tot}$ sets the baseline pressure from which inflation begins (Figure 5). The product of cycling frequency and the sum of these three pressure–volume areas is one expression of work per unit time (in this case, per minute), or power. The *total* inflation power that is actually experienced by the lung (for which the local Ptm equivalents of these components applies) is an attractive unifying variable that includes all contributors to the imposed workload. However, although energy load and power are necessary to inflict injury, they, in themselves, are not the culprits; exactly how total inflation power biophysically mediates the risk for tissue damage remains uncertain. One appealing possibility is that repeated high-energy cycles apply intolerable stresses and/or eventually cause materials failure within the extracellular matrix of the lung or

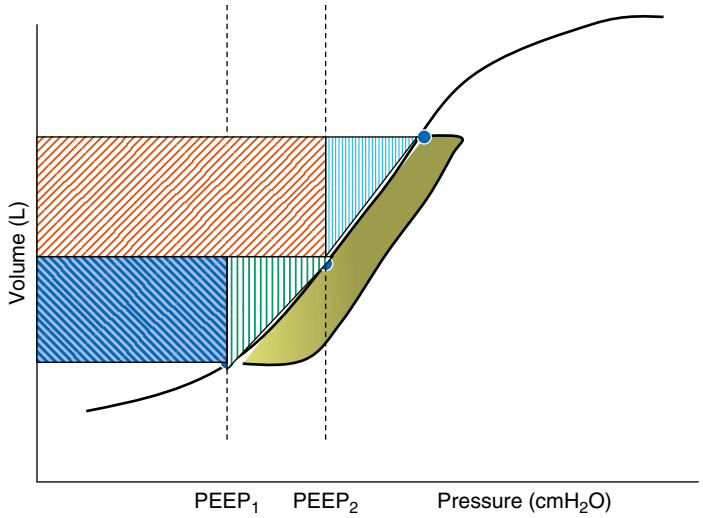

Figure 5. Tidal energy during constant flow. The rectangular crosshatched areas represent positive end-expiratory pressure (PEEP)-related inflation energy at two different levels of PEEP ($PEEP_1$ and $PEEP_2$). The triangular crosshatched areas indicate the corresponding "driving energy" components. The solid area corresponds to flow-resistive energy. The sigmoidal line indicates the pressure–volume curve of inflation for the respiratory system. Note that the total elastic energy increases at the higher PEEP level, despite the same driving pressure as at the lower PEEP.

disruption of plasma and alveolar–capillary membranes by imposing repeated excessive strains on its interdependent micro-structures. Overt wounding, or perhaps integrin-mediated inflammatory signaling, then results. To scale externally measured power to the reduced size of the baby lung, one suggested cofactor is to multiply measured power by the ratio of predicted to observed tidal compliance (33). This approach, though undoubtedly imprecise, assumes that compliance of the acutely injured lung reflects primarily the *number* of aerating lung units rather than their stiffness (48).

It should be noted that the sudden release of elastic energy, and perhaps microvascular surge (49), at the onset of expiration also applies tissue stresses that have damaging potential. In fact, animal experiments that retarded and controlled the rates of expiratory flow attenuated lung injury (50, 51). The relative importance of these expiratory components to the overall damage occurring with adverse ventilation patterns, however, has yet to be defined.

Roles of frequency, power, and exposure duration. For many years, and even to the present day, clinical emphasis regarding lung protection has centered on the mechanics of the monotonously applied breath (52). Plateau and driving pressures—incomplete slices of the inflation energy applied during each cycle—are now closely watched and regulated. It is self-evident, however, that repetition of the damage caused by one tidal cycle must exacerbate it; both wounding and inflammatory signaling require recurrence of such insults. Intensity of tidal energy input (energy applied to a parenchymal lung unit per unit time) is clearly important, but so is duration of noxious exposure, either because the cumulative number of intolerable strain cycles (not energy *per se*) determines the extent of "dropout," or because the injury load eventually wins out in the ongoing competition between damage and repair (53). In either case, micro-strains progressively increase and stress thresholds decline. Once underway, therefore, the process of VILI may proceed inexorably unless the injurious ventilation pattern is interrupted by imposing a less noxious one. If the damage threshold has been crossed for some jeopardized lung units, even prone positioning may simply redistribute and

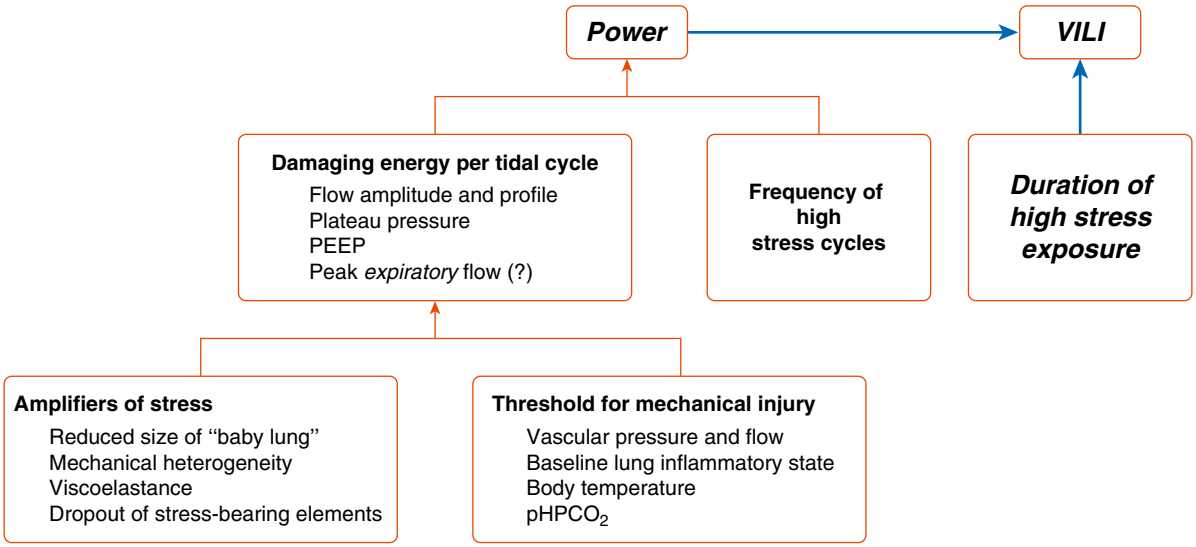

Figure 6. Proposed key contributors to ventilator-induced lung injury risk based on ergonomic principles. PEEP = positive end-expiratory pressure; VILI = ventilator-induced lung injury

delay the emergence of injury, whereas the eventual extent of VILI may prove similar (19, 54).

Conclusions

By applying incontestable principles of physics that relate energy to intolerable strain and damage, recent investigations appear to have made significant progress toward a deeper and more consistent understanding of the genesis of VILI (Figure 6). However, many important conceptual and research questions remain regarding how energy is channeled to cause tissue disruption and signal inflammation. Prominent among these are:

1. Can we confidently assign a direct causal role to VILI regarding mortality, and if so, what is the attributable risk? Relatively few patients die of lung failure, and the search for culprit circulating mediators that cause remote organ failure to date has been inconclusive.
2. How can ongoing VILI be separated from underlying acute lung disease (ARDS) in the clinical setting?
3. How can the clinician best assess and personalize the VILI thresholds for strain, straining intensity, and cumulative risk? Which are the pressure, flow, power, and exposure duration limits to be observed in the individual patient so as to avoid iatrogenic damage?
4. Which is the key damaging feature of excessive per-cycle inflation energy? Candidates may include total energy (including all three energy components), peak energy, driving energy, energy above threshold, and repeated excessive strain (static and dynamic).
5. Is tidal stress or stress intensity (e.g., ΔP, Pplat, and their products with f) an acceptable surrogate for damaging energy exposure?
6. Is damage caused by signal intensity (e.g., power with excessive tidal stress) or by the cumulative number of intolerable stress cycles, implying materials failure?
7. Is VILI the result of inflammatory signaling with preserved structural integrity or physical disruption (microwounding)?
8. What contributions, if any, do deflation characteristics and expiratory-phase energy release make to VILI? How can these be attenuated? ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1. Laffey JG, Kavanagh BP. Fifty years of research in ARDS: insight into acute respiratory distress syndrome. From models to patients. *Am J Respir Crit Care Med* 2017;196:18–28.
2. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A; Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–1308.
3. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, *et al*. Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015;372:747–755.
4. Guérin C, Reignier J, Richard JC. Prone positioning in the acute respiratory distress syndrome. *N Engl J Med* 2013;369:980–981.
5. Yoshida T, Amato MBP, Grieco DL, Chen L, Lima CAS, Roldan R, *et al*. Esophageal manometry and regional transpulmonary pressure in lung injury. *Am J Respir Crit Care Med* 2018;197:1018–1026.
6. Maeda Y, Fujino Y, Uchiyama A, Matsuura N, Mashimo T, Nishimura M. Effects of peak inspiratory flow on development of ventilator-induced lung injury in rabbits. *Anesthesiology* 2004;101:722–728.
7. Garcia CS, Abreu SC, Soares RM, Prota LF, Figueira RC, Morales MM, *et al*. Pulmonary morphofunctional effects of mechanical ventilation with high inspiratory air flow. *Crit Care Med* 2008;36:232–239.
8. Spieth PM, Silva PL, Garcia CS, Ornellas DS, Samary CS, Moraes L, *et al*. Modulation of stress versus time product during mechanical ventilation influences inflammation as well as alveolar epithelial and endothelial response in rats. *Anesthesiology* 2015;122:106–116.
9. Hotchkiss JR Jr, Blanch L, Murias G, Adams AB, Olson DA, Wangensteen OD, *et al*. Effects of decreased respiratory frequency on ventilator-induced lung injury. *Am J Respir Crit Care Med* 2000;161: 463–468.
10. Vaporidi K, Voloudakis G, Priniannakis G, Kondili E, Koutsopoulos A, Tsatsanis C, *et al*. Effects of respiratory rate on ventilator-induced lung injury at a constant Pa_{CO_2} in a mouse model of normal lung. *Crit Care Med* 2008;36:1277–1283.
11. Protti A, Andreis DT, Milesi M, Iapichino GE, Monti M, Comini B, *et al*. Lung anatomy, energy load, and ventilator-induced lung injury. *Intensive Care Med Exp* 2015;3:34.
12. Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med* 1998;157:294–323.
13. Marini JJ, Gattinoni L. Energetics and the root mechanical cause for ventilator-induced lung injury. *Anesthesiology* 2018;128:1062–1064.
14. Chiumello D, Carlesso E, Cadringher P, Caironi P, Valenza F, Polli F, *et al*. Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2008;178: 346–355.
15. Broccard AF, Shapiro RS, Schmitz LL, Ravenscraft SA, Marini JJ. Influence of prone position on the extent and distribution of lung injury in a high tidal volume oleic acid model of acute respiratory distress syndrome. *Crit Care Med* 1997;25:16–27.
16. Broccard A, Shapiro R, Schmitz L, Adams AB, Nahum A, Marini J. Prone positioning attenuates and redistributes ventilator-induced lung injury in dogs. *Crit Care Med* 2000;28:295–303.
17. Takeuchi M, Goddon S, Dolhnikoff M, Shimaoka M, Hess D, Amato MBP, *et al*. Set positive end-expiratory pressure during protective ventilation affects lung injury. *Anesthesiology* 2002;97:682–692.
18. Cressoni M, Gotti M, Chiurazzi C, Massari D, Algieri I, Amini M, *et al*. Mechanical power and development of ventilator-induced lung injury. *Anesthesiology* 2016;124:1100–1108.
19. Caironi P, Langer T, Carlesso E, Protti A, Gattinoni L. Time to generate ventilator-induced lung injury among mammals with healthy lungs: a unifying hypothesis. *Intensive Care Med* 2011;37:1913–1920.
20. Gattinoni L, Pesenti A. The concept of "baby lung". *Intensive Care Med* 2005;31:776–784.
21. Santos RS, Maia LA, Oliveira MV, Santos CL, Moraes L, Pinto EF, *et al*. Biologic impact of mechanical power at high and low tidal volumes in experimental mild acute respiratory distress syndrome. *Anesthesiology* 2018;128:1193–1206.
22. Serpa Neto A, Deliberato RO, Johnson AEW, Bos LD, Amorim P, Pereira SM, *et al*.; PROVE Network Investigators. Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. *Intensive Care Med* 2018;44:1914–1922.
23. Borgnakke C, Sontag RE. *Fundamentals of thermodynamics*,9th ed. Hoboken, NJ: John Wiley and Sons; 2017. p. 84.
24. Mauri T, Yoshida T, Bellani G, Goligher EC, Carteaux G, Rittayamai N, *et al*.; PLeUral pressure working Group (PLUG—Acute Respiratory Failure section of the European Society of Intensive Care Medicine). Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. *Intensive Care Med* 2016;42:1360–1373.
25. Faffe DS, Zin WA. Lung parenchymal mechanics in health and disease. *Physiol Rev* 2009;89:759–775.
26. Protti A, Maraffi T, Milesi M, Votta E, Santini A, Pugni P, *et al*. Role of strain rate in the pathogenesis of ventilator-induced lung edema. *Crit Care Med* 2016;44:e838–e845.

27. Felix NS, Samary CS, Cruz FF, Rocha NN, Fernandes MVS, Machado JA, *et al*. Gradually increasing tidal volume may mitigate experimental lung injury in rats. *Anesthesiology* 2019;130:767–777.
28. Kallet RH. Should PEEP titration be based on chest mechanics in patients with ARDS? *Respir Care* 2016;61:876–890.
29. Suter PM, Fairley HB, Isenberg MD. Effect of tidal volume and positive end-expiratory pressure on compliance during mechanical ventilation. *Chest* 1978;73:158–162.
30. Collino F, Rapetti F, Vasques F, Maiolo G, Tonetti T, Romitti F, *et al*. Positive end-expiratory pressure and mechanical power. *Anesthesiology* 2019;130:119–130.
31. Cressoni M, Chiumello D, Algieri I, Brioni M, Chiurazzi C, Colombo A, *et al*. Opening pressures and atelectrauma in acute respiratory distress syndrome. *Intensive Care Med* 2017;43:603–611.
32. Horie T, Hildebrandt J. Dependence of lung hysteresis area on tidal volume, duration of ventilation, and history. *J Appl Physiol* 1973;35: 596–600.
33. Marini JJ, Jaber S. Dynamic predictors of VILI risk: beyond the driving pressure. *Intensive Care Med* 2016;42:1597–1600.
34. Cressoni M, Chiurazzi C, Gotti M, Amini M, Brioni M, Algieri I, *et al*. Lung inhomogeneities and time course of ventilator-induced mechanical injuries. *Anesthesiology* 2015;123:618–627.
35. Cressoni M, Cadringher P, Chiurazzi C, Amini M, Gallazzi E, Marino A, *et al*. Lung inhomogeneity in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2014;189:149–158.
36. Mead J, Takishima T, Leith D. Stress distribution in lungs: a model of pulmonary elasticity. *J Appl Physiol* 1970;28:596–608.
37. Hubmayr RD, Kallet RH. Understanding pulmonary stress–strain relationships in severe ARDS and its implications for designing a safer approach to setting the ventilator. *Respir Care* 2018;63: 219–226.
38. Burgstaller G, Oehrle B, Gerckens M, White ES, Schiller HB, Eickelberg O. The instructive extracellular matrix of the lung: basic composition and alterations in chronic lung disease. *Eur Respir J* 2017;50: 1601805.
39. Hynes RO The extracellular matrix: not just pretty fibrils. *Science* 2009; 326:1216–1219.
40. Pelosi P, Rocco PR. Effects of mechanical ventilation on the extracellular matrix. *Intensive Care Med* 2008;34:631–639.
41. Lex D, Uhlig S. One-hit models of ventilator-induced lung injury: benign inflammation versus inflammation as a by-product. *Anesthesiology* 2017;126:909–922.
42. Tschumperlin DJ, Oswari J, Margulies AS. Deformation-induced injury of alveolar epithelial cells: effect of frequency, duration, and amplitude. *Am J Respir Crit Care Med* 2000;162:357–362.
43. Vlahakis NE, Hubmayr RD. Cellular stress failure in ventilator-injured lungs. *Am J Respir Crit Care Med* 2005;171:1328–1342.
44. Protti A, Cressoni M, Santini A, Langer T, Mietto C, Febres D, *et al*. Lung stress and strain during mechanical ventilation: any safe threshold? *Am J Respir Crit Care Med* 2011;183:1354–1362.
45. Hoegl S, Burns N, Angulo M, Francis D, Osborne CM, Mills TW, *et al*. Capturing the multifactorial nature of ARDS—"two-hit" approach to model murine acute lung injury. *Physiol Rep* 2018;6:e13648.
46. Piacentini E, López-Aguilar J, García-Martín C, Villagrá A, Saenz-Valiente A, Murias G, *et al*. Effects of vascular flow and PEEP in a multiple hit model of lung injury in isolated perfused rabbit lungs. *J Trauma* 2008;65:147–153.
47. Marini JJ, Rodriguez RM, Lamb V. Bedside estimation of the inspiratory work of breathing during mechanical ventilation. *Chest* 1986;89: 56–63.
48. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M. Pressure–volume curve of total respiratory system in acute respiratory failure: computed tomographic scan study. *Am Rev Respir Dis* 1987;136: 730–736.
49. Katira BH, Engelberts D, Otulakowski G, Giesinger RE, Yoshida T, Post M, *et al*. Abrupt deflation after sustained inflation causes lung injury. *Am J Respir Crit Care Med* 2018;198:1165–1176.
50. Goebel U, Haberstroh J, Foerster K, Dassow C, Priebe HJ, Guttmann J, *et al*. Flow-controlled expiration: a novel ventilation mode to attenuate experimental porcine lung injury. *Br J Anaesth* 2014;113: 474–483.
51. Borgmann S, Schmidt J, Goebel U, Haberstroh J, Guttmann J, Schumann S. Dorsal recruitment with flow-controlled expiration (FLEX): an experimental study in mechanically ventilated lung-healthy and lung-injured pigs. *Crit Care* 2018;22:245.
52. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med* 2013;369:2126–2136.
53. Dreyfuss D, Soler P, Saumon G. Spontaneous resolution of pulmonary edema caused by short periods of cyclic overinflation. *J Appl Physiol (1985)* 1992;72:2081–2089.
54. Valenza F, Guglielmi M, Maffioletti M, Tedesco C, Maccagni P, Fossali T, *et al*. Prone position delays the progression of ventilator-induced lung injury in rats: does lung strain distribution play a role? *Crit Care Med* 2005;33:361–367.