Energetics and the Root Mechanical Cause for Ventilator-induced Lung Injury

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SINCE the discovery that acute lung injury could be worsened by unwise choices for mechanical ventilation, investigators have sought the mechanisms and clinical parameters that initiate such damage (ventilator-induced lung injury).[1] Our understanding has progressed from simply confining tidal volumes to fixed guideline values to limiting the plateau and driving pressures of the tidal cycle. But damage requires energy and ventilator-induced lung injury is not caused by single deep inflations. Recent attention has logically (if somewhat belatedly) turned toward better defining the place of ventilation frequency and cumulative energy load delivered to the lung over the span of multiple cycles.[2] Such loading has been described as "power," a variable related to exposure intensity that quantifies energy imparted per minute and includes all mechanical factors shown experimentally to influence ventilator-induced lung injury. The root mechanical cause that initiates ventilator-induced lung injury at the tissue level, however, remains elusive. Laboratory work reported by Santos *et al.* in this issue of Anesthesiology[3] helps enlighten by demonstrating that tidal pressures and power have overlapping influence on development of biomarker-detected inflammation and histologic changes.

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Fundamental concepts of physics must be applied at the micro level to put these observations into perspective. As an analogy to electricity, pressure corresponds to voltage, flow to amperage, and their product, the *within cycle* inflation power, the wattage. Over the span of multiple cycles occurring within a fixed time period, cumulative energy load ("power," as defined previously[3]) is analogous to the kilowatt-hour. Although actual tissue tensions cannot be directly measured, lung stresses relate loosely to transpulmonary pressure. Strain is the stress-related elongation of structural microelements from their relaxed states.[4] Because compliance more closely parallels the number of aeratable lung units than their individual recoil properties, the stress increment that occurs during tidal inflation is reflected in the driving pressure—plateau minus positive end-expiratory pressure (PEEP), numerically equivalent to the quotient of tidal volume and respiratory system compliance.[5] Transpulmonary driving pressure may be the most important measurable variable of the individual cycle that determines the propensity for lung injury. However, its associated risk is conditioned by the pressure range over which it operates, *i.e.*, there exists a pressure "threshold" for causing damage.[6] Peak tissue stresses are encountered at end inspiration and early expiration. Although seldom considered, abrupt release of stored energy at the onset of exhalation accentuates viscoelastic drag, adding to potentially damaging tissue distortion.

Static variables of the individual tidal cycle such as PEEP, plateau, and driving pressures cannot of themselves fully explain propensity to injure. Forces in static balance do not expend damaging energy. To perform mechanical work, unbalanced forces must move the object in the direction of their net action. Therefore, it is not PEEP, plateau, or even the difference between these two static tidal variables that counts, but the dynamic process of moving from one to the other.

This kinetic mechanical energy of inflation can deform and damage, dissipate as heat against friction, or transition to stored potential energy. As a tightly conserved "zero sum" quantity, tidal mechanical energy must be accounted for among these categories with no overlaps. Total machine energy imparted to the respiratory system during a breath is the product of the applied airway pressure and resulting volume change—the area of the corresponding airway pressure volume plot (fig. 1). Energy input concentrates in inverse proportion to the capacity of the "baby lung" to receive it.

The three pressure components influencing energy are resistive, tidal elastic (driving pressure), and PEEP. Resistive energy spent in moving gas and deforming tissue against frictional forces is not stored, but converts to heat. Some fraction of the relatively high resistive energy losses that occur

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within parenchymal tissues in acute respiratory distress syndrome have potential to deform, inflame, and injure. Faster flow rates increase resistive losses and viscoelastic drag in the parenchyma, augmenting stress and strain.[4,7,8] Most elastic inflation energy associated with PEEP transitions to its potential form and then dissipates during exhalation in driving gas flow through the airways, connecting circuitry, and exhalation valve, as well as in rearranging tissue elements. The energy component associated with driving pressure is the primary dynamic stretching force and seems the most likely of the three energy elements to cause damage.[9] Raising PEEP "ups the ante" for driving pressure, bringing the system onto a higher global strain platform, upon which the driving pressure can cross the critical threshold for damage. Much of the stretching energy applied against PEEP and driving pressure during inflation is temporarily stored and then discharged in driving expiratory flow, but a portion remains unaccounted. Arguably, this "hysteretic" elastic energy relates most directly to tissue damage.

During the individual tidal cycle, only small amounts of mechanical energy are applied and retained within the lung. It stands to reason that to contribute to damage, tidal energy must concentrate on a very small mass of stress-bearing tissue and its effect accumulate and intensify with successive cycles. Amplifiers of the stress experienced in the heterogeneous tissues of acute respiratory distress syndrome include stress risers at boundaries of closed and open tissue, viscoelastic drag, and progressive loading of intact stress-bearing microelements as weaker ones fail.[4,10] It is this last mechanism that helps explain why ventilating frequency and power may be crucial to initiating ventilator-induced lung injury. Once dynamic tidal stress exceeds a critical level, weak microelements break down and wounding begins. The "progressive loading/sequential microelement failure" explanation is supported by experimental work demonstrating that once initiated, damage accelerates catastrophically.[11] When tidal strain is high but subcritical for all but a minor proportion of units, injury may eventually occur, but be delayed[12] or even quickly repaired.[13] Release of inflammatory biomarkers may be an early signal of potential distress, whereas overt damage requires many cycles.

It is against this background that the work of Santos *et al.* makes its significant contribution.[3] The pattern of histologic and inflammatory biomarker changes observed in this study suggests that the most vulnerable microelements reside in the interstitium, specifically at the basement membrane and ground substance of the extracellular matrix.[3,14] At low levels of driving pressure, strain, and per cycle energy input, relatively little histologic injury was observed at either of two power levels achieved only by increasing frequency. At the higher end of the "acceptable" driving pressure range, evidence of intolerance appeared at those same power levels.

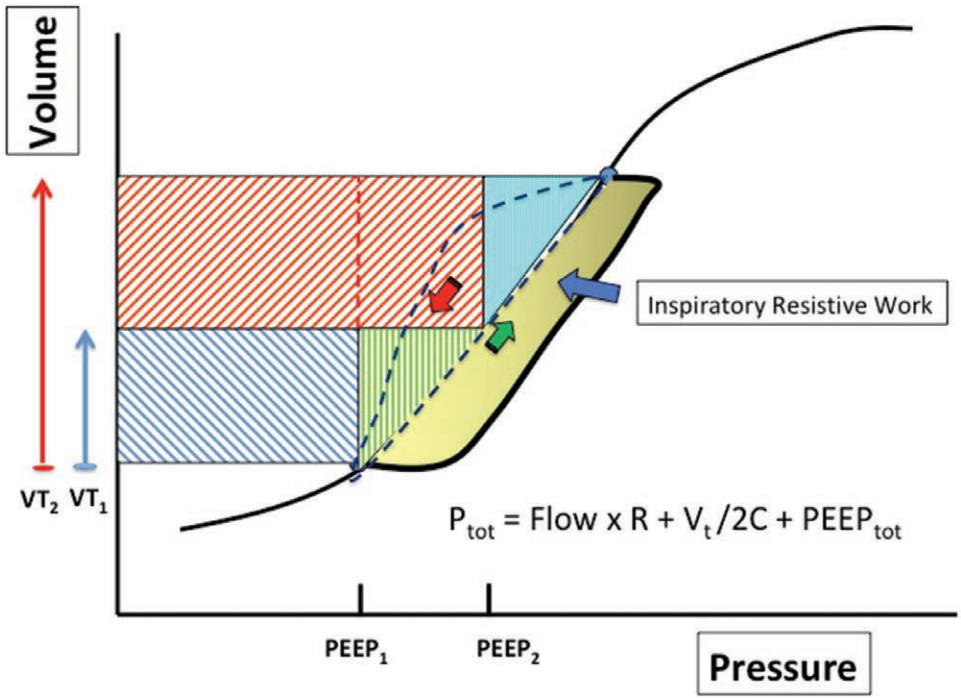

Fig. 1. Machine-delivered energy components for one passive inflation cycle. Inflation is depicted for two tidal volumes (VT_1, VT_2) and two positive end-expiratory pressure (PEEP) levels ($PEEP_1$, $PEEP_2$). Raising PEEP increases the energy input with the same tidal volume (*crosshatched blue* and *red rectangular areas* correspond to PEEP-associated energy components). At the same PEEP, doubling tidal volume from VT_1 to VT_2 disproportionately increases dynamic work in comparison to two smaller tidal volumes (*triangular areas*). *Loop area* enclosed by *dashed blue line* represents the hysteresis-related energy lost during deflation from VT_2.

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Such data beg the question: is the proximate ventilator-induced lung injury culprit cumulative energy load itself, energy load in excess of a damaging threshold, or the repetition of supra-threshold tidal strains with serial failure of vulnerable stress bearing elements? To the extent that they show that it is not simply "power," but how it is applied that matters, the results of Santos *et al.* might favor the third explanation.[3]

Potential clinical messages from this elegant bench research are clearly stated and intuitively convincing: keep tidal transpulmonary plateau and driving pressures well within safe boundaries, but also restrain the dose of energy exposure by reducing frequency and minute ventilation. To those we might logically add the admonition to moderate inspiratory—and perhaps expiratory[15]—peak flows and to avoid elevating tidal power by unnecessarily high PEEP. Clinical decisions are sometimes best guided by basic principles of biophysics and micromechanics.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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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. Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, Protti A, Gotti M, Chiurazzi C, Carlesso E, Chiumello D, Quintel M: Ventilator-related causes of lung injury: The mechanical power. Intensive Care Med 2016; 42:1567–75
3. Santos RS, Maia LA, Oliveira MV, Santos CL, Moraes L, Pinto EF, Samary CDS, Machado JA, Carvalho AC, Fernandes MVS, Martins V, Capelozzi VL, Morales MM, Koch T, Gama de Abreu M, Pelosi P, Silva PL, Rocco PRM: Biologic impact of mechanical power at high and low tidal volumes in experimental mild acute respiratory distress syndrome. Anesthesiology 2018; 128:1193–206
4. Faffe DS, Zin WA: Lung parenchymal mechanics in health and disease. Physiol Rev 2009; 89:759–75
5. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, Richard JC, Carvalho CR, Brower RG: Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015; 372:747–55
6. Protti A, Cressoni M, Santini A, Langer T, Mietto C, Febres D, Chierichetti M, Coppola S, Conte G, Gatti S, Leopardi O, Masson S, Lombardi L, Lazzerini M, Rampoldi E, Cadringher P, Gattinoni L: Lung stress and strain during mechanical ventilation: any safe threshold? Am J Respir Crit Care Med 2011; 183:1354–62
7. 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; 101:722–8
8. Protti A, Maraffi T, Milesi M, Votta E, Santini A, Pugni P, Andreis DT, Nicosia F, Zannin E, Gatti S, Vaira V, Ferrero S, Gattinoni L: Role of strain rate in the pathogenesis of ventilator-induced lung edema. Crit Care Med 2016; 44:e838–45
9. Marini JJ, Jaber S: Dynamic predictors of VILI risk: Beyond the driving pressure. Intensive Care Med 2016; 42:1597–600
10. Marini JJ: Dissipation of energy during the respiratory cycle: Conditional importance of ergotrauma to structural lung damage. Curr Opin Crit Care 2018; 24:16–22
11. Cressoni M, Chiurazzi C, Gotti M, Amini M, Brioni M, Algieri I, Cammaroto A, Rovati C, Massari D, di Castiglione CB, Nikolla K, Montaruli C, Lazzerini M, Dondossola D, Colombo A, Gatti S, Valerio V, Gagliano N, Carlesso E, Gattinoni L: Lung inhomogeneities and time course of ventilator-induced mechanical injuries. Anesthesiology 2015; 123:618–27
12. Valenza F, Guglielmi M, Maffioletti M, Tedesco C, Maccagni P, Fossali T, Aletti G, Porro GA, Irace M, Carlesso E, Carboni N, Lazzerini M, Gattinoni L: Prone position delays the progression of ventilator-induced lung injury in rats: Does lung strain distribution play a role? Crit Care Med 2005; 33:361–7
13. Dreyfuss D, Soler P, Saumon G: Spontaneous resolution of pulmonary edema caused by short periods of cyclic overinflation. J Appl Physiol (1985) 1992; 72:2081–9
14. Pelosi P, Rocco PR: Effects of mechanical ventilation on the extracellular matrix. Intensive Care Med 2008; 34:631–9
15. Goebel U, Haberstroh J, Foerster K, Dassow C, Priebe HJ, Guttmann J, Schumann S: Flow-controlled expiration: A novel ventilation mode to attenuate experimental porcine lung injury. Br J Anaesth 2014; 113:474–83

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