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Straining to Make Mechanical Ventilation Safe and Simple

It is remarkable how many research studies and manuscripts are devoted to the topic of ventilation-induced lung injury (VILI) decades after its initial description (1). This tells us that the topic is important, complex, and on some level still poorly understood. This is not to say that little has been learned during the ensuing four decades. Quite to the contrary, the discovery has widened the horizons of clinicians, physiologists, epidemiologists, engineers, biophysicists, immunologists, geneticists, and molecular biologists, and has fostered fruitful collaborations across seemingly divergent fields of biomedical science. While the motivations and perceptions of important knowledge gaps may vary among these disciplines, to a clinician the all-important question is this: “How do I turn the knobs on the ventilator to avoid this catastrophic iatrogenic complication?” For a while it seemed as if the ARDS-Network study on the efficacy of low-tidal-volume mechanical ventilation (the ARMA trial) had taught clinicians all they needed to know (2). However, uncertainties about “best PEEP” (positive end-expiratory pressure), the appropriate plateau pressure target (Pplat), value of recruitment maneuvers, and the efficacy of closed loop modes and high-frequency oscillation (to name only a few) have kept VILI at the forefront of mechanical ventilation-motivated clinical and translational research.

In this issue of the *Journal*, Protti and colleagues (pp. 1354–1367) report on the susceptibility of healthy porcine lungs to injury caused by mechanical ventilation with large tidal volumes (V_T) and conclude that lung damage only occurs when a strain greater than 1.5 to 2.0 is reached/overcome (3). Strain was defined as the fractional volume change between functional residual capacity (FRC) and the thoracic gas volume at end-inflation. Since none of the animals was ventilated with PEEP, strain equaled V_T /FRC. The nonlinear relationship between strain and subsequent injury suggested a threshold phenomenon with a large range of apparently “safe” V_T values. Injurious strains resulted in end-inspiratory lung volumes that fell above the linear portion of the respiratory system pressure–volume curve and hence were associated with disproportionately large parenchymal stresses. In that respect, the observations are entirely in line with the stress index hypothesis, which states that the preferred volume range over which lungs of patients with respiratory failure should be

ventilated is defined by the linear portion of the respiratory system pressure–volume curve (4, 5). Protti and colleagues’ findings are of particular interest not only because of their clinical implications, but also because the experimental approach was meticulous, the experiments were performed over many hours, and the care of the animals was comparable to that provided to anesthetized humans. It is of note that many animals that ultimately died from “pulmonary stress failure” seemed uninjured for long periods of time. However, once changes in respiratory system impedance became manifest, the animals decompensated rapidly. Consistent with the proposed pathogenesis, during volume preset ventilation the dropout of lung units increases the strain on the remaining open ones, setting in motion a “cascade of falling dominos” that culminates in organ failure.

Since Protti and colleagues place tissue strain at the center of the VILI pathogenesis, it might be useful to consider strain-dependent injury mechanisms and to relate strain to the more familiar ventilator parameters PEEP, V_r , and Pplat. A strain is a normalized measure of deformation representing the displacement between particles in the body relative to a reference length. For the purpose of this discussion one can think of strain as the fractional length change of a lung tissue element relative to its initial length. If the lung were an ideal elastic material, one in which energy is stored without dampening losses, its “injury threshold” would be defined by a single length (or volume) above which the material begins to yield (is permanently deformed). The injury threshold would not be sensitive to the rate of elongation (strain rate), nor would the initial length have any influence on the probability of tissue failure. However, like all other biological materials, the elastic properties of the lung are anything but “ideal,” insofar as global stress and tissue micro-architecture are sensitive to length history and time (6). Consequently, at a given end-inspiratory volume, transpulmonary pressure (a measure of lung parenchymal stress) varies with the rate of lung inflation as well as the initial or starting volume (7, 8). On a smaller scale, yet one that is relevant from a mechanotransduction and hence tissue injury perspective, rate and amplitude of deformation exert profound effects on cytoskeletal fluidity and hence cytoskeletal architecture (9, 10), on the hydration state of ground substance (11, 12), and consequently on a host of enzymes such as metalloproteinases, which are involved in inflammatory signaling and tissue remodeling responses (13).

Applying these observations from greatly reduced systems to the topic at hand leads to the prediction that putative strain injury thresholds must vary with flow, respiratory rate, and most importantly with end-expiratory lung volume. In fact, the classic experiments of Webb and Tierney, which underscored the lung-protective effects of PEEP, are entirely consistent with this prediction (14). Mechanical ventilation produced much less injury in anesthetized rats, when FRC was raised with PEEP, even though the lungs were inflated to similar end-inspiratory volumes. Lung-protective effects of PEEP (and consequently of increased FRC) are commonly attributed to prevention of so-called "atelect-trauma" resulting from injurious interfacial stresses (15, 16). However, given the effects of strain-amplitude on cell and tissue mechanics, it is quite possible that reductions in V_T *per se*, irrespective of the average volume about which lungs are oscillated, account for lung protection (14). Hager and colleagues' *post hoc* analysis of ARMA data, which suggested benefit of low-tidal-volume ventilation across all Pplat quartiles, may be interpreted in that context (17).

In summary, then, it seems inescapable that the risk of lung damage from mechanical ventilation, even when applied to healthy lungs, is multifactorial and cannot be linked to a single variable. As far as the strain-injury threshold is concerned it is conditional on PEEP and probably on flow and rate settings as well. This is not to distract from the conceptual advantage of quantifying lung deformation in terms of strain as opposed to V_T normalized by predicted body weight (PBW), because strain accounts for disease-related unit loss (18). Protti and colleagues appropriately caution against the uncritical application of a porcine model-derived strain threshold to patient care, but their message is unmistakable: a normal lung can tolerate fairly large tidal volumes for fairly long periods of time!

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Nitrogen Balance in the Ecosystem of the Cystic Fibrosis Lung

In this issue of the *Journal*, Grasemann and coworkers (pp. 1363–1368) report that levels of asymmetric dimethyl arginine (ADMA) are increased in cystic fibrosis (CF) airways (1). ADMA inhibits cellular arginine uptake and nitric oxide (NO) synthase (NOS) activity. Levels of ADMA decrease during antibiotic therapy in association with improved lung function. This observation may prove to have therapeutic relevance. However, it is

important to note that increased ADMA in CF airways may be both beneficial (through inhibition of NO production) and harmful (through inhibition of S-nitrosothiol production).

Nitric oxide in the concentrations measured in exhaled air (parts per billion) is generally irrelevant to normal lung physiology (2). However, NO can be relevant to lung pathology. It interacts with oxygen, superoxide, and other molecules to injure airway epithelium. Products of these reactions, such as nitrous acid and peroxynitrous acid, are potent cytotoxins downstream of inducible NOS activity (3).

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