Published in final edited form as:

Crit Care Med. 2014 July ; 42(7): 1745–1746. doi:10.1097/CCM.0000000000000383.

Regional Lung Strain and the Metabolic Signature of Injury

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Keywords

Strain; Regional Ventilation; Lung Injury

Most institutions have adopted the ventilator management protocol, which proved efficacious in the low tidal volume trial of the ARDS network, as the standard of care for patients with the Acute Respiratory Distress Syndrome (1). The centerpiece of this protocol is the scaling of tidal volume to predicted body weight as opposed to actual body weight and the scaling of positive end-expired pressure (PEEP) to the degree of gas exchange impairment. One of the reasons why the ARDS-NET protocol enjoys widespread acceptance is its ease of application. The required scaling factors, i.e. height, gender, the partial pressure of arterial oxygen (PaO₂) and the Fractional Concentration of Inspired Oxygen (FIO₂), are readily available at the bedside and require no knowledge of underlying physiologic mechanisms. Therefore, simply equipping each mechanical ventilator with a laminated card listing height, gender and the corresponding recommended tidal volume proved to be an effective means of ensuring provider adherence with the standard of care and in one institution led to a substantial decrease in the incidence of hospital acquired ARDS (2).

Since the publication of the low tidal volume trial in 2000, various aspects of the ARDS-NET approach to mechanical ventilation have been challenged. These challenges tend to be rooted in physiologic/mechanistic hypotheses about patient/ventilator interactions and their effects on putative biomarkers of lung injury and repair. Proponents of alternative ventilator management approaches have argued that the guidelines used in the low tidal volume ARDS-NET protocol are too insensitive to capture patient specific differences in respiratory mechanics and their associated risks for biotrauma (3). Concerns have centered on patient specific differences in the number of recruitable lung units, in the physical properties of the alveolar space filling material, and in the lung restrictive effects of the chest wall, all of which have bearing on the global and regional distributions of parenchymal stress and strain (4–7). Stress and strain ultimately define the physical input to which the organism responds.

Stress is a physical quantity that expresses the internal forces that neighboring particles of a continuous material exert on each other and like pressure is expressed in units of force per

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Copyright form disclosures: Dr. Hubmayr consulted for Philips Medica, served as a board member for Respithera, is employed by Mayo Clinic, lectured for ATS, and received support for article research from NIH (RO1 63178). His institution received grant support from NIH.

area. In a uniformly expanded homogenous parenchymal network the stress at any point in the parenchyma equals transpulmonary pressure (8). Strain, in turn, typically refers to the fractional length change of an elastic material relative to its unstressed state. The constant of proportionality relating stress and strain defines the stiffness of the material and for the lung parenchyma is typically expressed as tissue compliance. Since lung and chest wall are deformed by gravity and are constrained to assume identical shapes, parenchymal stress and strain can vary considerably between regions of the mammalian lung, accounting for the topographical heterogeneity in regional ventilation and ventilation/perfusion matching (9).

Tidal volume and by inference lung parenchymal strain are without a doubt the single most significant risk factors of mechanical ventilation associated lung injury (7, 10). Since both strain and the manifestations of injury are known to be regionally distributed, Wellman et al. sought to define the spatial and temporal correlations between strain and tissue metabolic activity using Positron Emission Tomography (PET) in an ovine model of high tidal ventilation injury (11). As postulated tissue strain and local changes in glucose uptake and metabolism, surrogate measures of local inflammation, were closely correlated in space and time. Histologic images of tissue sections revealed mild neutrophilic inflammation, but showed little to no interstitial or alveolar edema. Consistent with hypotheses concerning the interactions between diverse stressors (“hits”), the pro-inflammatory mechano-transduction response was particularly pronounced in animals that had been “primed” with endotoxin prior to the initiation of mechanical ventilation. Of note, sheep that were ventilated with small lung protective tidal volumes and PEEP adjusted to generate end-inspiratory airway pressures similar to the high tidal volume groups, had relatively uniform regional lung strains and showed no evidence of increased tissue metabolic activity.

Wellman’s observations emphasize that tidal volume dependent biophysical lung injury mechanisms operate on a small scale and that they are central to the pathogenesis of ventilator associated lung injury. Wellman et al. expressed regional tidal volumes as strain, which corresponds to the term “ventilation per unit lung volume” in the older regional ventilation literature. Consistent with previous studies, PET imaging in supine sheep revealed a large vertical gradient in alveolar volumes and parenchymal strain at Functional Residual Capacity (FRC, the volume at zero alveolar pressure). The heterogeneity in volume and strain is most pronounced at FRC, because the lung is soft and therefore easily distorted by gravitational forces and thoracic shape matching constraints (9, 12). For this reason a dependent region with a very low alveolar FRC may appear preferentially strained during breathing even though a non-dependent region with a much larger alveolar FRC might have received the same volume of inspired gas. Moreover, the two regions may not have experienced identical stresses, in part because they the two regions differ with respect to pre-stress (the local transpulmonary pressure at FRC) and because the stress/strain relationship of lung parenchyma is non-linear over the physiologic volume range. These observations and arguments are intended as cautionary note against the assumption that there is a single strain threshold, which forecasts the risk of biotrauma. This uncertainty exists, because in the intact chest local deformations cannot be referenced to the unstressed dimensions of the tissue network. Referencing ventilation to alveolar volume at total lung capacity (TLC) could in theory minimize the confounding influence of lung distortion, because the maximally stressed lung is uniformly expanded at TLC.

The uncertainty about the existence of a unique strain-injury threshold begs the question how macro-strain at the level of a single acinus relates to the known cell and molecular injury mechanisms thought to operate in affected lungs (13). Large alveolar volume excursions are certain to stress surfactant kinetics and may thereby mediate local flooding, tissue distortion and generate interfacial stress of sufficient magnitude to wound adjacent airway and alveolar epithelial cells. Large parenchymal deformations are also certain to raise the tensile stress of alveolar walls, of the connective tissue matrix and of cell-cell and cell-matrix contacts and can thereby trigger the release of bioactive molecules. In that context it should be noted that inflation of the lungs to high pressures and volumes activated pro-inflammatory mechano-transduction responses only when accompanied by large tissue strains. This is consistent with numerous prior reports on the lung protective effects of PEEP dating back as far as 1974 to the classic experiments by Webb and Tierney (14).

One of the hallmarks of ARDS in humans is the apparent flooding and collapse of dependent diaphragm apposed lung regions. The cyclic recruitment and derecruitment of neighboring unstable units is considered a major contributing factor in the evolution of the biotrauma syndrome. Of note, large tidal ventilation when limited to several hours in otherwise normal sheep was not associated with appreciable accumulation of interstitial or alveolar edema. It is therefore not entirely clear, if so-called opening and collapse contributed to the injury phenotype described by Wellman et al. For the same reason we can only speculate if the mechanism by which strain activated a pro-inflammatory metabolic response was identical across all regions of the lung.

In conclusion, Wellman et al.'s observations draw attention to tissue strain as a critical activator of metabolic lung injury pathways. They show that dependent regions of the lung, which in the full blown syndrome appear immobilized by an inflammatory exudate, may well have been subject to strain injury. They validate hypotheses, which favor PEEP and proning as lung protective interventions, because both reduce the topographical variability in lung strain, and remind us that seemingly safe global tidal volumes may at times be associated with unsafe regional parenchymal deformations.

Acknowledgments

Funding Number: Funded by NIH R01 HL63178

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