Commentary

Alveolar microstrain and the dark side of the lung

Richard A Oeckler and Rolf D Hubmayr

Thoracic Disease Research Unit, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA

Corresponding author: Rolf D Hubmayr, rhubmayr@mayo.edu

Published: 12 November 2007
This article is online at http://ccforum.com/content/11/6/177

Critical Care 2007, **11:**177 (doi:10.1186/cc6160)

See related research by Pavone *et al*., http://ccforum.com/content/11/5/R104

Abstract

Mechanical ventilation associated lung injury (VALI) negatively impacts the outcomes of critically ill patients. Research during the past two decades has led to a better understanding of key physiologic mechanisms of injury, yet uncertainty over the topographical distribution of these mechanisms continues to fuel controversies over "best ventilation practice" in injured lungs. In this issue Pavone and colleagues have explored the temporal and spatial evolution of VALI in an elegant use of intravital microscopy. Their findings reinforce the notion that regions which receive most of the inspired gas, in Pavone's case the non-dependent lung of a rat supported in the lateral decubitus posture, are particularly susceptible to injury. However, the inability to measure tissue strain remote from the pleura keeps important questions about small scale intra-acinar stress and strain distributions unanswered.

Mechanical Ventilation Associated Lung Injury (VALI) is a prevalent complication of supportive care and greatly impacts outcomes of critically ill patients [1,2]. Research during the past two decades has identified deforming stress as a major determinant of "biotrauma"[3], and has drawn attention to four interrelated lung injury mechanisms: regional over-expansion caused by the application of a local stress or pressure that forces cells and tissues to assume shapes and dimensions they normally would not during unassisted breathing; so-called "low volume injury" associated with the repeated recruitment and de-recruitment of unstable lung units, causing the abrasion of the epithelial airspace lining by interfacial tension; the inactivation of surfactant triggered by large alveolar surface area oscillations, that stress surfactant adsorption and desorption kinetics and are associated with surfactant aggregate conversion; and interdependence mechanisms that raise cell and tissue shear stress between neighboring structures with differing mechanical properties.[4] However, the many degrees of freedom in ventilator settings and uncertainty about the topographical distribution of mechanical properties in injured lungs continue to fuel controversies about best positive end expiratory pressure (PEEP)" and safe tidal volumes[5].

In this issue of Critical Care, Pavone and colleagues draw attention to the spatial and temporal evolution of VALI, as inferred from intravital microscopic recordings of alveolar microstrains in mechanically ventilated rats[6]. Microstrains were computed from the fractional area changes of the apical projections of subpleural alveoli onto the pleural surface. Increases in microstrain from baseline were interpreted as measures of alveolar instability and hence, manifestations of injury. Using the lateral decubitus posture to compare the evolution of VALI between dependent and nondependent lung regions, Pavone and colleagues conclude that instability is first manifest in non-dependent lung, that PEEP prevents alveolar instability, but does not reduce lung water and that alveolar instability, as defined, does not correlate with measures of pulmonary gas exchange.

The results of this elegant study reinforce the idea that regions of the lung, which receive a large fraction of inspired gas, aerated non-dependent lung in this instance, are particularly vulnerable to VALI. This form of injury is often attributed to hyperinflation. However, the term hyperinflation does not describe a specific injury mechanism, because the topographical distributions of regional tidal volumes (local strain referenced to end-expiration) and regional end-inspiratory transpulmonary pressure (local peak stress) need not be correlated[7]. In other words, the debate as to whether tidal volume and plateau airway pressure are independent or related predictors/risk factors of VALI pertains to regional lung mechanics and questions about the topographical distribution of parenchymal stress and strain as well.

Guided by the assumption that so-called alveolar opening and closure is the prevalent injury mechanism, Pavone and

PEEP = positive end expiratory pressure; VALI = mechanical ventilation associated lung injury.

colleagues equate the presence of alveolar deformation in the pleural plane with alveolar instability and injury. The authors defend this assumption with the observation that in the absence of injurious stress, the apices of subpleural alveoli undergo little to no apparent deformation, so that when they do, local stress must have reached injurious levels. It is theoretically possible to increase lung volume without changing alveolar dimensions, because acinar volume can be partitioned into alveolar volume and alveolar duct volume. This implies added degrees of freedom in microstructural configuration, which are ultimately governed by local geometry and surface tension[8]. However, it is highly unlikely that an unconstrained normal acinus would increase volume without increasing alveolar size and surface area, because the area strain of the pleural surface, to which subpleural alveolar walls are anchored, must scale with tidal volume to the 2/3 power[9,10]. Moreover, even in the presence of shear stress, correlations between macrostrain (for example, change in distance between pleural markers) and subpleural microstrain (for example, derived from diffuse light scattering or morphometric estimates of tissue architecture) are excellent[11]. In light of these observations it must be concluded that Pavone's index of alveolar instability is biased by the constraint to keep the local pleura in apposition with the microscope objective.

While these arguments are critical for interpreting pleural projection images, and speak to the question how a normal acinus deforms during a breath, there are nevertheless important lessons to be learned from Pavone's observations. There is no question that the choice of ventilator settings produced lung injury and that increases in the local area strain must have been driven by an increase in local stress. The movies also clearly show a progressive loss of subpleural air/liquid interfaces indicating local alveolar flooding or collapse, which presumably coincided with an increase in microstrains of aerated and therefore still observable subpleural alveoli. Interestingly, these changes were not accompanied by a decrease in overall tidal volume or changes in peak airway pressure, which is remarkable in light of unit dropout and the use of inflation pressures which should have expanded open units to their total lung capacity all along.

Could the constraint placed on the pleural surface by the imaging system have influenced the local tissue response? Did the changes in alveolar microstrain of the non-dependent lung merely reflect derecruitment of the dependent lung[12]? Are interdependence forces truly large enough to strain pleural and/or alveolar walls beyond their dimensions at normal total lung capacity? Do injury and the acompanying changes in barrier properties, lung water and surfactant function alter the strain distributions between alveoli and alveolar ducts? To answer these questions one would have to access the dark side of the lung, in other words, the lung interior, and define the architecture of parenchyma that is not anchored to the pleural surface. This is currently difficult in living tissue as even state of the art confocal imaging, while capable of illuminating deep below the pleural surface, cannot correct image distortions caused by air/liquid interfaces without *a priori* knowledge of local geometry. Until we overcome such limitations, tests of mechanistic hypothesis concerning the spatial and temporal evolutions of VALI will suffer from a blind spot.

Competing interests

Grant support by the National Institute of Health and service on a Data Safety and Monitoring Board for Novartis

References:

1. Houston P: **An approach to ventilation in acute respiratory distress syndrome.** *Can J Surg* 2000, **43:**263-268.
2. Yilmaz M, Keegan MT, Iscimen R, Afessa B, Buck CF, Hubmayr RD, Gajic O: **Toward the prevention of acute lung injury: protocol-guided limitation of large tidal volume ventilation and inappropriate transfusion.** *Crit Care Med* 2007, **35:**1660-1666; quiz 1667.
3. Tremblay LN, Slutsky AS: **Ventilator-induced injury: from barotrauma to biotrauma.** *Proc Assoc Am Physicians* 1998, **110:** 482-488.
4. Hubmayr R: **Pulmonary Micromechanics of Injured Lungs.** In *Ventilator-Induced Lung Injury. Volume 215*. Edited by Claude Lenfant DD, Georges Saumon and Rolf D Hubmayr: Taylor and Francis; 2006.
5. Hager DN, Krishnan JA, Hayden DL, Brower RG: **Tidal volume reduction in patients with acute lung injury when plateau pressures are not high.** *Am J Respir Crit Care Med* 2005, **172:** 1241-1245.
6. Pavone L, Albert S, Dirocco J, Gatto L, Nieman G: **Alveolar instability caused by mechanical ventilation initially damages the nondependent normal lung.** *Crit Care* 2007, **11:**R104.
7. Hubmayr RD, Rodarte JR, Walters BJ, Tonelli FM: **Regional ventilation during spontaneous breathing and mechanical ventilation in dogs.** *J Appl Physiol* 1987, **63:**2467-2475.
8. Bachofen H, Schurch S: **Alveolar surface forces and lung architecture.** *Comp Biochem Physiol A Mol Integr Physiol* 2001, **129:**183-193.
9. Gil J, Bachofen H, Gehr P, Weibel ER: **Alveolar volume-surface area relation in air- and saline-filled lungs fixed by vascular perfusion.** *J Appl Physiol* 1979, **47:**990-1001.
10. Oldmixon EH, Suzuki S, Butler JP, Hoppin FG, Jr.: **Perfusion dehydration fixes elastin and preserves lung air-space dimensions.** *J Appl Physiol* 1985, **58:**105-113.
11. Butler JP, Miki H, Squarcia S, Rogers RA, Lehr JL: **Effect of macroscopic deformation on lung microstructure.** *J Appl Physiol* 1996, **81:**1792-1799.
12. Rehder K, Sessler AD, Rodarte JR: **Regional intrapulmonary gas distribution in awake and anesthetized-paralyzed man.** *J Appl Physiol* 1977, **42:**391-402.