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WHAT'S NEW IN INTENSIVE CARE

What the concept of VILI has taught us about ARDS management

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The substantial decline in mortality from acute respiratory distress syndrome (ARDS) constitutes one of the most rewarding successes of intensive care medicine. Studies in the 1970s reported a mortality rate of approximately 90 %, whereas more recent ones indicate that rates had fallen below 40 %. This remarkable improvement in outcomes must be largely attributed to better supportive care and to strategies to prevent ventilator-induced lung injury (VILI) and hospital-acquired infections [1, 2].

The recognition that mechanical ventilation, while life-saving, can contribute to patient morbidity and mortality has been the most important advance in the management of patients with acute lung injury and ARDS [2]. This sentence was written after many years of experimental and clinical research on acute lung injury and reminds us of a visionary statement by Mead and co-workers [3] only 3 years after the initial description of the syndrome by Ashbaugh and Petty [4]: "Mechanical ventilators, by applying high transpulmonary pressure to the nonuniformly expanded lungs of some patients, who would otherwise die of respiratory insufficiency, may cause the hemorrhage and hyaline membranes found in such patients' lungs at death". Mead and colleagues based this statement on observations made in an elegant model of lung elasticity pointing out that alveolar wall stress (and strain) of open regions in contact with closed ones was substantially amplified on account of parenchymal interdependence. At the time the implications of this finding were not appreciated by clinicians, who when faced with hypoxemic patients with "stiff" lungs tended to use very high distending pressures. To this end extremely large tidal volumes of up to 24 ml/kg actual body weight [5] were occasionally employed. Similarly, some authorities proposed the application of huge amounts (up to 43 cmH_2O) of positive end-expiratory pressure (PEEP) [6]. Experimental research on animals eventually highlighted the adverse effects of high tidal volume mechanical ventilation, which produced severe permeability pulmonary edema with diffuse alveolar damage [7, 8]. Increased awareness of the deleterious effects of high volume mechanical ventilation led to a gradual change in clinical practice, so that by 1998 according to an international survey the average tidal volume in ARDS patients had fallen to less than 9 ml/kg actual body weight [9]. However, it was not until a large randomized clinical trial conducted by the ARDS Network demonstrated a significant survival benefit associated with low tidal volume ventilation that the clinical relevance of the VILI concept gained general acceptance [10].

While the ARDS Network's ventilator management protocol has become the standard of care in many institutions, there is an ongoing debate how to better tailor ventilator mode and settings to patient-specific information. The debate is fueled by uncertainty about the risks and merits of aggressive lung recruitment strategies, about the relationships between airway pressure and lung stress, between tidal volume and lung strain, and most importantly uncertainty about the effects of disease on these relationships. Clinicians typically infer lung stress in mechanically ventilated patients from airway pressure and volume change recordings, implicitly assuming that the impedance of the chest wall is invariable and that the lungs behave like a resistive and elastic element arranged in series. However, these grossly simplifying assumptions preclude a mechanistic understanding of the stress–strain relationships and associated mechanotransduction responses at the microscale level [11]. During a normal breath alveolar surface area increases largely by tissue unfolding as opposed to alveolar wall stretch. Only at high volumes is breathing associated with a

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significant elastic deformation of the tissue matrix and of the cells that decorate it. The associated parenchymal stress is largely carried by an elastin and collagen fiber network, which anchors broncho-vascular bundles and parenchyma to the visceral pleura. While in comparison the stress carried by epithelial and endothelial cells that decorate alveolar walls is small, deformations produce both active and passive remodeling responses within and between cells and matrix. When rate and/or amplitude of deforming stress exceed the remodeling capacity of the matrix scaffold and of cellular networks, vascular barrier properties become compromised so that interstitial edema and alveolar flooding ensue. Flooding impairs surfactant function, raises alveolar surface tension, and exposes small airway and alveolar epithelia to injurious interfacial stress, while changes in matrix composition and structure raise the affinity of the interstitium for water (i.e., generate an osmotic force) [12]. Since the availability of water has profound effects on enzyme kinetics, this sequence of events may serve as one biophysical mechanism linking parenchymal stress, strain, and innate immune responses. Moreover, in the edematous lung, surface forces associated with the movement and fracture of air/liquid interfaces can become large enough to wound the plasma membranes of small airway and alveolus resident cells and thereby trigger a proinflammatory response [13].

Because of the topographic heterogeneity in disease distribution and its effects on regional parenchymal mechanics, specific biophysical injury mechanisms are regionally distributed. The parenchymas of regions that are effectively closed and are not in communication with a central airway are largely protected from stretch injury. Their epithelial lining may nevertheless be subject to interfacial injury particularly if air spaces are filled with a gas/liquid mixture (i.e., foam), which is being agitated during breathing (Fig. 1) [14, 15]. This injury mechanism is typically referred to as "opening and collapse" or "atelectrauma" in the clinical literature [16, 17]. In contrast overdistension implies injurious alveolar wall stretch of open units, and is determined by local driving pressure and the unit's dynamic compliance. The latter varies with frequency, surface tension, tissue elastic moduli, and by virtue of interdependence is increased in open units neighboring closed ones. Unfortunately, these variables lack a single deterministic relationship with global measures of respiratory system mechanics and can therefore only be inferred from ancillary knowledge about disease type and state, measures of lung plasticity, and of chest wall elastic properties. In light of this complexity it is not surprising that to date clinical trials on the efficacy of PEEP management and recruitment strategies have yielded inconclusive results.

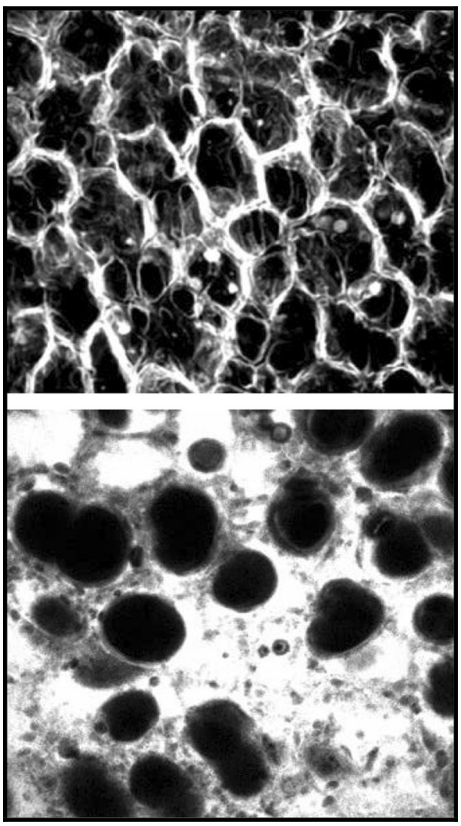

Fig. 1 Laser confocal images of subpleural alveoli of a normal (*upper panel*) and an edematous (*lower panel*) rat lung. The perfusate was labeled with fluorescent dextran, i.e., edema fluid appears *white*, the alveolar walls *gray*, and air pockets are *black*. Note that the air pockets have different dimensions and shapes indicating local differences in pressure and/or surface tension. In turn this implies that the communication between them is occluded by liquid bridges (reproduced with permission from Ref. [14])

While the "volutrauma" concept and the subsequent ARDS Network trial have focused attention on tidal volume as the primary target variable for ensuring safe ventilator settings, a recent post hoc analysis of several large clinical trials suggested that driving pressure (the difference between end-inspiratory and end-expiratory airway occlusion pressure) was the more appropriate target [18]. One argument in favor of this recommendation is that the tidal volume scaling factor "predicted body weight" does not take the severity of lung impairment into account, while the compliance of the respiratory system does, because it is largely determined by the number of open lung units. Defenders of the more conventional ARDS Network approach will argue that the plateau pressure limit of 30 cmH_2O will in effect set an upper limit to driving pressure, while patients with less severe lung impairment may not need bigger tidal volumes than recommended by the

classic approach. Nevertheless, both approaches ignore potentially confounding effects of chest wall mechanics.

Newer approaches may improve ARDS prognosis by enabling further reductions in stress on diseased lungs. While high frequency oscillatory ventilation did not fulfill this promise, arguably because of too high static distending pressure and frequency [19], refinements in extracorporeal support do enable the use of much lower driving pressures [20]. Nevertheless, its efficacy compared to conventional care including early paralysis and prone positioning remains to be established.

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Compliance with ethical standards

Conflicts of interest
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