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Lung Metabolism During Ventilator-Induced Lung Injury: Stretching the Relevance of the Normally Aerated Lung

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Concerns about pulmonary complications of positive pressure ventilation (1) are at least as old as the description of the Acute Respiratory Distress Syndrome (ARDS) (2). Yet, it took about a decade until experimental findings (3) shifted the focus from air leaks and oxygen toxicity to the biological effects of large excursions of the lung parenchyma (4). The demonstration that mechanical ventilation with high peak inspiratory pressures and low positive end-expiratory pressure (PEEP) could produce edema, increased alveolo-capillary permeability, leukocyte infiltration, and inflammation in normal lungs established the current understanding of ventilator-induced lung injury (VILI) (4, 5). The clinical relevance of VILI was confirmed by the demonstration of a 22% decrease in mortality of ARDS patients when lung stretch was reduced through lower tidal volumes (V_T). (6). In addition to excessive lung stretch due to large V_T , it has been recognized that VILI can also be caused by low end-expiratory lung volumes, even at low airway pressures. Mechanisms proposed to explain such injury include concentration of stresses in the heterogeneously expanding lung parenchyma (7), and propagation and rupture of liquid plugs producing injurious fluid mechanical stresses during cyclic recruitment-derecruitment of distal lung units (8, 9). Mitigation of these low-volume phenomena by optimizing lung recruitment with higher PEEP levels (10) and proning (11) has been beneficial in patients with moderate and severe ARDS. However, despite the large number of experimental and clinical studies, uncertainty persists about the relative contribution of overdistension versus low-volume injury to the ultimate lung damage produced by VILI (12). Topographically, in supine patients, nondependent (ventral) injury would be expected if overdistension would predominate (13), whereas dependent (dorsal) damage would be expected for predominant low-volume injury

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(14). The clinical relevance of the topic has been emphasized by the suggestion that the mass of opening-closing lung is an independent risk factor for death in patients with ARDS (15), and that regional forces during mechanical ventilation determine lung parenchyma abnormalities found in ARDS survivors (16).

In this setting, there is growing interest on the application of positron emission tomography (PET) with 18-F-fluoro-deoxy-glucose (^{18}F -FDG) as a non-invasive *in vivo* tool to measure global and regional lung metabolism during lung injury indicative of lung inflammation (17, 18). Previous experimental studies have shown that lung ^{18}F -FDG uptake is a sensitive biomarker of lung neutrophilic accumulation and activity during VILI (14, 19, 20). In the current issue of *Critical Care Medicine*, Borges et al use ^{18}F -FDG PET to locate and quantify lung inflammation in a two-hit porcine model of ARDS (severe surfactant depletion + injurious mechanical ventilation) (21). Consistent with observations in supine patients, the model yielded topographically heterogeneous lung inflation with nondependent tidal hyperinflation and dependent cyclic recruitment together with complete derecruitment. Surprisingly, these most nondependent and dependent regions did not exhibit significant larger ^{18}F -FDG uptake than corresponding regions in control animals despite plateau pressures of 44 cm H₂O. Instead, increases in ^{18}F -FDG uptake occurred more evidently in regions of normal and poor aeration located at intermediate vertical distances. This lead Borges et al to theorize that tidal stretch, not overdistension or cyclic recruitment-derecruitment, is the main mechanical determinant of VILI in those severe experimental conditions. The higher regional compliance in normally- and poorly-aerated regions would determine their increased ventilation and large tidal stretch igniting lung inflammation. Hyperinflated and non-aerated regions would have the indirect relevance of diverting ventilation to those areas of higher compliance. Importantly, the authors addressed the effect of heterogeneous lung density indicating it was unlikely that the observed differences in regional ^{18}F -FDG uptake were solely due to local density changes.

This clinically relevant large animal study invites several considerations. Given that the presumed injurious factors such as regional strain (or regional ventilation as a surrogate of strain) were not measured, a definite statement could not be made on the causes of the increased regional lung metabolism. Interestingly, Borges et al findings appear to contradict a previous unilateral surfactant depletion (saline lavage) study where regional ventilation *was* measured and found to be *higher* in normal (non-lavaged) than in surfactant depleted lung regions. ^{18}F -FDG-uptake in that study was still higher in *low* ventilation surfactant depleted regions (14). This suggests that in the study by Borges et al either the combination of tidal stretch and surfactant depletion lead to increased regional ^{18}F -FDG uptake, or the redistribution of regional aeration resulted in regional tidal strains substantially larger than those observed with that unilateral injury. PET images were acquired only at the end of experiment following three interventions: alveolar lavage, 210 min of high V_T (20 mL/kg) and low PEEP (4 cm H₂O), and 4 h of less high V_T (15 mL/kg) and high PEEP (15 cm H₂O). As such, the specific mechanisms producing the regional metabolic changes await identification. It is conceivable that non-aerated and/or cyclically recruited regions during the low PEEP-high V_T phase could have been recruited during the higher PEEP-lower V_T phase and at least partially contributed to findings assigned to normal or poorly aerated

regions. However, the minimal change in compliance between those phases suggests minimal lung recruitment. The specific tissue determinants of the increased lung metabolism will also need to be identified (17, 20, 22, 23). Borges et al. data show intriguing trends for increases in ^{18}F -FDG uptake both in non-aerated and hyperinflated regions, which might not have reached consistent statistical significance due to the small number of animals. In this case, their findings would point to the multifactorial nature of regional metabolic activation during severe injury, including factors such as heterogeneities in lung parenchymal impedances underlying the imaging resolution (24). Finally, given the deliberately exaggerated ventilatory settings used in this physiological study, the topographical findings need to be translated to clinical scenarios with great care.

In conclusion, Borges et al alert us that the safety of aerated lung regions cannot be taken for granted during mechanical ventilation, even when their computed tomography appearance suggests normality. Ventilatory strategies should not only avoid overdistension and derecruitment, but also prevent excessive stretch and inflammation of the normally and poorly aerated lung.

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