New images, new insights for VILI

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Prioritization of high-volume vs. low-volume mechanisms of ventilator-induced lung injury (VILI) is an issue that is often discussed and debated in clinical ventilator management. Abundant laboratory studies (7), as well as several prominent clinical studies (1, 3, 14, 19), have emphasized the role of large tidal volumes and high plateau pressures in damaging the lung during mechanical ventilation. The mechanism is generally agreed to be excessive stretch of lung cells and tissues. Numerous laboratory studies have suggested that ventilating the lung at low volumes can also damage the lung (7, 11, 17), although demonstration of this concept in large clinical studies has to date been more elusive. Low lung volumes are associated with atelectasis and, in some cases, cyclical recruitment of atelectasis with each breath (4), which can contribute to VILI. The mechanism here is also thought to be excessive stretch, in this case locally concentrated strains and stresses of lung tissues at a distorted boundary between fully expanded and fully collapsed lung. It should be noted that the classic study by Mead et al. (10) is sometimes misquoted in this context as showing cyclical recruitment is required to generate these concentrated stresses. In fact, this study suggested that all that is required for stress concentration is a distorted boundary between atelectatic lung and fully expanded lung, whether the atelectasis is cyclically recruited or not.

The dilemma facing the clinician is that, in general, efforts to avoid damage from low volume ventilation, for example increased PEEP and increased tidal volume, can potentially augment high volume injury. The converse is also true. Owing to the heterogeneous nature of injury in ARDS and ALI (8), it is generally recognized that it is impossible to completely eliminate both of these mechanisms through some magical combination of ventilator settings. Thus it becomes important to know, in any specific circumstance, which mechanism is more damaging and deserving of the higher priority in adjusting ventilator settings.

Unfortunately, laboratory studies have to date offered little assistance in this prioritization. One method to approach this problem takes advantage of the heterogeneous nature of most models of ALI. Atelectasis and low aeration regions of the lung are largely confined to dependent lung regions, whereas stretch and overdistention are largely confined to the most nondependent lung regions (8). These two divergent mechanisms of VILI can therefore be compared by examination of lung tissue on a regional basis and assessment of inflammation and edema by immunologic, biochemical, and histopathological methods. These approaches, however, are extraordinarily labor intensive and have seen very limited application (5, 12, 15, 18).

The study by de Prost and colleagues (6a) in this issue of the Journal of Applied Physiology is a welcome addition to the investigations of the role of low-volume lung injury in VILI. The authors use a PET method, under emerging nomenclature one that would be termed a molecular imaging method, to measure and image the regional use of glucose. Although the overall signal is no doubt a complex mixture of the metabolic activity of many cell types, prior work has established that the major influence on the regional signal is the high metabolic activity of recruited neutrophils. The images can therefore be interpreted, as a good approximation, as the regional distribution of inflammation. These molecular imaging methods were performed in concert with conventional transmission scans to provide regional assessment of aeration, as well as novel PET methods developed by the authors to provide regional measurements of ventilation and perfusion. The results clearly show that in this specific model (surfactant depletion by saline lavage in a large animal model), ventilated with these specific settings (moderate Pplat of 30 cmH2O; moderate PEEP of 10 cmH2O; RR 23), dependent regions of the lung suffer from the earliest inflammatory changes. Consistent with some, but not all, prior studies based on regional excised tissue analysis (5, 12, 15), the results suggest that early in the course of acute lung injury, the low volume mechanisms make important contributions to VILI. Perhaps more importantly, these authors demonstrate the utility of a novel new method that can be used to visualize, in vivo, the spatial distribution and progression of inflammation.

Of course there are some remaining questions. The specific role of cyclical recruitment in this dependent lung damage is not revealed in this study, since the methods used do not have adequate temporal resolution to assess cyclical recruitment (4). Another key question is whether these results are model dependent: different injury models, different degrees of injury severity, different time courses during the injury, and different ventilation approaches, will likely give different results, and so little is known on these topics that the differences are not very predictable. Probably the most pressing unanswered question is the relative role of severe stretch, or even moderate stretch, vs. low-volume injury. The de Prost study was not specifically designed to address this question, instead focusing on a definitive demonstration of the role of low-volume injury by the use of these novel imaging methods. It would be easy to summarily dismiss any role for overdistention. Pplat was limited to 30 cmH2O and overall tidal volume was 17 ml/kg, ranges previously shown by these authors to be noninjurious after 2 h of ventilation in normal sheep lungs (6). Closerr inspection, however, reveals that in this single lung lavage model, the differences in lung compliance resulted in a nonlavaged normal lung that was operating at a much larger mean volume than the left lung (quite obvious in Fig. 1) and also at a much larger tidal volume. At an overall tidal volume of 17 ml/kg, divided 77% into the right lung, the effective tidal volume in the normal lung would be 26 ml/kg if the lungs were symmetric in anatomic size, slightly less when accounting for the usually larger right lung. This is entering the range of thresholds reported to induce stretch injury in normal lungs of several animals (2, 9, 13, 16) (excluding rodents, which generally are...
susceptible to stretch injury at lower tidal volumes). Given that the method used should be very sensitive to small and early changes in inflammation, it is remarkable that the 18F-FDG activity in the right lung was not elevated compared with previously reported normal levels.

The fact remains, however, that this study was designed specifically to look at low-volume injury, not to compare low-volume and high-volume injury mechanisms. As these novel methods are applied to further studies in the future, our community looks forward to answers to the remaining questions that impact clinical ventilator management.

DISCLOSURES

Conflict of interest statement: No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES