Ventilator-induced lung injury without biotrauma?

Once the critical care community accepted the hypothesis that mechanical ventilation could damage the lungs in more ways than “barotrauma,” as defined by Macklin and Macklin some 60 years ago (6), literally hundreds of preclinical trials were conducted with the aim of establishing cause-and-effect relationships between specific ventilator settings and some biological responses (4). In aggregate, these studies have established four specific ventilator-induced lung injury (VILI) mechanisms, namely 1) regional overdistension caused by the application of a local stress or pressure that forces cells and tissues to assume shapes and dimensions that they do not assume during unassisted breathing (11); 2) so-called “low-volume injury” associated with the repeated recruitment and derecruitment of unstable lung units, which causes the abrasion of the epithelial airspace lining by interfacial forces (8); 3) 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 (10); and 4) interdependence mechanisms that raise cell and tissue stress between neighboring structures with differing mechanical properties (7).

However, as the appreciation for specific-injury mechanisms has grown so has the realization that lung responses to injurious stress can be quite nuanced and nonuniform with respect to space and time. In fact, in 1998, Tremblay and Slutsky (9) coined the term “biotrauma” to precisely underscore this point. Because it would be naïve to assume that the many distinct manifestations of biotrauma contain identical prognostic or mechanistic information, it would seem prudent to differentiate between specific pulmonary stress responses. After all, the term injury has been used to describe biological responses as diverse as altered gene or protein expressions, abnormal respiratory mechanics, inefficient gas exchange, impaired vascular barrier properties, and the remodeling of lung structures.

In this vein, D’Angelo and colleagues (2) in this issue of Journal of Applied Physiology considered different injury dimensions in an attempt to separate immune-mediated from nonimmune-mediated effects of low-volume injury on lung function. Lung mechanics, edema formation, nitric oxide concentrations in expired gas (eNO), and the concentration of TNF-α in plasma and bronchoalveolar lavage fluid were measured in a rabbit model of low-volume injury. They observed that mechanical ventilation at low lung volumes was associated with an increase in lung impedance, a mild increase in lung water, and a decrease in eNO but that it was not associated with the release of the proinflammatory cytokine TNF-α into alveoli and small airways. On the basis of these observations, D’Angelo and colleagues concluded that direct airway injury, i.e., necrosis of small airway epithelial lining cells, as opposed to “biotrauma” was responsible for the changes in lung mechanics and eNO.

This is an interesting and provocative finding because, if confirmed, it would reduce enthusiasm for testing anti-inflammatory therapies in low-volume injury syndromes and provide a rationale for serial eNO measurements in intubated patients with injured lungs. However, the low specificity of the many surrogate injury end points raises some concerns over readily accepting these results and their interpretation. It is not my intent to comment on the sometimes passionate debate about the pathogenetic role of cytokines in different VILI models (3) except to say that it is dangerous to think of inflammation as a binary response variable that can be assessed on the basis of a single cytokine. Even time-tested surrogates of lung injury, such as altered mechanics, are sometimes difficult to interpret. For example, there is still no consensus that apparent changes in lung elastance and resistance can be uniquely attributed to specific molecules and structures such as parenchyma and airways (5). Lung mechanical properties are undoubtedly sensitive to changes in vascular barrier properties, surfactant composition, and airway dimensions. However, even the most detailed analysis of the lungs’ mechanical properties is unlikely to provide specific enough information that would allow one to distinguish between distinct VILI mechanisms. NO is an unstable molecule that interacts with hemoglobin and reactive oxygen species so that its concentration in expired gas must reflect a net balance between production and clearance. The reduction in eNO that accompanied low-volume injury in rabbits was previously observed in humans with the acute respiratory distress syndrome as well (1). Results in alternative animal models of lung injury, however, have been more variable (12).

To the extent to which the term biotrauma refers to a coordinated immune response to injurious deforming stress, it is hard to imagine that airway epithelial cell necrosis would not trigger a repair response that involves inflammatory signaling molecules. What the observations of D’Angelo and colleagues do suggest, however, is that the repair response to low-volume injury may well be delayed and does not contribute to early changes in mechanics and eNO. The lesson to be drawn is that VILI is a dynamic process that is hard to capture at a single point in time. Hence, the relative value of specific surrogate treatment targets, such as oxygenation, lung aeration, or cytokine concentrations for example, is likely to change as a function of time as well. Although it would be easy to get paralyzed by such complexity, the critical care community will be better off for having acknowledged and embraced it.

REFERENCES


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