

Commentary

Protective ventilation of patients with acute respiratory distress syndrome

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Abstract

In a recent issue of the *British Journal of Anaesthesia*, Moloney and Griffiths reviewed clinically pertinent issues surrounding the management of the acute respiratory distress syndrome (ARDS) patient, particularly as it pertains to the treatment of ventilator induced/associated lung injury (VILI). In addition to highlighting the important observations that have contributed to further our understanding of the relationship between the mechanical ventilator and inflammatory lung injury, the authors also offer a concise reappraisal of the clinical strategies used to minimize VILI in ARDS. Special emphasis is placed on the theory of biotrauma, which attempts to explain how multi-organ failure may develop in patients who ultimately succumb to this syndrome.

Keywords biotrauma, lung injury, ventilator associated, ventilator induced

In a recent issue of the *British Journal of Anaesthesia*, Moloney and Griffiths [1] reviewed basic issues surrounding the ongoing debate on ventilator induced/associated lung injury (VILI) and the implications for patient care. The potential importance of VILI/biotrauma is not only that it can aggravate ongoing lung injury but also that it may have important systemic consequences, and may explain why most patients with acute respiratory distress syndrome (ARDS) who go on to die, succumb to multiple organ failure (MOF) [2,3]. VILI/biotrauma offers a clinically relevant window of therapeutic opportunity in the management of ARDS/acute lung injury (ALI). Rarely do clinicians know when sepsis or systemic inflammatory response syndrome begins. Often the process of systemic inflammatory response syndrome has been initiated hours if not days before admission to the intensive care unit. In contrast, we know exactly when VILI/biotrauma begins – with intubation and initiation of mechanical ventilation. A full understanding of the mechanisms that mediate lung injury may permit potential strategies directed at reducing the incidence of VILI-induced MOF to be instituted early in the course of illness. This is no

small issue for a syndrome with an incidence of 64.2 cases per 105 person-years and with a 40–50% mortality rate [4].

Results from the ARDSNet trial [5] have underscored the potential importance of biotrauma in the management of ARDS: the results from that large multicenter trial showed a relative risk reduction of 22% in patients ventilated with the lower tidal volume. This indicates that the mortality attributable to VILI is at least 9–10%. This improvement in mortality in patients ventilated with low tidal volumes was not due to a decrease in barotrauma between groups. It is postulated that injurious strategies of mechanical ventilation can cause pulmonary inflammation with release of various cytokines/mediators – biotrauma. The initial insult (pneumonia, acid aspiration, or contusion are a few examples) 'primes' the lung. A 'second hit', or subsequent insult, such as mechanical ventilation, leads to an overwhelming pulmonary inflammatory response. Loss of pulmonary compartmentalization allows for important mediators to escape the confines of the lung and gain access to the systemic circulation. Recent experiments have shown

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; MOF = multiple organ failure; PEEP = positive end-expiratory pressure; SP = surfactant protein; VILI = ventilator-induced/associated lung injury.

that this is associated with apoptosis of cells in distal organs (kidney, villi of colon) and end-organ dysfunction (kidney), which potentially underlies the development of MOF [6].

In a randomized controlled trial conducted in 44 patients, Ranieri and coworkers demonstrated that a lung protective strategy attenuated the levels of proinflammatory cytokines in plasma and bronchoalveolar lavage fluid [7], and was associated with a lower incidence of MOF [8]. However, the measurement of proinflammatory cytokines does not address the issue of maintenance of alveolar–epithelial barrier integrity. In a recent study conducted by Eisner and coworkers [9], circulating levels of surfactant protein (SP)-A and SP-D were evaluated in plasma samples from participants in the ARDSNet randomized trial. Baseline plasma SP-A levels were not found to be related to clinical outcome. In contrast, higher baseline plasma SP-D levels were associated with a greater risk for death (odds ratio 1.21 per 100 ng/ml increment; 95% confidence interval 1.08 to 1.35) as well as higher overall morbidity. In addition, use of a lower tidal volume strategy significantly attenuated the rise in plasma SP-D levels ($P = 0.0006$). Because injury to the alveolar–epithelial barrier is a hallmark of ALI, levels of circulating SPs may not only represent a potential biomarker for ALI/ARDS but they may also, in the future, be used to gauge the effects of treatment [9].

Ample evidence supports the use of a relatively low tidal volume, but what about the use of an open lung strategy (e.g. recruitment maneuvers, positive end-expiratory pressure [PEEP], proning)? The ALVEOLI study (Prospective, Randomized, Multi-Center Trial of Higher End-expiratory Lung Volume/Lower FiO_2 versus Lower End-expiratory Lung Volume/Higher FiO_2 Ventilation in Acute Lung Injury and Acute Respiratory Distress Syndrome), performed by the ARDSNet investigators to study the use of higher PEEP levels, was discontinued prematurely because of lack of efficacy [10]. Accumulating evidence from both animals and human experiments suggest that not all patients are recruitable [11]; moreover, if improved oxygenation does not seem to affect outcome [5], then should recruitment be pursued for the sole purpose of decreasing atelectrauma [12]?

Data have been reported that suggest that recruitment maneuvers may be deleterious if sufficient PEEP is not used to maintain recruitment [13,14]. Repeated de-recruitments accentuate lung injury during mechanical ventilation [14], and it has also been suggested that allowing the lung to remain in a state of de-recruitment may mitigate biotrauma [13]. One of the mechanisms for upregulation of cytokines during mechanical ventilation of acutely injured lungs is alteration in alveolar mechanics (i.e. the dynamic change in alveolar size and shape during ventilation) – alveolar instability and recruitment/de-recruitment. Using direct visualization of subpleural alveoli, Schiller and coworkers [15] demonstrated that normal alveoli are extremely stable with minimal

movement during mechanical ventilation. In contrast, surfactant deactivation (also a classic finding in ARDS) causes a continuum of altered alveolar mechanics seen as repetitive collapse of alveoli at end-expiration and re-inflation at end-inspiration. In a recent follow-up study, Steinberg and coworkers [16] demonstrated that alveolar instability can mechanically injure the lung independent of inflammatory damage. Moreover, the application of PEEP in this animal model was sufficient to stabilize the alveoli. That group also noted that alveolar instability was associated with modest increases in interleukin-6 levels after 4 hours of mechanical ventilation, even in the absence of neutrophil infiltration, and that this increase could be attenuated by the application of PEEP. These data suggest that mechanical injury alone is sufficient to cause a rise in tissue and bronchoalveolar lavage levels of proinflammatory cytokines, and that stabilization of alveoli is a key issue in reducing atelectrauma.

The debate on how to best manage patients with ARDS is an exciting one. The questions are many but certain important points are becoming much clearer. First, how does lowering tidal volume improve clinical outcome? This probably occurs via a direct attenuation of the mechanical injury to the capillary–alveolar membrane, thereby limiting the effects of mechanotransduction (the response of cells to mechanical force) on cellular molecular physiology. Second, does an ‘open lung strategy’ matter? The answer to this is probably ‘yes’. Preliminary evidence suggests that use of strategies that stabilize alveoli are lung protective, but definitive clinical outcome data are not yet available. Further research is required to determine whether alveolar stabilization is achievable, measurable, and desirable. Finally, are proinflammatory mediators involved in this process? Again, the answer is probably ‘yes’, both as a consequence of mechanical injury and as the mechanism underlying the development of MOF in this patient population. However, as pointed out by Moloney and Griffiths [1], a definitive answer to this latter question requires a study that monitors outcomes after specifically targeting certain mediator(s).

Competing interests

None declared.

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