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EDITORIAL

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Ventilator-induced lung injury: another sign of aging?

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Acute respiratory distress syndrome (ARDS) is, as its name implies, a syndromic clinical entity, which attempts to capture and characterize a specific type of inflammatory lung injury, reflected pathologically (at least in its early stages) by diffuse alveolar damage [1, 2]. ARDS is important because it can affect an extremely heterogeneous population and result from a wide variety of risk factors and conditions that can injure the lungs either directly or indirectly [3–5]. In addition, ARDS is not a rare condition. Recent rigorous measurements reveal a high incidence, and it may affect as many as 16% of mechanically ventilated patients in an intensive care setting [6–8]. The mortality from ARDS ranges from 30% to 60% depending on the specific patient mix and selection criteria, with most deaths resulting from multiple organ failure and sepsis [6–10]. Patients who do survive frequently suffer reduced health-related quality of life that can persist for years after hospital discharge [11–13].

Unfortunately, despite extensive clinical research in the field, most clinical trials have failed to demonstrate a survival benefit of new therapies [4]. Indeed, although mortality may have decreased for some subtypes of ARDS, particularly younger trauma patients [14], not much progress has been made in the past decade to decrease the high burden of mortality in other populations [15]. It is reasonable to say that the only measure that has been convincingly shown to affect mortality is optimization of mechanical ventilation, particularly by means of limiting tidal overdistension, reducing tidal volume [16–18]. However, decreasing tidal volume and alveolar pressure cannot be considered a therapeutic intervention per se; rather, this represents an improvement in our supportive care and avoidance of iatrogenic injury.

Why does ventilation with lower tidal volumes improve outcomes? A strong rationale and a considerable body of scientific evidence support this association. Higher volumes result in overdistension of alveolar units, inducing further mechanical damage and thereby increasing the inflammatory response affecting an already injured lung. Animal models of lung injury have been key in the process of furthering our understanding of ventilator-induced lung injury (VILI). In animal models injurious ventilation strategies with large tidal volumes and/or zero positive end-expiratory pressure result in a local inflammatory response and release of cytokines into the systemic circulation [19–21]. It has also been observed, in experimental models of acutely acid-injured rat lungs, that protective ventilation may reduce damage, not only to the epithelium but also to the endothelium. As a result, there is less pulmonary edema and capillary

leak in the animals ventilated with low tidal volumes [22, 23]. Moreover, VILI caused by high tidal volume excursions with high transpulmonary pressures has also been shown to impair the ability to clear alveolar edema [24]. Evidence has also been obtained in human clinical trials. Mechanical ventilation can induce a local and systemic inflammatory response, resulting in increase of cytokines both in bronchoalveolar lavage fluid and in serum. It has been shown that this increase in pro-inflammatory mediators can be attenuated by ventilation strategies that reduce overdistension and recruitment–derecruitment of the lung [25].

In this issue of *Intensive Care Medicine* two intriguing studies from the same research group provide further insight into these issues [26, 27]. In these two papers Nin and colleagues present results from an animal model that focuses on the effects of deleterious ventilation with high tidal volumes on the lungs of otherwise healthy rats. These studies offer compelling evidence of the damage induced by aggressive ventilation with high volumes, demonstrated both in lung histology and, with more novelty, in abnormal contractile function of ex vivo arterial vascular rings suspended in organ baths. The first experiment showed, as expected, that injurious ventilation with higher tidal volumes generated a higher inflammatory response and greater pulmonary and vascular dysfunction than lower tidal volumes [26]. Interestingly, the age of the animals was strongly associated with the extent of damage produced by aggressive ventilation. Whether this finding is explained by age-related differences in inflammatory response, susceptibility to organ damage, or lung or chest wall mechanics could not be elucidated. In particular, it is not clear whether the observed phenomena were caused directly by VILI or indirectly through cardiovascular dysfunction, as older animals in the high tidal volume group developed significantly more hypotension than other groups. These results cannot be extrapolated to clinical practice, as aged patients may have higher mortality associated with ARDS, but they also may have different risk factors, epidemiology and co-morbidity, which cannot be replicated easily in an animal model. However, the authors' suggestion that lower tidal volume could provide further benefit in elderly patients is a reasonable one.

In addition, this study raises the point that all animals in experimental studies may not respond equally to the same noxious stimulus. We would not think about evaluating a clinical paper without comparing baseline characteristics between groups. The weight of experimental rats has previously been shown to influence VILI experiments [28], and this report by Nin and colleagues further suggests that investigators should ensure and report that their experimental animals are well matched in baseline characteristics [26].

Their second study, which uses similar methodology, is also remarkable. Again the local and systemic effects of injurious ventilation are well described. Most interesting is their documentation of the time course to recovery from these alterations after the insult is discontinued [27]. In surviving animals, major respiratory and vascular dysfunction was reversed in 24–72 h after the animals were released from mechanical ventilation. Thus, survival and repair mechanisms are able to manage the damage produced by otherwise nearly destructive ventilation. In animal models one is able to produce severe lung injury using only injurious mechanical ventilation in a very short time; while repair mechanisms may not be quite as rapid, they do appear to take effect faster than previously thought. Again, this information is important, but cannot be translated directly to a clinical setting. These experimental animals were submitted only to the injury of high tidal volume ventilation. In the clinical situation, the lungs and systems of a patient may have to cope with at least two consecutive hits: first, the underlying cause of ARDS initiating direct or indirect damage to the lungs; second, VILI, which can be minimized by protective ventilation. The time course and molecular mechanisms of recovery in patients with ARDS needs further study.

There is evidence suggesting that the use of higher tidal volumes and inspiratory pressures, even days before the onset of ARDS, results in a higher incidence of this condition [29]. Indeed, approximately half of ARDS cases arise after the patient has been mechanically ventilated for another indication [10]. Thus in some cases, ARDS could be considered a complication of mechanical ventilation, and we may soon see non-protective ventilation finding a place in the list of risk factors associated with ARDS. This issue and others related to treatment and prevention of ARDS can only be addressed through careful experimental studies, which will subsequently inform clinical trials. Experimental studies such as those presented in this issue are of great importance: to highlight the need for rigorous attention to detail in experimental design and reporting, to reinforce the impact of VILI and focus attention on lung-protective ventilatory strategies in clinical practice, and to provide a framework upon which to build further experimental knowledge in areas such as repair and recovery from lung injury.

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