

Ventilator-induced Lung Injury

Less Ventilation, Less Injury

THE publication of the seminal article by the Acute Respiratory Distress Syndrome Network (ARDSNet) on ventilation with lower tidal volumes in 2000 has changed the way we ventilate patients with ARDS.^{1,2} The use of low tidal volumes was the first therapy ever proven to improve survival of patients who were diagnosed with ARDS. Despite initial reluctance and even open criticism,^{3,4} clinicians across the world have embraced this practice,⁵ and ventilation with a tidal volume of 6 ml/kg of ideal body weight has become the standard of care for patients with acute lung injury and ARDS of various etiologies.^{6,7,8}

Remarkably, evidence is accumulating that ventilation may inflict damage to the injured lung, even with these small tidal volumes. The reason lies in the anatomical inhomogeneity of the lesions of the ARDS lung, in the face of a diffuse inflammatory response.⁹ Early computed tomography scans of the lungs in patients with ARDS^{10,11} documented seemingly normal airspaces next to collapsed and fluid-filled spaces, resulting in smaller lungs that were ventilated with larger volumes.¹² Advances in lung imaging techniques and bedside ventilator waveform analysis^{13,14,15} are providing support to the concept that any tidal volume, regardless of how small, has the potential to damage the ARDS lung by: (1) overinflating compliant alveoli (tidal hyperinflation)¹⁵ and (2) allowing the cyclical closure of heavy, fluid-filled terminal airways (tidal recruitment).¹⁵ As a result, ventilator-induced lung injury is a regional phenomenon, and it may not be sufficiently reflected by our bedside measurements of respiratory mechanics until we have methods to monitor the individual mechanical behavior of specific areas of the lung.

In this issue of ANESTHESIOLOGY, Terragni *et al.*² test the effect of further decreasing the tidal volume of a group of ARDS patients who, along with signs of worsening lung damage, developed inspiratory airway pressures of 28-30 cm H₂O, previously shown to be associated with tidal hyperinflation.¹⁵ The tidal volume was decreased to 4 ml/kg of ideal body weight; in an Italian woman of average height‡ (the study was performed in Italy), that

turns out to be between 200 and 250 ml. The consequent increase of the PaCO₂ was predictable, and the authors prospectively planned to remove the excess carbon dioxide through an extracorporeal circuit modified from a standard continuous veno-venous hemofiltration setup. The intervention was safe and produced notable physiologic improvements. As this approach will undoubtedly be investigated further, a number of considerations seem important.

When should carbon dioxide removal be initiated? Growing evidence suggests that hypercapnic acidosis is well tolerated (permissive hypercapnia),¹⁶ and it may even be beneficial. A *post hoc* analysis of the ARDS-Net low tidal volume study suggested that hypercapnic acidosis was associated with a higher survival rate in the patients ventilated with 12 ml/kg tidal volume (average airway pressure, 33 cm H₂O), but not in those ventilated with the 6 ml/kg tidal volume (average airway pressure, 25 cm H₂O).¹⁷ In that study, the PaCO₂ was limited by design, and just a handful of patients reached a PaCO₂ above 65 mmHg. In the current study,² the 4 ml/kg tidal volume group reached PaCO₂ values of 80 and 90 mmHg, a ceiling that most clinicians would not feel comfortable leaving untreated. However, a safe or a best level of PaCO₂ has not been established. Moreover, it is still unclear the relative importance of the acidosis *versus* hypercapnia *per se*, and of the protection inferred by a low tidal volume *versus* the one of hypercapnia *per se*. A clinical trial that separates tidal volume from hypercapnic acidosis is due, and it could now be designed by using a setup of extracorporeal carbon dioxide removal like that of Terragni *et al.*²

Although the pathways of lung protection by carbon dioxide are still unclear,^{17,18} it is tempting to hypothesize a beneficial role of hypercapnic acidosis in increasing regional blood flow in the lung. Local hyperinflation of higher compliance regions creates areas of high ventilation/perfusion ratio, where Pco₂ may be very low and pH very high and injurious. Such areas may be highly represented in some ARDS patients as a result of extensive microvascular occlusion of the pulmonary circulation.¹⁹ Permissive hypercapnia may prevent or correct the effects of regional hyperventilation and alkalosis. However, permissive hypercapnia is feasible only to the extent that the portion of the lung that receives ventilation is of sufficient size to allow an acceptable PaCO₂. When the PaCO₂ becomes uncomfortably high (60 mmHg? 80 mmHg?), then carbon dioxide needs to be eliminated in different ways.

Removing carbon dioxide by extracorporeal means is a powerful tool that allows control of the minute ventilation over its full range, from normal to zero. The current

This Editorial View accompanies the following article: Terragni PP, Del Sorbo L, Mascia L, Urbino R, Martin EL, Birocco A, Faggiano C, Quintel M, Gattinoni L, Ranieri VM: Tidal volume lower than 6 ml/kg enhances lung protection: Role of extracorporeal carbon dioxide removal. ANESTHESIOLOGY 2009; 111:826-35.

Accepted for publication July 10, 2009. The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

‡ Available at: www.wiki.answers.com; accessed June 30, 2009.

study of Terragni *et al.* does not go into important technical parameters of the extracorporeal circuit, such as the amount of carbon dioxide removed per minute and the proportion of total carbon dioxide was removed. From the reported PaCO_2 changes, we can infer that about 10–20% of the total carbon dioxide was removed. Is this transfer rate adequate, and what are the technical limits of this system? The most important determinant of any extracorporeal circuit is its capability to generate adequate blood flow. Luckily, the blood flow required for carbon dioxide removal is considerably less than that required for viable oxygenation.²⁰ Venous blood contains large amounts of carbon dioxide, most carried as bicarbonate ion (approximately 500 ml/l of carbon dioxide under normocapnic conditions). So, with a blood flow through the extracorporeal circuit of 500 ml/min, the tidal volume could be reduced to zero.²¹ We could foresee the development of very efficient devices capable of removing a substantial amount of carbon dioxide production (30–100%) with blood flows of 250–500 ml/min. At such low flows, systemic heparinization may not be needed; it is already not needed with many continuous veno-venous hemofiltration circuits.²²

With this in mind, daring investigators like Terragni *et al.* may already be planning the next steps. If hypercapnia can be managed to a safe and beneficial extent through the proficient use of an extracorporeal circuit, then why would we need to ventilate these patients at all? Perhaps in the near future, management of ARDS will include a minimally invasive extracorporeal carbon dioxide removal circuit, and noninvasive continuous positive airway pressure. This would embody the modern philosophy of mechanical ventilation: to avoid tracheal tubes, minimize sedation, and prevent ventilator-induced acute lung injury and nosocomial infections.

It has been over two decades since ANESTHESIOLOGY published one of the very first analyses of computed tomography scan images of the ARDS lung.¹¹ What at that time seemed *avant-garde*, untested, and unduly cumbersome, is now an invaluable research tool and a standard diagnostic procedure. Just like then, the current study of Terragni *et al.* may not have all the proper concurrent control groups and robust clinical endpoint. Also like then, however, these investigators make up for it with original thinking and sound understanding of the pathophysiology of this complex syndrome.

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