Do we really have other tools for respiratory failure besides mechanical ventilation?*

Mechanical ventilation has been the mainstay of treatment for respiratory failure. Modern-day mechanical ventilation has evolved from the days of the polio epidemic (1). As intensivists we have appreciated its benefits and risks through many years of experience and research. In striving to “do no harm,” we have adopted methods to ventilate patients that subject them to less lung injury as we treat their respiratory failure. For example, we have discovered the use of noninvasive positive pressure ventilation in respiratory failure. In addition, newer drugs and technologies are helping our unlucky patients to accommodate to the ventilator while they recover.

Nonetheless, in the past decade, we have come to appreciate the impact of ventilator-induced lung injury. Ventilator-induced lung injury is a result of barotrauma, volutrauma, atelectrauma, and biotrauma (2). A result of this recognition led to the pioneering Acute Respiratory Distress Syndrome Network study, which suggested that tidal volumes of 6 mL/kg and plateau pressures of 30 cm H₂O reduce this type of intrinsic injury to the lung (3). While it is true that techniques of sedation interruption and better patient/ventilator synchrony are now being used, how can we be sure that patients are not harmed despite lower tidal volume ventilation as suggested by the Acute Respiratory Distress Syndrome Network study? Could there be a better way to support lung failure altogether?

Investigators have addressed this dilemma in the past. This year’s Society of Critical Care Medicine lifetime achievement award winner, Professor Luciano Gattinoni, and colleagues (4) demonstrated that we could use extracorporeal membrane oxygenation to permit the lungs to “rest” in patients with severe acute respiratory distress syndrome. The mortality rate in that series was 51%, which was acceptable as a form of rescue therapy. However, Professor Gattinoni also showed the untoward effects of extracorporeal support, including blood loss. More recently, a form of pumpless arteriovenous lung support (iLA Novalung GmbH, Hechingen, Germany) was used for critically hypoxic/hypercapnic patients (5). The requisite arterial access carries with it the risk of limb ischemia, which has ultimately been the limiting factor in these studies.

In this issue of Critical Care Medicine, Batchinsky et al (6) demonstrate that extracorporeal removal of carbon dioxide can decrease the required minute ventilation in a swine model while maintaining normocarbia. The authors studied anesthetized subjects over a 72-hr period of mechanical ventilation combined with extracorporeal carbon dioxide removal. They were able to maintain a “normal” blood gas in their uninjured model. They differentiate venovenous carbon dioxide removal from other modes of extracorporeal support. Extracorporeal membrane oxygenation is the more labor intensive one that requires higher blood flows. Arteriovenous carbon dioxide removal requires less blood flow to achieve similar results, but it also requires that the patient’s heart is functioning adequately. In Batchinsky’s experiment, a new motor-driven extracorporeal venovenous carbon dioxide removal device (Hemolung, ALung Technologies, Pittsburgh, PA) was able to eliminate CO₂ at even lower blood flows that were more comparable to those of conventional dialysis. This aspect of their preliminary study makes their work appealing. CO₂ removal via the Hemolung was demonstrated to reduce the minute ventilation by half while maintaining normocarbia.

While the Hemolung device is more portable and user-friendly, the management of the extracorporeal membrane oxygenation circuit is a resource-intensive process that requires, among other things, a team of specialists, limiting its availability to only a handful of quaternary care centers. Extracorporeal membrane oxygenation uses a higher blood flow (4–5 L/min) across its circuit to deliver oxygen and remove carbon dioxide. In contrast, the Hemolung only requires 450 mL/min to achieve the same results. The goal of the present work is to achieve maximal CO₂ elimination with less blood flow through the circuit. This concept could be used as an adjunct to limit the duration of mechanical ventilation. Along the same vein, Terragni et al (7) looked at the reduction of tidal volume to below ARDSNet levels to limit volutrauma. In this way, the multitude of challenges that clinicians face can be adequately overcome.

In using the Hemolung device, a possible concern is that the infectious risk of an invasive cannula and the need for heparinization to run through the extracorporeal circuit must be weighed against the risks of conventional mechanical ventilation and more sophisticated modalities of lung support such as high-frequency oscillatory ventilation and airway pressure release ventilation. The authors argue that any risks associated with the use of the Hemolung device are comparable to risks associated with conventional renal replacement therapies. Heparinization was monitored by activated clotting times, which were in the same range as for conventional dialysis, and plasma-free hemoglobin was not affected during venovenous carbon dioxide removal (8).

The current experiment is a good foundation to help demonstrate that a more portable extracorporeal gas exchanger could be useful as an adjunct to mechanical ventilation in the treatment of respiratory failure and acute respira-

*See also p. 1382.
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Invasive pneumococcal disease, defined as infection of otherwise sterile sites such as bacteremia and meningitis, is a leading cause of morbidity and mortality worldwide. Invasive pneumococcal disease accounts for >43,000 cases and 5000 deaths annually in the United States alone (1). Among adults, Streptococcus pneumoniae is the leading cause of pneumonia, both in the outpatient and inpatient setting, and often leads to bacteremia, severe sepsis, and death (2). Pneumococcus often resides in the nasopharynx without adverse sequelae. Why some individuals develop pneumonia or invasive pneumococcal disease has been the focus of several studies. Both pathogen and host-related factors leading to pneumococcal pneumonia and invasive pneumococcal disease have been identified (3). The polysaccharide capsule allows for efficient phagocytosis. The Fcγ receptor, particularly the FcγRIIa or CD32a receptor on the immune cells, plays an important role in immunophagocytosis (4). A single nucleotide polymorphism within the gene encoding this receptor leads to a histidine (H) to arginine (R) substitution at amino acid position 131 (FcγRIIa [H/R]) within the ligand binding site, resulting in lower affinity for IgG and impaired phagocytosis.

Understanding the effect of the FcγRIIa (H/R) polymorphism on susceptibility to infections has generated considerable interest. Several studies examined the role of this polymorphism in susceptibility to infections with encapsulated organisms, including pneumococcal and meningococcal disease. Early studies suggested that the arginine allele was associated with a higher risk of invasive pneumococcal disease (5–7). However, the small sample size (<100 cases of pneumococcal disease enrolled in these studies) was an important limitation and some studies suggested no association (8).

In this issue of Critical Care Medicine, Solé-Violán et al (9) present results of a multicenter observational cohort study in 1262 patients with community-acquired pneumonia (CAP). In a subset of patients with pneumococcal pneumonia (n = 319), they examine the role of the FcγRIIa (H/R) polymorphism on susceptibility to pneumococcal disease and risk of bacteremia, severe sepsis, and mortality. A case–control design was used to determine the association with susceptibility and an inception cohort approach to determine the association with outcomes of pneumococcal CAP. This study has several strengths. To date, it is one of the largest cohorts of pneumonia, particularly pneumococcal pneumonia, to examine the role of this genotype. Rigorous assessment was conducted to determine the microbiological etiology, and pneumococcal disease was identified in 319 (41.5%) cases. The authors used appropriate statistical methods, using a conservative approach (Bonferroni correction) to adjust for multiple comparisons performed on additional polymorphisms analyzed in the present study and those assessed previously in this cohort. They also adjusted for known risk factors associated with invasive pneumococcal disease, including age and chronic diseases.

In contrast to prior studies that showed either no association or a higher risk of invasive pneumococcal disease for subjects homozygous for arginine genotype, this study showed a twofold higher risk of bacteremic pneumococcal disease for subjects homozygous for the histidine genotype. Several potential explanations for these conflicting results are possible.

## References