How Much PEEP in Acute Lung Injury

Gordon D. Rubenfeld, MD, MSc

Acute lung injury (ALI) is a common, lethal, and complex syndrome. Estimates of attributable mortality from ALI or its more severe form, acute respiratory distress syndrome (ARDS), in the United States place it above asthma and human immunodeficiency virus infection as a cause of death. The current mortality of 35% associated with ALI is roughly 3-fold higher than that associated with ST-segment elevation myocardial infarction. Most of the salient features of ARDS, including the therapeutic use of positive end-expiratory pressure (PEEP), were described by Ashbaugh et al in their classic description of the syndrome: “Ventilation without positive end-expiratory pressure resulted in immediate hypoxaemia. . . .” Collapsed alveoli require greater pressures for reopening, thus explaining the notable loss of compliance. Positive end-expiratory pressure would theoretically prevent complete collapse and improve oxygenation by maintaining alveolar ventilation.

Ashbaugh et al thought that mechanical ventilation merely prevented hypoxic death, thereby providing clinicians with time to treat the underlying cause of ARDS. However, recent research has focused on the degree to which mechanical ventilation is injurious, depending on how it is applied, by causing inflammation and multiple organ failure. There is little disagreement about the principles of mechanical ventilation in patients with ALI: a PEEP sufficient to recruit collapsed lung areas should be used while delivering small tidal volumes to protect the uninjured lung from overdistention. These basic concepts do not provide any of the details required to manage the care of patients at the bedside.

Although the use of PEEP is a simple physiological intervention, it has potentially deleterious effects on right and left ventricular function, pulmonary vascular resistance, and thoracic compliance, leading to unpredictable effects on gas exchange and hemodynamics in individual patients. Airway pressures necessary to recruit collapsed lung areas can improve oxygenation but also can overdistend normal areas of pulmonary parenchyma, worsen inflammation, and reduce cardiac output. Therefore, identifying the optimal PEEP to use in ALI has been the focus of a substantial amount of clinical investigation. Many strategies exist: clinicians can increase PEEP to achieve the maximal improvement in oxygenation, sacrificing overdistention of normal alveoli; balance oxygenation benefits against cardiac output or blood pressure; use pressure-volume curves or dynamic stress indices to identify a trade-off point of lung recruitment; or use sophisticated imaging techniques to assess how much lung has been opened.

However, in clinical practice, patients with ALI do not appear to benefit from any of these strategies. Large cohorts of patients receiving mechanical ventilation show that patients with ALI, ARDS, acute respiratory failure that is neither ALI nor ARDS, and patients with chronic obstructive pulmonary disease all receive, on average, about 8 cm H2O of PEEP. Current practice may reflect the lack of evidence demonstrating a patient-centered outcome benefit of any specific approach to titrating PEEP.

Four recent clinical trials address the question of “How much PEEP in acute lung injury?”: ALVEOLI, LOVS, EXPRESS, and EPVENT. All of these investigations were designed to measure the benefits of a protocolized higher PEEP strategy in a broad range of patients with ALI receiving tidal volumes thought to be protective. The protocols tested were related only in that they delivered approximately 14.5 to 18 cm H2O of PEEP on day 1 to patients in the intervention groups. The usual set of explanations were invoked to interpret the results of high-quality, well-conceived, but statistically negative trials; ie, the wrong patients were enrolled; too few patients were enrolled because of overly optimistic projections of the effect of PEEP on mortality; and unlucky randomization led to sicker patients in the intervention groups and to investigators not using the right approach to setting PEEP.

In this issue of JAMA, a meta-analysis of individual-patient data by Briel and colleagues addresses 3 of these 4 important limitations. Using primary data from the actual trials, the authors demonstrated that, after adjusting for individual patient covariates, higher PEEP was associated with

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a 4% absolute reduction in hospital mortality, which just met the accepted statistical criterion for significance ($P=.049$) in the subset of patients with ARDS. In patients with less severe hypoxemia (ratio of partial pressure of oxygen to fraction of inspired oxygen concentration $> 200 \text{ mm Hg}$), there was no significant association between higher levels of PEEP and clinical benefit.

The meta-analysis by Briel et al\textsuperscript{12} validates a large body of physiological evidence that higher levels of PEEP are protective in patients with more severe lung injury.\textsuperscript{13} It also suggests that mechanical ventilation trials designed to study mortality differences in patients with ALI receiving protective tidal volumes should include at least 2000 patients to detect realistic treatment benefits. This is not welcome news for critical care research, in which there are no valid surrogate markers to reliably screen treatments worthy of such an investment.\textsuperscript{14}

This meta-analysis provides strong evidence and valuable lessons for researchers but less evidence and direction for clinicians. Informed physicians with strong opinions and a personal strategy for using higher levels of PEEP will certainly find support in this meta-analysis, even if their clinical approach differs from the ones studied in the trials. However, physicians looking for specific treatment recommendations must consider different approaches to delivering higher levels of PEEP that were evaluated in the 4 trials in this meta-analysis. Even though the trials strongly endorse the use of tidal volumes less than 6 mL/kg of predicted body weight, it is not clear whether clinicians should select any one of these protocols, construct a hybrid, or simply use any strategy that delivers PEEP in this range. The available data also do not answer the important question of whether physicians should be guided in most cases of ARDS by a specific protocol for using mechanical ventilation or whether they should individualize care with a PEEP “trial,” considering together the oxygenation change, the PacO$_2$ change, the alterations of mechanics, and the hemodynamic response.\textsuperscript{15}

Briel et al,\textsuperscript{12} along with Reade et al,\textsuperscript{16} are optimistic about the role of prospectively planned meta-analyses of individual-patient data to address the multifaceted challenges of critical care clinical trials.\textsuperscript{16} Such meta-analyses may be superior to those using data extracted from the published articles because individual-patient data permit performance of adjusted analyses that account for differences in allocation of patients to treatment groups. When multiple trials using different drug regimens can be studied across varying patient populations, meta-analyses of individual-patient data can be used to evaluate patient subsets and treatment interactions. However, there are few examples in critical care in which multiple trials of drugs or devices have evaluated specific treatment regimens. Many clinical questions that might be considered for meta-analyses of individual-patient data in critical care are evaluating complex strategies for hemodynamic resuscitation, dialysis, mechanical ventilation, infection control, intensivist staffing, and nutrition. Prospectively planned meta-analyses can harmonize data collection, ensure collaboration, and set a priori research hypotheses to prevent data dredging. However, meta-analyses of individual-patient data performed on studies of complex interventions often will provide statistically precise but clinically vague answers. Patients may be better off with a single sufficiently powered and well-designed clinical trial that rigorously tests a specific approach than with a meta-analysis of individual-patient data from 4 clinical trials that poses the question, “How much PEEP in acute lung injury?” and can only provide the answer, “More.”

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REFERENCES