PEEP in ARDS — How Much Is Enough?

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In 1967, Ashbaugh et al. introduced the use of positive end-expiratory pressure (PEEP) during mechanical ventilation to treat refractory hypoxemia in patients with the acute respiratory distress syndrome (ARDS). Almost 40 years later, the question of how much PEEP is enough remains relevant. Controversy regarding the optimal level of PEEP has persisted despite years of investigation into this question. An increase in our understanding of the pathophysiology of ARDS and ventilator-induced lung injury has led to a renewed interest in the debate.

Studies in animals, designed to illuminate the cause of ventilator-induced lung injury, show that two primary mechanistic factors may contribute to the evolution of ventilator-induced lung injury: overdistention of the alveoli by high transpulmonary pressures and shear-stress forces produced by repetitive alveolar recruitment and derecruitment (collapse) in patients with ARDS who are receiving mechanical ventilation. The first proposed mechanism was addressed by the initial ARDS Clinical Trials Network study. This randomized trial demonstrated a significant survival benefit among patients who received a low tidal volume (6 ml per kilogram of body weight) rather than the once widely accepted higher tidal volume of 12 ml per kilogram. This milestone study convincingly illustrated how lung-protective strategies of ventilation could improve the outcome of ARDS.

In this issue of the Journal, the ARDS Clinical Trials Network investigators examine the second potential mechanism of ventilator-induced lung injury. In patients with ARDS, the qualitative and quantitative surfactant defect leads to considerable end-expiratory alveolar collapse. During inspiration, exaggerated transpulmonary pressures may be generated at the junction of collapsed, nonrecruitable, and recruitable units, leading to the development of shear stress. In animal models, this repetitive cycle of alveolar collapse and re-recruitment has been associated with worsening lung injury. The extent of this lung injury has been reduced in animals through the use of PEEP levels that prevent derecruitment at end-expiration. Computed tomography in patients with ARDS has shown that PEEP does lead to recruitment of previously collapsed alveoli and that lung regions recruited with PEEP may not completely collapse at end-expiration. These animal models and observational studies led to randomized trials. A previous randomized trial involving 53 patients showed improved survival when a strategy involving a low tidal volume was used in combination with high PEEP levels in order to prevent derecruitment. These bench-to-bedside studies have rekindled the debate surrounding optimal PEEP levels for the treatment of ARDS.

The ARDS Clinical Trials Network investigators have conducted a rigorous, prospective, randomized, controlled trial that addresses a vital clinical question posed at the bedside on a daily basis: Does the addition of higher PEEP levels to the strategy of a low tidal volume in an attempt to prevent derecruitment during tidal ventilation further increase survival? Several aspects of this trial provide important insights into the mechanisms and management of ARDS.

One of the most important findings of this study is that the overall rates of death before hospital discharge among patients with ARDS who were receiving mechanical ventilation with a tidal-volume goal of 6 ml per kilogram ranged from 25 to 28 percent. Combining the current results with the results of the initial ARDS Clinical Trials Network study, a total of almost 1000 patients with ARDS have been treated with a protective, low-tidal-volume strategy, resulting in a mortality rate in the intensive care unit of 25 to 31 percent. Although other mechanical-ventilation or pharmacologic approaches may further improve survival among patients with ARDS, the mortality rates in these trials provide a benchmark for clinical practice and future clinical trials.

Although the overall results of this study demon-
strate no significant difference in mortality between the higher-PEEP and lower-PEEP groups, several aspects do require close scrutiny for a full appreciation and better understanding of the data. After the first 171 patients had been enrolled in the trial, the investigators concluded that “the difference in mean PEEP levels between study groups on study days 1 through 7 was less than the difference in the previous study that tested the effect of higher PEEP levels and smaller tidal volumes.”11 In order to maintain an appropriate separation between the two groups and to clearly test the initial hypothesis, the protocol was changed to require a minimal PEEP of 14 cm of water in the higher-PEEP group for the first 48 hours. As clearly stated by the authors, this change was made without knowledge of the clinical-outcome data. Without this change, adequate separation of PEEP between the two groups would not have occurred. Unfortunately, this change raises the question of whether the initial 171 patients enrolled in the trial (31 percent of the total number) should have been included in the analysis. The authors chose to combine the initial 171 patients with the subsequent 378 patients for the purpose of the second interim analysis. With the data from these two groups of patients taken together, the lack of a difference in mortality between the two study groups met the criteria defined a priori for stopping the trial early because of a low probability of a reduced mortality rate in the higher-PEEP group (the futility stopping rule), leading to early termination of the study.

The interpretation of the results is also complicated by significant differences between the two groups at baseline. Patients in the higher-PEEP group were significantly older and had a lower (worse) ratio of the partial pressure of arterial oxygen (PaO2) to the forced inspiratory volume in one second (FiO2) than patients in the lower-PEEP group. When combined with a trend toward a higher score for the Acute Physiology, Age, and Chronic Health Evaluation (APACHE III) in the higher-PEEP group, the differences indicate that these patients were not only older, but perhaps also sicker. After adjustment for age and the PaO2/FiO2 ratio, the mortality rate among the first 171 patients favored the higher-PEEP group, but the difference was very small and not significant. In the subsequent 378 patients, the adjusted absolute mortality rate was 4.5 percent less in the lower-PEEP group than in the higher-PEEP group. This difference was not significant, since the study was powered to show an absolute difference between groups of 10 percent. However, had the interim analysis included only these 378 patients, the study would probably not have met the criteria for early termination. Premature termination of the study may well have resulted.

Given the a priori target of an absolute difference of 10 percent in mortality rates, the authors are correct in their conclusion that higher PEEP did not confer an additional survival benefit beyond that already seen with the use of a tidal volume of 6 ml per kilogram and a low PEEP. However, an absolute difference of 4.5 percent in the adjusted mortality rate, although not statistically significant, may represent a clinically significant difference, making early termination of the trial for meeting the futility stopping rule unfortunate.

In the end, we can conclude that, for the 378 patients in the latter part of the trial, the use of higher PEEP did not result in a statistically significant survival benefit. This trial has contributed important new clinical information regarding the ventilatory management of ARDS. As is often the case with clinical trials, the study also raises new questions. The manner in which “optimal” PEEP is identified and its appropriate duration are being investigated in several ongoing, international PEEP trials. For clinicians, this study is both helpful and challenging. It should establish a mortality rate of 25 to 30 percent as the standard for the management of ARDS to which all future trials and ventilatory strategies should be held. For now, however, a clear answer to the question of optimal PEEP levels remains elusive.

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10. Muscedere JG, Mullen JB, Gan K, Slutsky AS. Tidal ventilation at...
New Treatment Options for Colorectal Cancer

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Epidermal growth factor receptor (EGFR) is a member of the HER family of tyrosine kinase cell-surface receptors that are dysregulated in many types of tumor; its expression has been associated with a poor prognosis in colon cancer.\(^1\) There are at least two opportunities to interfere with EGFR signaling that are being exploited clinically.\(^2\) In one approach, the extracellular receptor domain is bound by antibodies, such as cetuximab, that block ligand-mediated dimerization and subsequent activation of the receptor. In the second, the tyrosine kinase domain is bound by drugs that inhibit phosphorylation, such as gefitinib and erlotinib. 

Irinotecan is a topoisomerase I inhibitor that has been approved for the treatment of metastatic colorectal cancer when given either alone or in combination with fluorouracil and leucovorin. Studies have shown that the addition of irinotecan to fluorouracil and leucovorin increases the objective response rate, the time to tumor progression, and overall survival.\(^3,4\)

Cetuximab has been shown to enhance the antitumor activity of irinotecan in preclinical studies.\(^5\) The mechanism underlying this enhancement is unclear, but it may involve an antiapoptotic effect or the independent antiangiogenic effect of the inhibition of EGFR signaling. The experimental paradigm of combining agents that interfere with signaling pathways that make cells resistant to chemotherapy or agents that target a mechanism that independently influences tumor growth, such as angiogenesis, has been gaining traction in the clinical setting.\(^6\)

In this issue of the _Journal_, Cunningham and colleagues\(^7\) report the results of a randomized trial of cetuximab monotherapy as compared with cetuximab and irinotecan in combination in a population of patients with advanced, irinotecan-refractory colorectal cancer. It is difficult to achieve a meaningful treatment benefit in such patients. Those in the study by Cunningham et al. were carefully selected, and their disease was independently confirmed as refractory to irinotecan. Thus, a meaningful interpretation of the results could be expected.

Although the trial was designed to assess the efficacy of cetuximab monotherapy and of cetuximab and irinotecan in combination, it implicitly addressed the question of whether adding cetuximab to irinotecan resensitizes tumors that are refractory to irinotecan. In that sense, the trial was a success, and the findings clearly support the notion that interfering with EGFR signaling can overcome the resistance to irinotecan. Nevertheless, the appropriateness of the authors’ reporting methods warrants discussion. The primary end point of the trial was a tumor response, and the planned sample size was based not on a comparison of groups but on an estimation of the response rate to a specified level of precision. Thus, the trial could be best labeled as a randomized, phase 2 trial. However, the authors present multiple comparative analyses, including an analysis of overall survival, which was underpowered to detect a clinically meaningful difference (having less than 60 percent power to detect a two-month improvement in median survival).

In addition, two of Cunningham and colleagues’ conclusions are perhaps overstated. First, they suggest single-agent cetuximab for those patients who may not be able to tolerate the combination. The toxicity profile of the single agent is sufficiently favorable to justify such a statement, but the response rate — 10.8 percent, with a median time to progression of 1.5 months — raises the question of the magnitude of the benefit. Furthermore, the population for whom the authors suggest single-agent therapy should be considered was not specifically studied in this trial. Second, the authors state, “Cetuximab compares favorably with oxaliplatin-based therapy in patients with irinotecan-refractory disease.” The efficacy of oxaliplatin-based therapy in this setting has been established in a large, randomized, phase 3 trial;\(^8\) cetuximab has not yet been subjected to such rigorous validation.

This trial raises several additional questions. The authors attempt to address the critical issue of whether EGFR expression is a predictive marker of a response. Although the investigators performed this analysis in a central laboratory and in a standardized manner, several caveats should be noted.