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High Positive End-Expiratory Pressure and Lung Recruitment in Moderate to Severe Acute Respiratory Distress Syndrome
Does One Size Really Fit All?

Since David Ashbaugh turned the positive end-expiratory pressure (PEEP) knob for the first time to stabilize a 12-year-old patient with acute respiratory distress syndrome (ARDS) in 1964, ARDS as well as PEEP have transitioned to behemothian entities in respiratory critical care (1).

Although PEEP was initially considered primarily an oxygenation-improving intervention, its major role in preventing ventilator-induced lung injury through alveolar recruitment, reduction of stress between heterogeneously ventilated airspaces, and minimization of cyclic distal airway closing was soon recognized. Recruitment maneuvers, consisting of a transient and pronounced elevation of transpulmonary pressure over a few seconds to multiple minutes, were proposed shortly thereafter to achieve even larger aeration of the lung. However, despite their strong theoretical foundation, neither high PEEP nor recruitment maneuvers have succeeded in improving clinical outcomes. Much to the contrary, their potential to harm has become readily apparent (2, 3).

In this issue of the *Journal*, Dianti and colleagues (pp. 1300–1310) report a Bayesian network meta-analysis of 18 randomized trials in which they attempt to unravel the effects of lower and higher PEEP, as well as brief and prolonged lung recruitment maneuvers, on 28-day mortality in patients with moderate to severe ARDS ($Pa_{O_2}/F_{I_{O_2}} \leqslant 200$ mm Hg) (4). Network meta-analyses allow comparison of multiple therapy combinations by merging direct and indirect evidence. Direct evidence emanates from pooling of effectively performed head-to-head treatment trials. Indirect evidence, on the other hand, is estimated by modeling "loops" of evidence. In this way, trials comparing treatments A and B are combined with trials comparing treatments B and C to estimate the effect of treatment A against that of treatment C, thus enabling exploration of previously untested hypotheses. In addition, through the Bayesian approach prior knowledge is included into Bayesian network meta-analyses, which permits estimation of the intuitive posterior probability of treatment efficacy.

In their well-performed Bayesian network meta-analysis, Dianti and colleagues show that, in the included 4,646 patients with moderate to severe ARDS, the use of higher PEEP was superior to that of lower PEEP regarding 28-day mortality, with a posterior probability of treatment efficacy of 99% and a high certainty of benefit. Similarly, the use of a brief recruitment maneuver (<60 s) coupled to higher PEEP and the titration of PEEP by means of an esophageal pressure probe were both associated with moderate

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certainty of benefit and posterior probabilities of treatment success of 96% and 87%, respectively, compared with lower PEEP. Conversely, the combination of a prolonged recruitment maneuver ($\leqslant$60 s) used in conjunction with higher PEEP, compared with a higher PEEP setting alone, was associated with a 99% probability of harm with moderate certainty.

The strengths of this work include the adherence to a prespecified and reproducible protocol, the selection of a subpopulation of ARDS with $Pa_{O_2}/Fi_{O_2} \leqslant 200$ mm Hg, and the sole consideration of trials in which both arms had been ventilated with a low-V_T strategy (4–8 ml/kg of predicted body weight). In addition, the Bayesian network meta-analysis methodology used allows an in-depth comparison between vastly different PEEP and lung recruitment strategies that would otherwise not have been achievable.

Au contraire, the weaknesses of this meta-analysis are mainly linked to the underlying trials. Indeed, heterogeneity among trials was substantial, with some of the trials including prerandomization enrichment of their populations (2), whereas in others, treatment was provided dependent on specific morphological patient characteristics (5), limiting generalizability of the results. Furthermore, the definition of high PEEP can be hardly regarded as homogeneous across trials and includes PEEP titration strategies as diverse as the high PEEP/Fi_{O_2} table, titration by highest compliance, targeting of a plateau pressure of 28–30 cm H_2O, and titration by maximal aeration on lung ultrasound. These "factors that may modify treatment effects includ[ing] differing patient characteristics; differing co-interventions; [and] differing extent to which interventions of interest are optimally administered," as emphasized by Puhan and colleagues (6), likely represent a violation of the "transitivity assumption" on which unbiasedness of effects in a network meta-analysis is based (6). We can best exemplify this by focusing on the "higher PEEP versus lower PEEP" comparison. In the ALVEOLI (Assessment of Low Tidal Volume and Elevated End-Expiratory Volume to Obviate Lung Injury) trial (7), PEEP was targeted according to the low and high PEEP/Fi_{O_2} tables, resulting in mean PEEP values of 9 ± 4 cm H_2O in the lower PEEP group and 15 ± 4 cm H_2O in the higher PEEP group on the first day. Similarly, in the ExPress (Comparison of Two Strategies for Setting Positive End-Expiratory Pressure in Acute Lung Injury/Acute Respiratory Distress Syndrome) trial (8), PEEP was titrated to reach an end-inspiratory plateau pressure of 28–30 cm H_2O in the intervention group and was set between 5 and 9 cm H_2O in the control arm, leading to a mean PEEP of 8 ± 2 cm H_2O in the lower PEEP group and 16 ± 3 cm H_2O in the higher PEEP group. On the other hand, in the study by Pintado and colleagues (9), PEEP was selected according to best compliance in the intervention group (12 [10–13] cm H_2O) and according to the low PEEP/Fi_{O_2} table in the control group (10 [10–13] cm H_2O). While in the study by Salem and colleagues (10), PEEP was selected using lung ultrasound in the intervention arm (10 [8–14] cm H_2O) and the lower PEEP/Fi_{O_2} table in the control arm (8 [8–10] cm H_2O). Hence, given the discrepant PEEP settings, we are left wondering if the pooled treatment effect was indeed driven by higher PEEP settings alone.

Time and time again we have attempted to elucidate if a certain PEEP setting or recruitment maneuver improves the outcomes of our patients, despite our knowledge that the lungs of subjects with ARDS are highly heterogeneous and respond differently to mechanical ventilation (11). Merely enriching trials by choosing a specific Pa_{O_2}/Fi_{O_2} cutoff has repeatedly proved insufficient and has most probably led to the provision of a possibly harmful intervention to more than 60% of our trialed patients (2, 11). Furthermore, we continue discussing recruitment as if it were a well-defined concept, although it remains critically dependent on the chosen methodology, and no two approaches produce the same conclusion (12). Maybe it is time to step back from further, ever larger PEEP and recruitment trials and instead strive for unified consensus on how to best define recruitment and how to successfully predict it at the bedside? After all, recent years have brought a plethora of new pulmonary imaging tools, such as lung ultrasound (13), electric-impedance tomography (14), and dual-energy computed tomography (15). In combination with direct inference of the mechanical properties of the lung given by pressure–volume loops (16), esophageal pressure probes (17), or the recently described recruitment-to-inflation ratio (18), as well as the promising concept of ARDS phenotypes (19, 20), we might finally be able to individualize our recruitment interventions and perform trials including only patients who decidedly profit from them. Indeed, and despite its limitations, we recently saw an auspicious trial paving the way to this individualized treatment future (5).

Will this study change our daily clinical practice? We do not believe that high PEEP settings fit all our patient's lungs. Instead, PEEP should ideally be adjusted according to each patient's individual propensity for lung recruitability. From a pragmatic and clinical point of view, we will continue to set a moderate PEEP (10–12 cm H_2O) in our patients with moderate to severe ARDS, while providing prone positioning, the only proven beneficial intervention to date (21). In patients with refractory oxygenation impairment, when suspecting stiff chest-wall properties, and when measuring low static respiratory system compliance, we will consider the insertion of an esophageal pressure probe for PEEP titration (22, 23). Finally, given that our patients exhibit sufficient recruitment capability as assessed using pressure–volume loops at the bedside (16, 24), we will contemplate a brief recruitment maneuver (25). ■

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Scrutinizing the Mechanisms of West Non–Zone 3 Conditions during Tidal Ventilation

A long time ago, it was demonstrated that blood flow through arterioles, capillaries, or veins is well mediated by the Poiseuille law (the gradient between the upward and backward pressures of the vessel), provided the proper backward pressure is used, taking into account the surrounding pressure of the vessel and its closing pressure, leading to the principle of the vascular waterfall and the Starling resistor with different vessel zone conditions in which zone 3 regards the absence of any flow limitation (1). West zones are no more than the application of this principle to the pulmonary capillaries (2). Figure 1 illustrates its application to the vena cava as well as the pulmonary capillaries.

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