



## EDITORIAL

## Positive end-expiratory pressure, or the perennial conundrum surrounding lung recruitment



### Presión positiva al final de la espiración o el perenne enigma que rodea el reclutamiento pulmonar

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Six decades have passed since Ashbaugh and colleagues described the use of positive end-expiratory pressure (PEEP) to counteract alveolar collapse in adult (acute) respiratory distress syndrome, leading to the conception of the *open lung approach*.<sup>1</sup> Elevating the static alveolar distending pressure and reducing cyclic alveolar distension, were proposed as the optimal strategy to reduce the three mechanical components of ventilator-induced lung injury (VILI), namely baro-, volu- and atelectrauma.

While today we have robust evidence that the use of high tidal volumes ( $V_T$ ) is accompanied by a significant increase in mortality risk,<sup>2</sup> the role of PEEP setting has remained controversial. For three decades randomized controlled trials attempting to prove the benefits of higher PEEP strategies (~15 cmH<sub>2</sub>O versus ~8 cmH<sub>2</sub>O) have been following up to each other, but compelling evidence has been lacking ever since. Even the implementation of more sophisticated PEEP titration strategies, such as oesophageal manometry<sup>3</sup> and the use of staircase recruitment manoeuvres<sup>4,5</sup> have only added to the list of negative trials.

In the current issue of the *Journal*, Alapont and colleagues attempted to compile the current available evidence by pursuing a systematic review and meta-analysis of all randomized trials having investigated high PEEP strategies published to date.<sup>6</sup> Not surprisingly, the heterogeneity of the meta-analysis was moderate to substantial, reflecting the high clinical and methodological variability in these studies. The pooled relative risk for mortality was indicative (0.90, 95% Confidence Interval 0.78–1.03), albeit inconclusively, of a protective effect of the *open lung approach* and presented a low GRADE quality of evidence. Similar results have been observed in a recently published large network meta-analysis,<sup>7</sup> which indicated an inconclusive protective effect for a low  $V_T$  – high PEEP strategy (defined in said study as  $V_T < 8 \text{ ml/kg}$  and PEEP > 10 cmH<sub>2</sub>O).

This brings us to the perennial question as to why high PEEP resists conclusive proof as opposed to low  $V_T$ ? Conceptually we may break this apparent paradox down into the two opposite effects that  $V_T$  and PEEP exert on the total energy delivered to the lung. This energy and the response of the lung's parenchyma to it can be expressed through the mechanical power.<sup>8</sup> Consequently, in contrast to the obvious reduction in mechanical power achieved by lowering  $V_T$ , a high PEEP setting will mostly be associated

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with an increase in delivered pulmonary energy. As recently shown in an animal model, VILI is directly dependent on the delivered mechanical power.<sup>9</sup> Interestingly, the sensitivity analysis performed by Alapont and colleagues does indicate exactly towards this relationship. Studies in which a high PEEP setting induced a higher mechanical power relative to the control group were associated with a disappearing protective effect of high PEEP.

The high collinearity between the mechanical power and the driving pressure shown by the sensitivity analyses of Alapont et al. illustrates that the main mediator between PEEP increase and mechanical power reduction is a decreasing respiratory system elastance. In other words, only when an increase in PEEP leads to an effective distension of alveoli does it reduce the applied mechanical power. However, as Gattinoni et al. showed in their landmark paper, lung recruitability is highly heterogeneous, and less than 40% of patients seem to actively recruit a significant proportion of lung tissue during a recruitment manoeuvre.<sup>10</sup> Most strikingly, the authors observed that up to 24% of the total lung tissue cannot be recruited at end-inspiratory plateau airway pressures of 45 cmH<sub>2</sub>O.<sup>10</sup> Hence, one can speculate that more than half of the patients included in PEEP trials did not experience any alveolar recruitment and in the worst-case scenario experienced alveolar overdistension due to excessive PEEP settings. This possibly induced VILI, increasing mortality in the intervention group and drastically reducing statistical power. Ideally, we should fine tune  $V_T$  according to elastance, and PEEP according to lung recruitability.

But how do we recognize recruitable patients? Performing two CT studies at different PEEP levels, might be a very elegant option and the current gold standard,<sup>10</sup> but is impractical at the bedside. On the other hand, recruitment assessment methods based on lung mechanics are generally limited in discerning between actual atelectatic tissue recruitment and overdistension of the baby lung. The recently proposed recruitment-to-inflation ratio might provide guidance in balancing the risk of atelectrauma against the risk of overdistension during recruitment.<sup>11</sup> Another emergent technique, thoracic electric impedance tomography, can enable to discern alveolar recruitment from overdistension in a more visual approach, whilst concomitantly allowing assessment of regional pulmonary perfusion.<sup>12,13</sup>

In a further sensitivity analysis, Alapont et al. illustrate that patients with a  $P_aO_2/F_iO_2$  ratio below 160 mmHg profit from high PEEP as opposed to patients with higher  $P_aO_2/F_iO_2$  ratios. Briel et al. showed a similar  $P_aO_2/F_iO_2$  ratio dependant protective effect for high PEEP in their individual data meta-analysis.<sup>14</sup> Indeed, the fraction of pulmonary recruitable patients increases with decreasing  $P_aO_2/F_iO_2$  ratio,<sup>10,15</sup> a property that has already successfully been implemented to enrich ARDS trials targeting pulmonary recruitment by means of prone position.<sup>16</sup> However, and as the ART,<sup>4</sup> EPVent-2<sup>3</sup> and PHARLAP<sup>5</sup> trials have exemplified, simple enrichment of PEEP trials with a  $P_aO_2/F_iO_2$  ratio below 200 mmHg does not suffice.

How do we proceed from here? As exemplified by this meta-analysis, pursuing larger and more complex trials attempting to show the benefit of high PEEP in heterogeneous ARDS populations is a futile enterprise. Instead, it is time to step back to mechanistic research and reassess how to best characterize the mechanical properties of the lung

and best recognize patients with recruitable lungs. It will be the task of phenotyping and *individualized* medicine to pave the way towards a successful implementation of the *open lung approach*. If this will be achieved through biological and inflammatory phenotypes,<sup>17</sup> by a more lung centred characterization of pulmonary morphology and mechanical properties<sup>15</sup> or if advanced pulmonary imaging tools are the key,<sup>18</sup> remains unknown. However, it all points to an exciting future, full of research possibilities, ahead of us.

Up until then, we suggest a do no harm approach. From a pragmatic point of view, PEEP settings of 8–12 cmH<sub>2</sub>O will likely provide for a balanced choice, while we employ a simple and proven lifesaving intervention in ARDS: low  $V_T$  and prone position.

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