

CORRESPONDENCE



Some remaining important questions after LUNG SAFE

Discussion of “Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study”

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Comments from Drs Dreyfuss and Gaudry

The LUNG SAFE study is a major advance in the understanding of epidemiology and prognosis factors of ARDS [1].

The “Discussion” states that the use of higher PEEP in moderate or severe ARDS was independently associated with improved hospital survival, suggesting “benefits with higher PEEP particularly in more severe ARDS”. This assertion is disputable:

- Figure 2 shows that higher PEEP was associated with improved survival only in moderate ARDS. Moreover, this observation is at variance with the results of a meta-analysis which found beneficial effects of higher PEEP in both moderate and severe ARDS [2].
- There was no benefit of higher PEEP on ICU mortality (see “supplementary appendix”). It is puzzling why a baseline PEEP level affected hospital mortality but not ICU mortality.
- The authors equate statistical and causal links. The association of higher PEEP with survival might reflect the fact that patients with better prognosis tolerated higher PEEP.
- The authors “forced” PEEP in their multivariate analysis. Though acceptable this is not specified in the “Methods”, which indicate that only variables with $P < 0.05$ on bivariate analysis were entered in multivariate analyses. P values for association of PEEP with mortality were >0.6 .

Analysis of patients with true plateau pressure measurement deserves more attention to the respective interest of driving and plateau pressures. Both parameters predicted mortality with acceptable accuracy and neither seemed superior. LUNG SAFE suggests that pending an adequate prospective study, the two parameters should be closely monitored. The advantage of plateau pressure is that it requires no computation. Clinicians should not consider that dynamic distension (reflected by driving pressure) is the major culprit in ventilator-associated complications. Maximal distension, irrespective of driving pressure, is an important contributor to both the generation of ventilator-induced lung injury and mortality [3]. Physicians should simply monitor plateau pressure and adequately use early muscle paralysis and prone positioning in severe cases. LUNG SAFE brilliantly shows that these simple tools are too rarely used.

Reply from Drs Madotto and Laffey

We used hospital mortality because it is a robust and patient-centred parameter. This was a predefined choice, reported as the major outcome across the LUNG SAFE studies [4, 5].

We reported multivariable analyses relating to PEEP and hospital mortality. Higher PEEP [OR 0.95 per cmH₂O PEEP (95% CI 0.92–0.98); $P = 0.001$; Table 2] was independently associated with better outcome in all patients with ARDS. When we dichotomized the dataset into lower versus higher PEEP, only patients with moderate ARDS that received lower PEEP (<12 cmH₂O) had a higher risk of hospital mortality. In contrast to the authors’ contention, we found that higher PEEP was associated with improved ICU survival (Table E2).

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We agree that an observational study permits no causal inferences regarding the relationship between PEEP and outcome. The association between PEEP and hospital mortality was independent of other factors included in the multivariate analysis, including multiple illness severity indices.

We did not ‘force’ PEEP into the multivariable analysis, but selected variables on the basis of stepwise regression, evaluating at each step the statistical significance of all “candidate” predictor variables, until there was no justification for entering or removing more (see “Methods”). Therefore, PEEP statistical significance was always checked during the stepwise “process” even if this variable showed a *P* value exceeding 0.05 initially.

We entirely agree on the need for more routine measurement of plateau pressure. In regard to the relative merits of plateau versus driving pressures, we prefer to leave this debate to others. In LUNG SAFE, when both measurements were included in multivariable analysis, plateau pressure was no longer associated with outcome, likely due to colinearity (Table E4). When driving pressure was excluded, plateau pressure was associated with outcome (Table E5). It is indeed important to consider the potential for both static and dynamic distension to cause harm, although we did not address this specific issue.

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Compliance with ethical standards

Conflicts of interest

The authors declare no conflict of interest. This article does not contain any studies with human participants or animals performed by any of the authors.

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