Editorial Commentary

Positive-end expiratory pressure titration and transpulmonary pressure: the EPVENT 2 trial

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Brief overview of trials about positive-end expiratory pressure in acute respiratory distress patients before the EPVENT 2 study

The acute respiratory distress syndrome (ARDS) is an acute inflammatory lung edema. The current definition includes three severity stages based on PaO_2/FiO_2 ratio measured at positive end-expiratory pressure (PEEP) of 5 cmH_2O or more (1). ARDS was described for the first time by Ashbaugh *et al.* in 1967; it was suggested that PEEP could have beneficial effects (2). More than 50 years after its initial description ARDS is still of great concern for the intensivist because it accounts for 10% of ICU admissions and still supports a rough 40% mortality rate (3). Furthermore, ARDS can only be treated in the ICU environment because it very often requires invasive mechanical ventilation and because the mechanical ventilation settings can impact patient outcome. Indeed, the use of low tidal volume (VT) is strongly recommended as it has been demonstrated to decrease absolute mortality by 9% in the landmark ARMA randomized control trial (RCT) (4). It is worth mentioning that this trial was innovative in many aspects, like the titration of VT according predicted (PBW), not measured, body weight, the monitoring of plateau pressure (Pplat), the adjustment of respiratory rate up to 35 breaths/minute, and a pragmatic way to set PEEP. The oxygenation target (PaO_2 55–80 mmHg) was managed via a table that modulated FiO_2 and PEEP together. However, the main target was to protect the lung from overdistension. The ARMA trial compared VT of 12 mL/kg PBW and Pplat targeted to 50 cmH_2O (control group) to VT of 6 mL/kg PBW and Pplat targeted to 30 cmH_2O (intervention group). It confirmed that excessive strain was the most important determinant of ventilator-induced lung injury (VILI). The other component of VILI is the atelectrauma resulting from the shear stress imposed by the repeated opening and closing of peripheral lung units to their neighboring lung areas. This component may be prevented by setting PEEP. Therefore, three large trials were done comparing higher to lower PEEP at same low VT. However, none of them was associated with a better outcome from using one strategy over the other. The ALVEOLI trial (5) enrolled a total of 549 ARDS patients at PaO_2/FiO_2 <300 mmHg between a Low FiO_2/High PEEP and a High FiO_2/Low PEEP table. The LOVS trial (6) included 985 ARDS patients with PaO_2/FiO_2 ratio lower than 250 mmHg and tested similar PEEP/FiO_2 table as that described in the ALVEOLI trial. Pplat in the high PEEP group was targeted to 40 cmH_2O, while in the low PEEP group it was kept under 30 cmH_2O. There was no difference between the two groups in terms of mortality and barotrauma.

The EXPRESS trial (7) involved 768 patients with ARDS (PaO_2/FiO_2 <300 mmHg) and used another strategy to set PEEP from the two previous trials. Were compared, at similar VT of 6 mL/kg PBW, PEEP set up to reach a Pplat of 28 to 30 cmH_2O (increased recruitment strategy group) to a control group in which PEEP was set up between 5 and 9 cmH_2O. The oxygenation target was the same as in the previous trials but was managed by using FiO_2 alone. No statistically significant difference was found between the two groups in terms of mortality. However, with the increased recruitment strategy the number of ventilator-free days and organ failure–free days were significantly higher than in the control group. These three trials were meta-analyzed at the individual patient level and it came out a slight but statistically significantly better survival by using higher PEEP than lower PEEP in ARDS patients with PaO_2/FiO_2 <200 mmHg (8). Finally, the ART trial (9) compared a lung maximal recruitment strategy mostly based on high PEEP to a control group in which PEEP averaged 13 cmH_2O, in ARDS patients (PaO_2/FiO_2 <200 mmHg). Of notice VT was 5 mL/kg PBW in both groups. The mortality was significantly higher by 10% in the lung recruitment group than in the control group. This trial actually strongly suggests that very high PEEP is associated with worst outcome as compared to high PEEP. Surprisingly, the driving pressure (DP), which is the difference between Pplat and PEEP (or better Pplat and total PEEP), was lower in the experimental group than in the controls. This result was therefore in contrast to the findings of a previous landmark study that showed DP as the strongest predictor of death and moreover the mediator of the effect of Pplat, PEEP and VT on mortality in ARDS patients.

In all these trials the PEEP set at the ventilator was based on airway pressure (Paw) and not on transpulmonary pressure (P_L). Talmor *et al.* found out that P_L at end-expiration (P_L,ee), computed as the difference between Paw and absolute esophageal pressure (Pes), was frequently negative in ARDS patients, due to very positive values of Pes,ee (10). This finding was interpreted as resulting from a prevalent loss of lung volume in the dependent lung parts, close to the Pes sensor location. Their idea was to propose to set PEEP up to the point at which P_L,ee was equal to 0 cmH_2O or more. They hypothesized that this would promote some recruitment in the dependent lung regions and furthermore provide a personalized approach in tailoring PEEP. They tested this hypothesis in a single center randomized controlled trial, EPVENT 1, over 61 patients (PaO_2/FiO_2 <300 mmHg) (11). P_L was also measured at the end of inspiration (P_L,ei) in EPVENT1 to provide some safety because it was expected that Pplat would be very much greater than 30 cmH_2O with the higher PEEP likely generated by the Pes-guided strategy. They used a threshold of 25 cmH_2O P_L,ei as the upper safety limit, which should prompt VT to be reduced down to 4 mL/kg PBW. However, it is worth mentioning that P_L,ei can be measured by another method, ie the elastance ratio method (12):

$$P_L,ei = Pplat \times (E_L/Ers) \quad [1]$$

where E_L and *Ers* are elastance of the lung and of the respiratory system, respectively, given by:

$$E_L = [(P_{plat} - P_{es,ei}) - (PEEP_{TOT} - P_{es,ee})]/VT \quad [2]$$

$$Ers = (P_{plat} - PEEP_{TOT})/VT \quad [3]$$

where, $P_{es,ei}$ is Pes measured during an inspiratory hold, $PEEP_{TOT}$ is total PEEP and Pes,ee Pes both measured during an expiratory hold. It is worth mentioning that recent data suggest that absolute P_L,ei reflects dependent P_L and elastance-related P_L,ei method non-dependent P_L and P_L,ee lung regions in-between (13).

The EPVENT 1 study also included a specific PL,ee/FiO_2 table. In the control group they used a PEEP/FiO_2 table, as used in the trials led by the ARDSnet work mentioned above, with a slight different oxygenation target. The results showed significant better oxygenation, better compliance and a strong trend towards better survival in the intervention group.

The results of EPVENT1 logically prompted the authors to perform a large multicenter RCT to try to confirm these promising, though preliminary, findings.

The EPVENT 2 trial

EPVENT 2 was a multi-centered RCT conducted between 2012 and 2017 in 14 intensive care units in North America (14). Patients enrolled had moderate-to-severe ARDS criteria according to the Berlin definition. In the patients belonging to the intervention group an esophageal catheter was placed, in order to obtain P_L. In this group, PEEP was titrated according a P_L,ee/FiO_2 table, which was slightly different from the one used in the EPVENT 1 trial. In particular, the range of P_L,ee in this table was 0–6 instead 0–10 cmH_2O in EPVENT 1. To limit the risk of overdistension in the intervention group, when PL,ei was

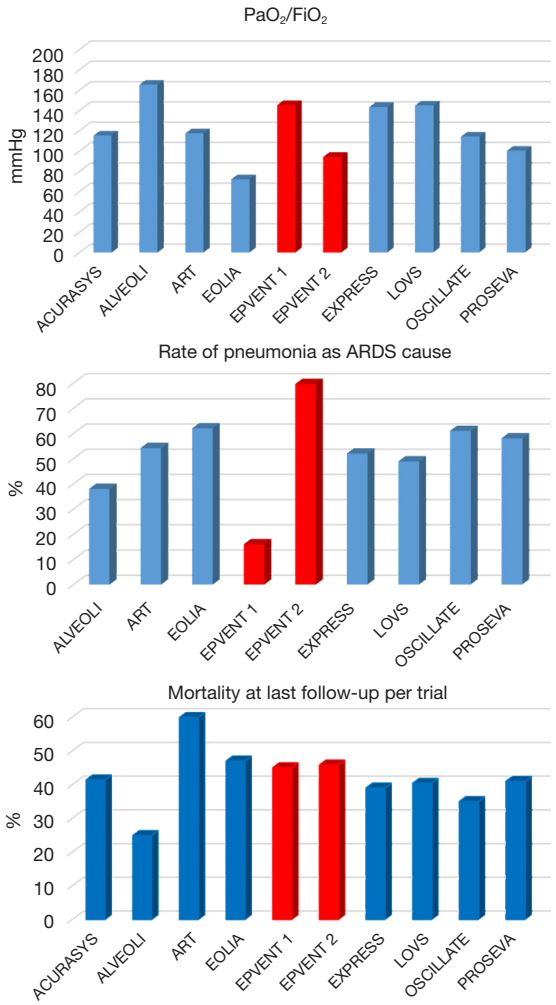

Figure 1 Mean values of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen in air (FiO_2) ratio, prevalence of pneumonia, and mortality at the last follow-up in the trial in the control groups of recent randomized control trials in acute respiratory distress patients. The studies are shown in alphabetic order in each plot and the references are (5-7,9,11,15-18).

above 20 cmH_2O, VT could be reduced down to 4 mL/kg PBW. The assessment was done once a day. In the control group, the authors used the same PEEP/FiO_2 table as in the control group in the OSCILLATE trial. Furthermore, in this group Pplat had to be maintained below 35 cmH_2O and not 30 cmH_2O. The primary end point was a composite score incorporating death and days free from mechanical ventilation at day 28. There was no difference between the two groups regarding the primary end-point: a more favorable outcome was observed in 49.6% among the 102 patients in the experimental group and in 50.4% among the 98 patients in the control group (P=0.92). Mortality at day 28 was 32.4% *vs.* 30.6% (P=0.88) and the median days free of mechanical ventilation were 22 and 21 (P=0.85), in experimental and control groups, respectively. There were no other statistical difference between other end-points, like barotrauma, shock-free days, acute kidney injury, PaO_2/FiO_2 ratio, PEEP and DP between the two groups.

Differences between EPVENT 1 and EPVENT 2 trials

In the EPVENT 2 *vs.* EPVENT 1 trial, the range of P_L,ee used in the P_L,ee/FiO_2 table was narrower. As an example, for FiO_2 0.6 P_L,ee should be 4 cmH_2O in EPVENT 1 and 2 cmH_2O in EPVENT 2. The Pplat upper safety limit in the control group was 35 cmH_2O in the EPVENT2 but unspecified in the EPVENT1 and that of P_L,ei of 25 cmH_2O in EPVENT1 and 20 cmH_2O in EPVENT2. These findings would increase the risk of overdistension in the control group in EPVENT2 and result in setting lower PEEP in the experimental group in EPVENT2. ARDS patients were different between the two trials: ARDS was mostly from a secondary or indirect lung injury in EPVENT1 and mostly from pneumonia in EPVENT2 (*Figure 1*). Gattinoni *et al.* showed that secondary ARDS has a higher incidence of increased chest wall elastance compared to primary ARDS (19). In this kind of patients, largely prevalent in the EPVENT 1 study, it is reasonable to think that the measure of the P_L has an impact on clinical outcome. It could be interesting to focus the Pes-guided PEEP in obese patients without ARDS, representing a population characterized by an increased chest wall elastance, and for which it is difficult to predict the elastance of the chest wall without using the esophageal pressure (20-22). It could also be helpful to test the benefits of P_L in a selected population of secondary ARDS, since also this group of patients is likely to have increased chest wall elastance.

The rate of pneumonia was even higher in EPVENT2 than in any other recent trial in ARDS (*Figure 1*). Zampieri *et al.* went back to the ART trial using a machine-learning approach. They found that experimental strategy was more detrimental in patients with pneumonia (23). This could explain the EPVENT 1 positive results, due to the low number of pneumonia ARDS patients, where the high PEEP strategy obtained using P_L, could be dangerous.

In EPVENT 1 the intervention treatment was applied for only three days *vs* 28 days in the EPVENT 2.

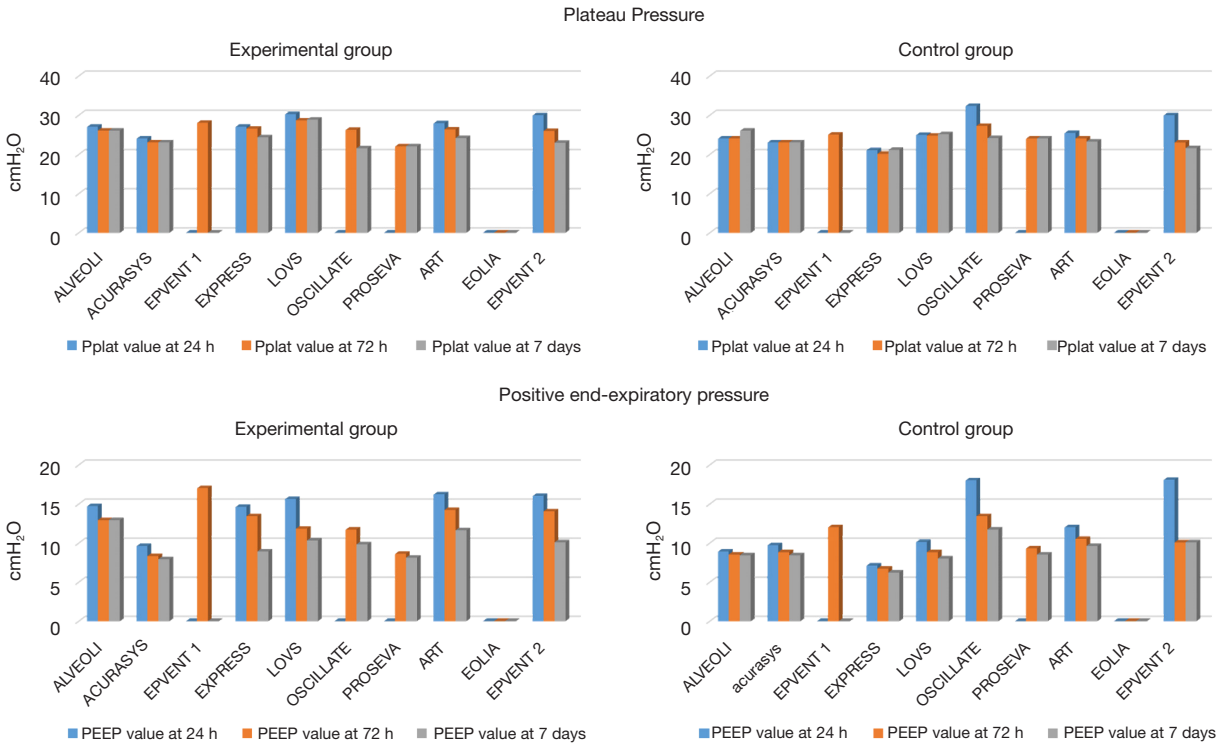

Figure 2 Mean values of positive end expiratory pressure (PEEP) in the lower panels and Plateau pressure (Pplat) in the upper panels for control (right panels) and intervention groups (left panels) recent randomized control trials in acute respiratory distress patients. The studies are shown in alphabetic order in each plot and the references are (5-7,9,11,15-18).

Finally, oxygenation was more severely impaired in EPVENT2 than in EPVENT1 at baseline (*Figure 1*).

Despite of these differences the mortality rate was similar in the control groups of EPVENT2 as in the ones of other recent trials in ARDS patients (*Figure 1*) (5-7,9,11,15-18). In the experimental group the mortality at day 28 was 17% in EPVENT1, ie twice lower than in EPVENT2.

Reasons for the negative results of the EPVENT 2 trial

Apart from the differences between EPVENT 1 and EPVENT2, other specific reasons may explain the negative results observed in EPVENT2.

A first reason may be a lack of power. The strategy used to power the trial with a composite score minimizes the number of patients to include (24). For instance, in the EPVENT 2 the absolute difference of rescue therapy prevalence between the groups was 8.3% and didn't reach the statistically significance contrary to the rate of 4.2%, which was statistically significant in the LOVS trial.

Another reason could have been that the control group of EPVENT 2 had a better outcome as compared with the control groups of other RCTs. This was not the case as discussed above (*Figure 1*).

A third reason is that the PEEP set was the same between control and experimental groups in EPVENT2 contrary to EPVENT1 where PEEP was significantly higher in the Pes-guided group. This can be explained by the case mix as discussed above. However, since the hypothesis for the trial to be beneficial is based on PEEP difference it is not surprising that at same PEEP, same VT and same DP in both groups no difference in mortality was found. We recently set PEEP according to a Pes-guided strategy and a PEEP/FiO_2 table as that used in the ARMA trial in 32 ARDS patients, most of them from pneumonia, in supine and prone positions (25). On average the Pes-guided strategy resulted in a 2 cmH_2O higher PEEP than with the other strategy whatever the position.

EPVENT2 protocol resulted in higher PEEP in both groups than in the recent ARDS trials (*Figure 2*).

Finally, it could be that the concerns about the use of

absolute Pes to measure P_L,ee were valid (26,27).

Conclusions

EPVENT 2 is a methodologically correct trial with some minor limitations. Overall, this study supports the evidence that the routine use of the Pes-guided PEEP titration doesn't change the mortality rate. This finding is probably associated with the homogeneity of the chest wall elastance distribution within an ARDS population with a high prevalence of pneumonia.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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