PEEP titration in moderate to severe ARDS: plateau versus transpulmonary pressure

Marie Bergez1, Nicolas Fritsch1, David Tran-Van1, Tahar Sagh1, Tan Bounkim3, Ariane Gentile1, Philippe Labadie1, Bruno Fontaine1, Alexandre Ouattara4,5 and Hadrien Roze4*

Abstract

Background: Although lung protection with low tidal volume and limited plateau pressure (Pplat) improves survival in acute respiratory distress syndrome patients (ARDS), the best way to set positive end-expiratory pressure (PEEP) is still debated.

Methods: This study aimed to compare two strategies using individual PEEP based on a maximum Pplat (28–30 cmH2O, the Express group) or on keeping end-expiratory transpulmonary pressure positive (0–5 cmH2O, Plexpi group). We estimated alveolar recruitment (Vrec), end-expiratory lung volume and alveolar distension based on elastance-related end-inspiratory transpulmonary pressure (PLEL).

Results: Nineteen patients with moderate to severe ARDS (PaO2/FiO2 < 150 mmHg) were included with a baseline PEEP of 7.0 ± 1.8 cmH2O and a PaO2/FiO2 of 91.2 ± 31.2 mmHg. PEEP and oxygenation increased significantly from baseline with both protocols; PEEP Express group was 14.2 ± 3.6 cmH2O versus 16.7 ± 5.9 cmH2O in Plexpi group. No patient had the same PEEP with the two protocols. Vrec was higher with the latter protocol (299 [0 to 875] vs. 222 [47 to 483] ml, p = 0.049) and correlated with improved oxygenation (R2 = 0.45, p = 0.002). Two and seven patients in the Express and Plexpi groups, respectively, had PLEL > 25 cmH2O.

Conclusions: There is a great heterogeneity of PLEXP when Pplat is used to titrate PEEP but with limited risk of overdistension. A PEEP titration for a moderate positive level of PLEXP might slightly improve alveolar recruitment and oxygenation but increases the risk of over-distension in one-third of patients.

Keywords: ARDS, PEEP titration, Monitoring, Transpulmonary pressure

Background

Mechanical ventilation for acute respiratory distress syndrome (ARDS) may lead to ventilation-induced lung injury [1]. A lung protective ventilation strategy, with low tidal volume (VT), limited plateau pressure and positive end-expiratory pressure (PEEP), aims to improve survival [2, 3]. Different protocols have been proposed to set PEEP in order to avoid alveolar collapse with limited end-inspiratory distension of the lungs [4]. Some of these strategies use a table of PEEP values which depend on inspired fraction of oxygen (FiO2), while others are based on individual respiratory mechanics. The Express protocol, developed by Mercat et al., consists of attaining airway plateau pressure (Pplat) up to 28–30 cmH2O with a fixed VT of 6 ml kg−1 predicted body weight [5]. These authors reported a significant reduction in morbidity but not mortality. Because airway pressure is an oversimplified surrogate for lung stress in patients with abnormal chest wall elastance, it could be relevant to assess lung distending pressure estimated from transpulmonary pressure (P1). This later, in static airway conditions, can be estimated by measuring pleural via esophageal pressure [6]. This estimation can be affected by elastic recoil of the balloon, of the esophagus, esophageal muscular tone and pressures transmitted from the heart beat and mediastinum [7]. The relationship between esophageal and pleural

*Correspondence: hadrien.roze@chu-bordeaux.fr
4 Magellan Medico-Surgical Center, South Department of Anaesthesia and Critical Care, CHU Bordeaux, 33000 Bordeaux, France
Full list of author information is available at the end of the article

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pressure, and its measurement in ARDS patients with an important anteroposterior gradient in the supine position, requires the acceptance of several assumptions [8]. However, a recent study directly measured pleural pressure in pigs and human cadavers and found that esophageal pressure accurately reflects pleural pressure close to the balloon, corresponding to dependent lung regions to mid-chest [7]. Thus, collapse and trauma from recurrent alveolar collapse and re-opening can be related to end-expiratory $P_{L}$ [9, 10] Elastance-derived calculation of relative end-inspiratory $P_{L}$ ($P_{L,EL}$) is close to direct measurement of pleural transpulmonary end-inspiratory pressure in the non-dependent lung region and might therefore give some information about alveolar distension in the non-dependent lung, more at risk for over-distension [11]. Different protocols have been proposed for setting PEEP according to $P_{L}$. The EPVent 1 and 2 trials titrated PEEP by measuring pleural pressure to achieve a positive end-expiratory transpulmonary pressure ($P_{L,EL}$) between 0 to 10 cmH$_2$O according to a sliding scale based on FiO$_2$ [12, 13] Grasso et al. used $P_{L,EL}$ to increase PEEP in severe ARDS until $P_{L,EL}=25$ cmH$_2$O [14]. Some patients improved their oxygenation significantly and avoided extracorporeal membrane oxygenation.

The aim of this study was to compare estimated alveolar recruitment ($V_{rec}$) with end-expiratory lung volume ($EELV$) measurement, and alveolar distension with measurement of $P_{L,EL}$, during individual PEEP titration using two different targets: $P_{plat}$ (28–30 cmH$_2$O) or positive $P_{Lexpi}$ (0–5 cmH$_2$O).

**Methods**

**Study design and participants**

This multicenter, prospective crossover physiological study was conducted in severe ARDS patients admitted to three French intensive care units in Bordeaux (Robert Picqué Military Teaching Hospital; North Bordeaux Aquitaine Clinic; Thoracic Intensive Care Unit, Bordeaux University Hospital) between 2016 and 2017. All patients had recent (within a week) bilateral opacities as described previously and with thoracic radiography (radio-opaque markers) [6, 17]. At baseline, patients were ventilated with a $V_T$ of 6 ml kg$^{-1}$ predicted body weight and a PEEP between 5–8 cmH$_2$O ($PEEP_{baseline}$). Twenty minutes later, PEEP was titrated according to the Express or $P_{Lexpi}$ protocols in a randomized order. For the Express protocol, PEEP was titrated in order to obtain a $P_{plat}$ between 28–30 cmH$_2$O. For the $P_{Lexpi}$ protocol, PEEP was titrated in order to obtain a $P_{Lexpi}$ between 0–5 cmH$_2$O. PEEP level according to each protocol was maintained for 20 min before recording all respiratory parameters and blood withdrawal for blood gas analysis. PEEP was returned to 0 cmH$_2$O between each protocol during less than 30 s. For hemodynamic assessment, respiratory variation of the arterial pulse pressure and the response to a passive leg raising test were used before PEEP titration, with an echocardiography. If positive, a fluid challenge was performed to avoid hypovolemia. After PEEP titration, echocardiography was done to assess right heart function and the occurrence of septal dyskinesia.

**Measurement of variables**

End-inspiratory and -expiratory airway and esophageal pressures were measured during a 5 s pause of the ventilator; $V_T$ were monitored continuously. EELV was measured using the nitrogen washin/washout technique; FiO$_2$ variation was 10% and the average of washin EELV and washout EELV for each PEEP levels was recorded.

Variables were calculated using the following equations:

- Absolute inspiratory transpulmonary pressure
  
  \[ P_{L,es} = P_{plat} - \text{end-inspiratory esophageal pressure} \]

- Elastance-related transpulmonary pressure
  
  \[ P_{L,EL} = P_{plat} \times \frac{\text{lung elastance/respiratory system elastance}}{\text{lung elastance/respiratory system elastance}} \]

- $P_{Lexpi} = \text{total PEEP - end-expiratory esophageal pressure}$

- Airway driving pressure ($DP_{aw}$)
  
  \[ DP_{aw} = P_{plat} - \text{total PEEP} \]
Transpulmonary driving pressure \( (DP_L) = DP_{aw} - \) (end-inspiratory – end-expiratory esophageal pressure);

Elastance-related driving pressure \( = DP_{aw} \times (lung elastance/respiratory system elastance)\).

Respiratory system elastance \( = (P_{plat} - total PEEP) / V_T\);

Lung elastance \( = DP_{aw} / V_T\);

Respiratory system elastance \( = Lung elastance + Chest wall elastance\).

The following were also measured:

- Estimated recruitment volume \( (V_{rec} \text{in ml}) = (EELV \text{at high PEEP} - EELV \text{at low PEEP}) - ((V_T / P_{plat} - low PEEP)) \times (high PEEP - low PEEP)\). [19]

Statistical analysis

No statistical power calculation was conducted prior to the study; the sample size was based on our previous studies with this design of physiological crossover study with pairing. Data are expressed, respectively, as mean \( \pm \) standard deviation (SD) and median [interquartile range] for variables normally and non-normally distributed. The outliers were evaluated, but no action was necessary. The categorical data were expressed as numbers (percentage of patients). Comparison of variables between three settings was performed by using one-way repeated measures analysis of variance (ANOVA) followed by post hoc Tukey’s test for multiple comparisons. Comparison between categorical variables was performed using the Chi-squared test. Correlations used Spearman’s test. All statistical tests were two-tailed, and a \( p \) value of less than 0.05 was considered significant. All statistical analysis was performed using NCSS2007 software (Statistical Solutions Ltd, Cork, Ireland) and Prism 6 (GraphPad Software, La Jolla, CA, USA).

Results

Nineteen patients were included; they were all enrolled in the study less than 48 h after intubation. The baseline characteristics of these patients are summarized in Table 1, and there were no missing data.

PEEP levels, oxygenation and alveolar recruitment

Respiratory mechanics according to each PEEP setting are summarized in Table 2. In comparison with \( P_{baseline} \), the Express and \( P_{Lexpi} \) protocols significantly increased PEEP and \( P_{plat} \) without any change in driving pressure (Table 2). These changes were associated with a significant improvement in oxygenation. Median PEEP value was not significantly different between the Express and \( P_{Lexpi} \) protocols. However, analysis of individual PEEP data according to each protocol shows that no patient had the same PEEP (Fig. 1) with a median of absolute difference of 5.0 [4.0–8.0] cmH2O and 13 patients had higher PEEP with \( P_{Lexpi} \) protocol.

EELV variation from baseline was significantly higher with \( P_{Lexpi} \) protocol 60 (58) % vs 36 (28) % with Express protocol, \( p = 0.025 \). Estimated \( V_{rec} \) was significantly higher with the \( P_{Lexpi} \) Protocol than with Express, 298 [0 to 845] vs 222 [47 to 483] ml, respectively. Vrec and \( PaO_2/\text{FiO}_2 \) ratio changes were significantly correlated

| Table 1 Baseline characteristics of the patients (n = 19) |
|------------------------------------------|
| Characteristic                          | Value            |
| Male, n (%)                             | 13 (68.4)        |
| Age (years)                             | 72 ± 10          |
| Body mass index (kg/m²)                 | 28 ± 6           |
| SAPS II score                           | 65 ± 15          |
| Etiology of ARDS, n (%)                 | 16 (84.2)        |
| Pneumonia/complication                  | 2 (10.5)         |
| Pancreatitis                            | 1 (5.3)          |
| Respiration at baseline (SOFA), n (%)   | 18 (94.7)        |
| Hemodynamic                             | 9 (47.4)         |
| Renal                                   | 0 (0)            |
| Hematological                           | 2 (10.5)         |
| Arterial blood gas                      |                  |
| \( PaO_2/\text{FiO}_2 \) ratio           | 92 ± 31          |
| \( \text{FiO}_2 \) (%)                  | 80 ± 21          |
| pH                                      | 7.31 ± 0.11      |
| \( \text{PaCO}_2 \) (mmHg)              | 45 ± 10          |
| \( \text{HCO}_3^- \) (mmol/l)            | 22.4 ± 4.0       |
| Base excess                             | −3.4 ± 5.1       |
| Lactates (mmol/l)                       | 1.6 ± 1.0        |
| Hemodynamic variables                   |                  |
| Heart rate (beats/min)                  | 99 ± 27          |
| Systolic arterial pressure (mmHg)       | 127 ± 23         |
| Diastolic arterial pressure (mmHg)      | 59 ± 12          |
| Mean arterial pressure (mmHg)           | 82 ± 13          |
| Respiratory mechanics                   |                  |
| Minute ventilation (L/min)              | 9.6 ± 1.6        |
| Tidal volume (ml/kg PBW)                | 6.1 ± 0.4        |
| EELV (ml)                               | 1319 ± 626       |
| Aspect of ARDS, n (%)                   |                  |
| Patchy                                  | 6 (31.6)         |
| Diffuse                                 | 10 (52.6)        |
| Focal                                   | 3 (15.8)         |
| Mortality at Hospital discharge         | 10/19 (53%)      |

Results are expressed as number (%), or mean \( \pm \) standard deviation

SAPS 2: Simplified Acute Physiology Score 2; ARDS: acute respiratory distress syndrome; PBW: predicted body weight. SOFA: sepsis-related organ failure assessment; EELV: end-expiratory lung volume (ml)
Table 2 Measurements of respiratory function and hemodynamics (n = 19)

| Protocols                  | PEEP baseline | Express protocol | P_{\text{Lexpi}} | p value |
|---------------------------|--------------|-----------------|-----------------|---------|
| PEEP (cmH₂O)             | 7.0 ± 1.8    | 14.2 ± 3.6*     | 16.7 (6.9)*     | < 0.0001|
| P_{\text{PaCO}} (cmH₂O) | 20.8 ± 4.0   | 28.8 ± 2.0*     | 33.9 ± 10.6*    | < 0.0001|
| P_{\text{PaO}} (cmH₂O)  | 7.0 ± 5.9    | 11.9 ± 6.2*     | 15.5 ± 8.5*     | 0.0013  |
| P_{\text{PE}} (cmH₂O)    | 153.4 ± 4.9  | 205.4 ± 4.7*    | 243.4 ± 11.4*   | 0.0025  |
| P_{\text{pH}} (cmH₂O)    | −2.6 ± 5.2   | 14.4 ± 5.1*     | 3.3 ± 1.6*      | < 0.0001|
| P_{\text{FiO}} (%)       | 80.0         | 2067 ± 924*     | 2287 ± 945*     | 0.001   |
| PaCO₂ (mmHg)             | 45.2         | 14.2 ± 5.0      | 16.4 ± 7.8      | 0.17    |
| PaO₂/FiO₂                | 91.2 ± 5.2   | 12.3 ± 8.3      | 0.20             |
| MAP (mmHg)               | 82.0 ± 13.4  | 74.7 ± 12.9     | 75.7 ± 12.0     | 0.06    |
| Crs (ml/cmH₂O)           | 33.3 ± 15.8  | 30.0 ± 10.7     | 28.3 ± 13.2     | 0.17    |
| E_{cw} (cmH₂O/l)         | 7.3 ± 4.3    | 8.1 ± 5.6       | 9.5 ± 8.1       | 0.30    |
| E_{L} (cmH₂O/l)          | 26.0 ± 11.9  | 28.0 ± 15.9     | 33.2 ± 25.1     | 0.25    |
| FIO₂ (%)                 | 80.0 ± 21.1  | 80.6 ± 21.2     | 81.1 ± 21.6     | 0.46    |
| PaO₂/FiO₂                | 91.2 ± 31.2  | 134.0 ± 67.2*   | 152.7 ± 80.1*   | 0.01    |
| pH                       | 7.31 ± 0.01  | 7.30 ± 0.11     | 7.31 ± 0.12     | 0.08    |
| PaCO₂ (mmHg)             | 45.2 ± 10.4  | 46.5 ± 9.6      | 45.3 ± 11.0     | 0.26    |
| MAP (mmHg)               | 82.0 ± 13.4  | 74.7 ± 12.9     | 75.7 ± 12.0     | 0.06    |
| Heart rate (beats/min)   | 99.2 ± 27    | 102.4 ± 26      | 107.2 ± 28      | 0.19    |
| Lactates (mmol/l)        | 1.6 ± 0.9    | 1.5 ± 0.8       | 1.5 ± 0.8       | 0.27    |

Results are expressed as mean ± standard deviation

P_{\text{PaCO}}: Plateau pressure; P_{\text{PaO}}: end-expiratory transpulmonary pressure; P_{\text{PaE}}: transpulmonary driving pressure; P_{\text{PE}}: absolute transpulmonary elastance-related pressure; P_{\text{PaE}}: relative end-expiratory pressure; P_{\text{L,EL}}: absolute inspiratory transpulmonary pressure; P_{\text{PaE}}: airway driving pressure; P_{\text{PaE}}: transpulmonary driving pressure; P_{\text{PaE}}: transpulmonary elastance-related driving pressure; E_{L}: lung elastance; EELV: end-expiratory lung volume; E_{cw}: elastance chest wall; Crs: compliance respiratory system; MAP: mean arterial pressure. p value refers to repeated measures ANOVA. *p < 0.05 of Express and P_{\text{Lexpi}} groups versus baseline group. †p < 0.05 of Express versus P_{\text{Lexpi}} groups.

With the Express protocol, six patients had negative P_{\text{Lexpi}} − 2.5 [−7.8 to −1.15] cmH₂O with a median PEEP of 14.0 [9.7 to 14.5] cmH₂O. These six patients had a significant lower respiratory system compliance (25.2 [15.8 to 29.0] vs. 30.7 [25.6 to 39.2] ml/cmH₂O, p = 0.027), and a significant lower EELV (1240 [835 to 2118] vs. 1900 [1700 to 3045] ml, p = 0.040). When these patients received the P_{\text{Lexpi}} protocol, median PEEP increased to 24.0 [18.0 to 26.5] cmH₂O, P_{\text{pl}} was 40.2 [33.1 to 51.0] cmH₂O, and PaO₂/FiO₂ increased by +31 [11 to 206] % (p = 0.031).

**Expiratory transpulmonary pressure**

P_{\text{Lexpi}} increased with both protocols (Table 2, Fig. 2). With the Express protocol, six patients had negative P_{\text{Lexpi}} − 2.5 [−7.8 to −1.15] cmH₂O with a median PEEP of 14.0 [9.7 to 14.5] cmH₂O. These six patients had a significant lower respiratory system compliance (25.2 [15.8 to 29.0] vs. 30.7 [25.6 to 39.2] ml/cmH₂O, p = 0.027), and a significant lower EELV (1240 [835 to 2118] vs. 1900 [1700 to 3045] ml, p = 0.040). When these patients received the P_{\text{Lexpi}} protocol, median PEEP increased to 24.0 [18.0 to 26.5] cmH₂O, P_{\text{pl}} was 40.2 [33.1 to 51.0] cmH₂O, and PaO₂/FiO₂ increased by +31 [11 to 206] % (p = 0.031).

**Inspiratory transpulmonary pressure**

With the Express protocol, mean P_{\text{L,EL}} was 20 cmH₂O, and P_{\text{L,EL}} was significantly lower than P_{\text{L,EL}} with a mean of difference of 8.5 cmH₂O (p < 0.0001) (Table 2). P_{\text{L,EL}} increased from baseline with the Express protocol (Table 2), one patient was > 25 cmH₂O, and the rest were below (Fig. 3), but 2 patients had P_{\text{L,EL}} > 20 cmH₂O.

With the P_{\text{Lexpi}} protocol, mean P_{\text{L,EL}} was 24 cmH₂O, and P_{\text{L,EL}} was significantly lower than P_{\text{L,EL}} with a mean of difference of 8.7 cmH₂O (p < 0.0001) (Table 2). P_{\text{L,EL}} increased from baseline with the P_{\text{Lexpi}} Protocol (Table 2), seven patients had P_{\text{L,EL}} > 25 cmH₂O (Fig. 3), and four of them had P_{\text{L,EL}} > 20 cmH₂O.
With the $P_{\text{Lexpi}}$ protocol, patients with $P_{L,EL} > 25$ cmH$_2$O had pH of 7.25 [7.17 to 7.42] with significantly lower respiratory system compliance, higher DP and PEEP, than those with $P_{L,EL} \leq 25$ cmH$_2$O (17 [15 to 22] ml/cmH$_2$O, 23 [18 to 25] cmH$_2$O and 21 [17 to 27] cmH$_2$O, respectively).

Airway, transpulmonary and elastance-related driving pressures were not different between groups (Table 2).

**Elastance**

In comparison with baseline, respiratory system elastance and lung elastance were not significantly modified by the increase in PEEP with the Express protocol; only chest wall elastance was statistically different (Table 2). PEEP increase from baseline with the Express protocol was significantly correlated with lung elastance ($R^2 = 0.38$, $p = 0.008$). Respiratory system and lung elastance were similar between Express and $P_{\text{Lexpi}}$ protocols.

**Complications**

No episodes of pneumothorax were detected by chest X-Ray after each protocol implementation. Hemodynamic assessment was done before PEEP titration, and fluid was given when required. Cardiac frequency and mean arterial pressure remained relatively stable with each PEEP protocol (Table 2). Fifteen patients underwent transthoracic echocardiography (four had no transthoracic echocardiography window), and none of them had right heart failure with septal dyskinesia after PEEP titration.

**Discussion**

This study demonstrates heterogeneity of end-expiratory or end-inspiratory transpulmonary pressures during PEEP titration with each method in severe ARDS. PEEP titration with a target of positive $P_{\text{Lexpi}}$ will suggest individually different levels of PEEP than with Express protocol in a large majority of patients (higher or lower PEEP). These two protocols are not interchangeable, as described previously with two other protocols based on expiratory $P_L$ [20, 21].

The goal of increasing PEEP from baseline with a specific titration protocol using $P_L$ is to improve alveolar recruitment and oxygenation with limited hyperinflation and morbi-mortality [4]. ARDS patients have a great variation in lung damage with a gravitational vertical gradient of alveolar injuries determining dependent and non-dependent regions [22]. Pleural pressure also has a vertical gradient in the supine position [23]. Interestingly, $P_{L,EL}$ is close to direct measurement of pleural transpulmonary end-inspiratory pressure in the non-dependent lung region and might therefore limit the risk of ventilator-induced lung injury by over-distension [11]. Our main results demonstrate that this risk is probably reduced when PEEP is titrated according to $P_{\text{plat}}$ (28–30 cmH$_2$O) instead of a moderate positive $P_{\text{Lexpi}}$ (0–5 cmH$_2$O).

**Oxygenation and alveolar recruitment, according to $P_{\text{Lexpi}}$**

In our study, when compared to baseline, the Express and $P_{\text{Lexpi}}$ protocols increased PEEP, Vrec and oxygenation at the same time significantly. These two protocols based on respiratory mechanic proposed high PEEP level which might explain the small differences in recruitment. In the 2 EPVent trials, the difference in the results might come from the comparator group with empirical PEEP-FiO$_2$ strategies, resulting in significantly different $P_{\text{Lexpi}}$ on protocol between groups. $P_{\text{Lexpi}}$ protocol proposed...
individually a different level of PEEP than Express protocol. The corresponding increase of PEEP with P\textsubscript{L,exp} protocol, when compared from baseline, was correlated to oxygenation. Patients with protective ventilation who respond to increased PEEP by improved oxygenation might have a lower risk of death [3]. The P\textsubscript{L,exp} protocol had a better alveolar recruitment than Express protocol with a median P\textsubscript{L,exp} of 3.6 cmH\textsubscript{2}O. Indeed, increasing PEEP in order to have a positive P\textsubscript{L,exp} of around 4.5 cmH\textsubscript{2}O can significantly reduce the risk of atelectasis in the dependent lung, whereas a P\textsubscript{L,exp} of 0 cmH\textsubscript{2}O might not be enough [23].

With the Express protocol, six patients had negative P\textsubscript{L,exp}, which meant that esophageal pressure was greater than airway pressure. This may occur when pressures in the thorax and abdomen are pathologically elevated [24]. These patients had lower respiratory system compliance and EELV. With the P\textsubscript{L,exp} protocol, these patients received higher levels of PEEP and a trend toward increased oxygenation. This protocol might improve alveolar recruitment and oxygenation, but over-distension has to be controlled at the same time [4].

**Over-distension, according to P\textsubscript{L,EL}**

In order to limit over-distension, P\textsubscript{plat} should remain <32 cmH\textsubscript{2}O and DP\textsubscript{aw} <15 cmH\textsubscript{2}O [2, 25]. P\textsubscript{L,EL} can also help to limit over-distension in animal study based on CT scan [26], and a limit of 25 cmH\textsubscript{2}O has been proposed in ARDS patients [13]. We found that DP\textsubscript{aw} remained unchanged and within a safer range below 15 cmH\textsubscript{2}O with all protocols [25]. DP\textsubscript{aw} and DP\textsubscript{plat} were highly correlated, and the mean difference was similar to previous data (approximately 4 cmH\textsubscript{2}O) [27]. The EPVent trial 2 proposed stopping the PEEP increase if P\textsubscript{L,es} was >20 cmH\textsubscript{2}O [13]. With the P\textsubscript{L,exp} protocol, four patients had P\textsubscript{L,es} >20 cmH\textsubscript{2}O, but seven patients had P\textsubscript{L,EL} >25 cmH\textsubscript{2}O. This can be explained by a significant difference between these two assessments of end-inspiratory transpulmonary pressure as described previously [9, 23].

With the Express protocol, PEEP was titrated on the basis of P\textsubscript{plat}, with the expectation that it closely approximated P\textsubscript{L}. In patients with normal chest wall elastance, P\textsubscript{plat} is a reasonable surrogate for P\textsubscript{L} and with Express protocol, we found a median P\textsubscript{L,EL} of 20 cmH\textsubscript{2}O which is lower than the target/limit of 25 cmH\textsubscript{2}O proposed by Grasso et al. [11]; this limit was crossed by only one patient in our study.

With the P\textsubscript{L,exp} protocol, V\textsubscript{rec} was slightly higher, but some patients had P\textsubscript{L,EL} >25 cmH\textsubscript{2}O; these patients had lower respiratory system compliance with higher DP and respiratory acidosis. Thus, for some patients having both moderate positive P\textsubscript{L,exp} and limited P\textsubscript{L,EL} is not possible, and moderate positive P\textsubscript{L,exp} between 0–5 cmH\textsubscript{2}O does not prevent P\textsubscript{L,EL} being >25 cmH\textsubscript{2}O. In these patients, P\textsubscript{L,EL} may need to be reduced and V\textsubscript{t} might be decreased below 6 ml kg\textsuperscript{-1} PBW in order to benefit from PEEP-induced alveolar recruitment with less distension and DP. The use of the prone position could also be interesting [28], but assessment of pleural pressure by esophageal pressure in prone position requires further investigations.

**Elastance**

Lung elastance in our patients was similar to previous studies [13, 26]. When chest wall elastance is high, P\textsubscript{plat} may be much higher than P\textsubscript{L}. Indeed, a substantial portion of P\textsubscript{plat} is dissipated in distending the chest wall. As the chest wall becomes stiffer, the proportion of P\textsubscript{plat} that distends the lung (P\textsubscript{L}) decreases progressively [29]. Chest wall elastance was within the same range as other data in ARDS patients [12, 13]. In the study of Grasso et al., patients improved by PEEP had a higher chest wall elastance with a mean of 17 cmH\textsubscript{2}O/L. Chest wall elastance can be elevated in patients with acute respiratory failure for various reasons [30]. Increases in chest wall elastance can occur as a result of intra-abdominal hypertension, pleural effusion, massive ascites, thoracic trauma and edema of the intra-thoracic and intra-abdominal tissues as a result of fluid resuscitation [7]. We found a significant increase of E\textsubscript{cw} with P\textsubscript{L,exp} protocol. This has already been described by Mezidi et al. and might be explained by an upward shift of the chest wall pressure–volume curve with more EELV [31].

**Severity and complications**

In our cohort, patients were severely ill with high Simplified Acute Physiology Scores II (SAPS II) and PaO\textsubscript{2}/FiO\textsubscript{2} ratio at baseline was lower than in most studies including the EPVent trials [12, 13], Express study [5] and ARMA study [2]. Titration of PEEP was achieved with the P\textsubscript{L,exp} and Express protocols in all patients without hemodynamic impairment.

**Limits and perspectives**

There are several limitations. First of all, it is a small physiological study of moderate to severe ARDS patients with the risk of underpowered statistical analysis. We assessed alveolar recruitment and the risk of over-distension only with bedside respiratory mechanics and not with a CT scan that is the gold standard. This study did not assess alveolar inflammation, and we did not assess any outcome according to a specific PEEP titration protocol. The majority of the patients had a direct insult of the lung with pneumonias or aspiration so it was not possible to compare respiratory mechanic between pulmonary and extrapulmonary ARDS [32]. All patients had a risk...
of derecruitment with a short ventilation with no PEEP between each protocol. Some of these limits need further investigations.

Conclusions

Our study demonstrates that, in comparison with a protocol using \( P_{\text{plat}} \) to titrate PEEP, a positive level of \( P_{\text{Lexp}} \) with PEEP might slightly improve alveolar recruitment and oxygenation but also increases \( P_{\text{LEL}} \) above 25 cmH\(_2\)O and the risk of over-distension in the dependent lung in one-third of patients.

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Authors’ contributions

MB, NF, HR were involved in study concept and design; MB, NF, DT, TS, AG, BF, HR contributed to acquisition of data; MB, NF, TB, HR were involved in analysis and interpretation of data; MB, HR, AG helped in drafting of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

If requested.

Ethics approval and consent to participate

The study was approved by the French South-West Ethical Committee on November 2015 (CPP: 2015/113 by Chairperson Dr. Berdai), and written informed consent was obtained from all patients in accordance with current regulations.

Consent for publication

From all authors.

Competing interests

The authors declare that they have no competing interests.

Prior presentation

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Author details

1 Anaesthesia and Intensive Care Unit, Robert Piqure Military Teaching Hospi
tal, Villenave d’Ornon, France. 2 Intensive Care Unit, North Bordeaux Aquitaine Clinic, Bordeaux, France. 3 Medical and Surgical Intensive Care, Saint Joseph Saint Luc Teaching Hospital, Lyon, France. 4 Magellan Medico-Surgical Center, South Department of Anaesthesia and Critical Care, CHU Bordeaux, 33000 Bor
deaux, France. 5 Biology of Cardiovascular Diseases, INSERM, UMR 1034, Univ. Bordeaux, 33600 Pessac, France.

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