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PEEP-induced changes in lung volume in acute respiratory distress syndrome. Two methods to estimate alveolar recruitment

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Abstract *Purpose:* Lung volumes, especially functional residual capacity (FRC), are decreased in acute respiratory distress syndrome (ARDS). Positive end-expiratory pressure (PEEP) contributes to increased end-expiratory lung volume (EELV) and to improved oxygenation, but differentiating recruitment of previously nonaerated lung units from distension of previously open lung units remains difficult. This study evaluated simple methods derived from bedside EELV measurements to assess PEEP-induced lung recruitment while monitoring strain. *Methods:* Prospective multicenter study in 30 mechanically ventilated patients with ARDS in five university hospital ICUs. Two PEEP levels were studied, each for 45 min, and EELV (nitrogen washout/washin technique) was measured at both levels, with the difference (Δ) reflecting PEEP-induced lung volume changes. Alveolar recruitment was measured using pressure-volume (PV) curves. High and low recruiters were separated based on median recruitment at high PEEP. Minimum predicted increase in lung volume computed as the product of ΔPEEP by static compliance was subtracted from ΔEELV as an independent estimate of recruitment. Estimated and measured recruitments were compared. Strain induced by PEEP was also calculated from the same measurements. *Results:* FRC was 31 ± 11% of predicted. Median [25th–75th percentiles] PEEP-induced recruitment was 272 [187–355] mL. Estimated recruitment correlated with recruited volume measured on PV curves ($\rho = 0.68$), with a slope close to identity. The ΔEELV/FRC ratio differentiated high from low recruiters (110 [76–135] vs. 55 [23–70]%, $p = 0.001$). Strain increase due to PEEP was larger in high recruiters ($p = 0.002$). *Conclusion:* PEEP-induced recruitment and strain can be assessed at the bedside using EELV measurement. We describe two bedside methods for predicting low or high alveolar recruitment during ARDS.

Keywords Nitrogen washout/washin · End-expiratory lung volume · Functional residual capacity · Acute respiratory distress syndrome · Mechanical ventilation · Positive end-expiratory pressure · Lung recruitment

Introduction

Acute respiratory distress syndrome (ARDS) is characterized by a major loss of lung volume. In this context, lung-protective ventilation combining low tidal volume and positive end-expiratory pressure (PEEP) aims to limit lung overdistension as well as opening and closing phenomenon of small airways and alveoli [1, 2]. Because low tidal volume ventilation could be responsible for alveolar instability, PEEP can be useful to keep open the recruited alveoli [3]. PEEP contributes to maintaining adequate oxygenation, to reduce FiO_2, and to recruit nonaerated lung volume, but its optimum level remains controversial [4]. Several approaches have been proposed to evaluate PEEP-induced recruitment. The amount of potentially recruitable lung has been best evaluated using computed tomography (CT) [5], but this approach is too complex for use in everyday practice. Multiple pressure-volume (PV) curves repositioned on the same volume axis can provide an acceptable bedside evaluation of PEEP-induced volume recruitment [6]. Measuring recruitment requires multiple PV curves, and therefore this technique also remains reserved for clinical research. The benefits of PEEP, however, may be greatest in patients with high lung recruitability [7, 8]. A method for evaluating the amount of potentially recruitable lung might therefore contribute to improved individual patient care. Moreover, lung deformation induced by tidal inflation and PEEP, also referred to as strain, contributes to the development of ventilator-induced lung injury (VILI) [9]. Measuring functional residual capacity (FRC) or end-expiratory lung volume (EELV) when PEEP is applied might help to monitor the effects of ventilation strategies and may also hold promise as a means of evaluating both lung recruitability and PEEP-induced strain.

The aim of this study was to evaluate simple indexes derived from bedside EELV measurements using the nitrogen washout/washin technique to assess PEEP-induced lung recruitment and to monitor strain in patients with ARDS. PEEP-induced recruitment was measured from PV curves as a reference technique. Our goal was to provide a method to measure or estimate PEEP-induced recruitment as well as strain at the bedside without the need to use pressure-volume curves or CT scan.

This study has been previously presented in abstract form [10].

Methods

This multicenter study was conducted in five medical intensive care units in French university hospitals: Henri Mondor Hospital in Créteil, European Georges Pompidou Hospital in Paris, Angers University Hospital, L'Archet Hospital in Nice, and Charles Nicolle Hospital in Rouen. In keeping with French law, the Ethics Committee (Comité de Protection des Personnes Ile-de-France IX) approved the protocol for all five centers. PEEP adjustment was considered part of standard care, and the ethics committee therefore waived the need for written informed consent. Oral and written information was given to the study patients or their next of kin.

Patients

Patients were enrolled if they met standard criteria for acute lung injury [11]: partial pressure of arterial oxygen over fraction of inspired oxygen (PaO_2/FiO_2) less than 300 mmHg, bilateral pulmonary infiltrates on the chest radiograph, and no clinical evidence of left atrial hypertension. Exclusion criteria were age younger than 18 years, pregnancy, history of chronic obstructive pulmonary disease, history of lung resection surgery, and hemodynamic instability defined as an increase in vasoactive drug (epinephrine, norepinephrine) level in the last 6 h.

Ventilation strategies

All patients received volume assist control ventilation using an Engström ICU ventilator (Engström, General Electrics, Madison, WI, USA) with continuous intravenous sedation for suppressing spontaneous ventilation, with or without paralysis. The oxygenation goal was achieved by adjusting FiO_2, which was maintained constant during the study. Tidal volume was set at 6 mL/kg of predicted body weight. All patients received two PEEP levels, each for 45 min, in random order. PEEP levels were set as in the EXPRESS study [12]. In the minimum distension strategy, PEEP and inspiratory plateau pressure were kept as low as possible while keeping arterial oxygen saturation at 88–92% or more. External PEEP was set to maintain total PEEP (the sum of external and intrinsic PEEP) between 5 and 9 cmH_2O. In the high recruitment strategy, PEEP was adjusted based on Pplat and was kept as high as possible without increasing Pplat above 28–30 cmH_2O. Each PEEP level was maintained for 45 min, and measurements were performed at the end of each 45 min period.

Measurements and derived variables

Lung volumes

At the end of each 45 min period, blood was drawn for arterial blood gas measurement and end-expiratory lung volume was measured three times using the nitrogen washout/washin technique, as previously described [13–15]. In brief, continuous measurement of end-tidal O_2 and CO_2 during a change in FiO_2 (here, 10%) allows the calculation of nitrogen washout and then washin of the aerated lung volume. The mean of the washout and washin data is computed automatically if the difference between the two is less than 20% (cut-off determined by the manufacturer). FRC is a volume measured without PEEP (i.e., at atmospheric pressure).

Prolonged exhalation (15 s) to FRC (at ZEEP) was performed at the end of a 45 min period to standardize lung volume history. PEEP-induced increase in lung volume above FRC (referred to as PEEP volume) was obtained by subtracting the insufflated tidal volume from the flow signal integration of this long exhalation. PEEP volume was measured at the end of each of the two PEEP periods. In patients who were not paralyzed, the absence of spontaneous breathing activity was checked during the recording. Two patients were excluded because spontaneous activity could not be suppressed.

FRC was calculated at high and low PEEP as the difference between EELV and PEEP volume. We decided against directly measuring FRC at ZEEP to avoid ventilating patients at ZEEP for several minutes. We did not find any difference between values calculated from measurements obtained at high PEEP and low PEEP and therefore give the mean FRC from calculations at high and low PEEP. This also permitted us to check that FRC remained constant whatever the PEEP at which it was measured. Theoretical FRC (FRCth) was calculated using the formula developed by Ibáñez and Raurich [16] for spontaneously breathing patients in the supine position.

PV curve technique and measurement of alveolar recruitment (Fig. 1)

The multiple pressure-volume (PV) curve technique allows measurement of alveolar recruitment. Low flow (5 L/min) insufflation of the tidal volume was performed from each PEEP level without disconnecting the ventilator [17], using a dedicated computer connected to the ventilator data recording using a 40 ms sampling time. Both PV curves (low and high PEEP) were stored and later plotted on the same graph. A minimum of two PV curves is necessary for measuring recruitment. The two PV curves are traced starting from two different end-expiratory pressures (a low PEEP and a high PEEP) and are subsequently plotted on the graph with the same volume axis, starting from zero pressure and zero volume or FRC. To do this, the volume above FRC at each PEEP level (i.e., PEEP volume) was measured, thus giving the starting volume above FRC for each curve. Recruitment is measured as the difference in volume between the two curves for a given static pressure (usually the highest PEEP level since the two curves pass through this pressure value). It is referred to as Rec_{mes}.

Lung volume change and estimation of alveolar recruitment using the minimum predicted increase in lung volume

Independently of PV curves and PEEP volume, we measured the increase in EELV (nitrogen technique) when PEEP was increased from a low level to a higher one. At the lowest PEEP level, the product of respiratory system compliance and the pressure increase between the two PEEP levels gives an estimate of the minimum predicted increase in lung volume for this change in pressure [18]. When the change in EELV was larger than this minimum predicted volume gain, the difference was considered to be an estimate of recruitment and is referred to as estimated recruitment, Rec_{estim}.

The *minimal predicted increase in lung volume* is the smallest possible increase in lung volume due to PEEP and is smaller than or equal to (if no recruitment occurs) ΔEELV. In four patients the minimum predicted increase in lung volume was >10% larger than the observed ΔEELV: this suggested substantial measurement errors in ΔEELV likely due to leaks; indeed, these patients were all ventilated with the highest PEEP levels used in this study (>16 cmH_2O), and we suspected that leakages explained these measurement errors during EELV measurements. We therefore decided to exclude these four patients from the analysis.

Rec_{estim} and Rec_{mes} were obtained independently, from different variables.

The equations describing these calculations are as follows:

$$Rec_{estim}(\text{mL}) = \Delta\text{EELV between the two PEEP levels} - \text{Minimal predicted increase in lung volume at low PEEP} \quad (1)$$

or

$$Rec_{estim}(mL) = \Delta EELV \text{ between the two PEEP levels} - [\textit{respiratory system compliance at low PEEP} \times \text{Difference between the two PEEP levels}] \quad (2)$$

or

$$Rec_{estim}(mL) = (\text{EELV at high PEEP} - \text{EELV at low PEEP}) - [(Vt/(Plat - \text{low PEEP}) \times (\text{high PEEP} - \text{low PEEP})] \quad (3)$$

Volumes are expressed in mL, and pressures in cmH_2O.

Analysis of recruiters

As no threshold has been widely accepted to consider a patient as "recruiter" or "nonrecruiter" and for comparison purposes, we classified each patient as a high or low recruiter based on whether Rec_{estim} was above or below the median for the study population. Two "groups" were thus compared.

Strain induced by PEEP

Lung deformation due to the stress induced by volume inflation (tidal volume and PEEP) from the FRC has been calculated as alveolar strain [18]. We speculated that it could be interesting at the bedside to weight the relative increase in strain versus the relative increase in recruitment. Here, we measured only PEEP-induced strain, excluding the strain induced by tidal volume inflation. When increasing PEEP, the newly opened lung regions should not generate additional strain. Strain was then calculated for high and low PEEP as follows:

$$\text{Strain high PEEP} = (\text{EELV at high PEEP} - \text{FRC})/(\text{FRC} + Rec_{mes})$$

$$\text{Strain low PEEP} = (\text{EELV at low PEEP} - \text{FRC})/\text{FRC}$$

Statistical analysis

Results are described as median [interquartile range]. Nonparametric tests were used. Mann-Whitney *U* test or Fisher's exact test, as appropriate, were applied for between-group comparisons. Paired values were compared using Wilcoxon test. The relationship between continuous variables was evaluated using Spearman rank order correlation. Bland and Altman plots [19] of differences between Rec_{mes} and Rec_{estim} versus their mean were constructed to evaluate agreement between these two values.

We constructed receiver operating characteristics (ROC) curves to evaluate the performance of ΔEELV/FRC for separating high from low recruiters. The area under the ROC curve and its 95% CI were estimated [20]. We chose the cutoff point giving the highest accuracy for the diagnosis of high recruiters. A p value <0.05 was considered significant.

Results

We studied 30 patients. The two PEEP levels were 5 [5–5] cmH_2O and 15 [13–16] cmH_2O and were well tolerated by all patients. Tables 1 and 2 report the main characteristics of the 30 patients, 29 with ARDS and 1 with ALI. Table 3 indicates ventilatory parameters and blood gases while Table 4 indicates volumes (measured and calculated) and strain in all patients and in the low and high recruiters. As expected, Pplat and PaO_2/FiO_2 were higher with high PEEP, whereas $PaCO_2$ was not affected by the PEEP level.

Table 1 Arterial blood gas values and ventilation during the minimum distension (low PEEP) and high recruitment (high PEEP) periods

	Low PEEP	High PEEP	*p* value
$PEEP_{tot}$ (cmH_2O)	5 [5]	15 [13–16]	<0.0001
Pplat (cmH_2O)	19 [16–23]	29 [29–31]	<0.0001
C_{stat} (mL/cmH_2O)	31.4 [24.1–38.6]	28.0 [23.4–31.9]	0.02
C_{lin} (mL/cmH_2O)	32.7 [25.0–40.8]	29.0 [24.5–32.9]	<0.0001
pH	7.38 [7.33–7.44]	7.37 [7.31–7.41]	0.03
PaO_2/FiO_2	142 [106–176]	173 [126–215]	<0.0001
SaO_2 (%)	95 [93–97]	98 [95–99]	<0.0001
$PaCO_2$ (mmHg)	39.5 [36.0–45.7]	41.0 [35.2–45.7]	0.8
EELV (mL)	888 [658–1,078]	1,487 [987–1,803]	<0.0001
PEEP volume (mL)	170 [112–245]	662 [463–961]	<0.0001
Strain	0.27 [0.19–0.34]	0.70 [0.53–0.83]	<0.0001

All data are median [interquartile range]
Low PEEP Lowest PEEP set to achieve $SaO_2 \geq 88\%$, *high PEEP* PEEP set to obtain a plateau pressure of 28–32 cmH_2O, C_{stat} static compliance calculated as VT/(Pplat–PEEP), C_{lin} linear compliance measured on the linear part of the pressure/volume curve
The *p* values refer to the comparison of low to high PEEP

Table 2 Main characteristics of patients in the low and high recruiter subgroups defined based on the median recruited volume (Rec_{mes}) measured on pressure-volume curves

	All patients $n = 30$	Low recruiters $n = 15$	High recruiters $n = 15$	*p* value
Age (years)	61 [50–72]	62 [54–74]	56 [46–63]	0.4
Males/females (*n*)	24/6	11/4	13/2	0.07
SAPS 2	56 [35–67]	56 [43–65]	56 [34–68]	0.9
Days of ARDS at inclusion (D)	2 [1–4]	3 [2–5]	2 [1–3]	0.05
Vasoactive agents (number of patients)	17	9	8	0.7
Pulmonary/extrapulmonary cause of ARDS (number of patients)	23/7	11/4	12/3	0.7
Focal/diffuse aeration loss (number of patients)	3/27	1/14	2/13	0.5

Values are median [interquartile range] unless otherwise indicated. Median recruitment was 272 mL [187–355]
The *p* values refer to the comparison of low and high recruiters

Table 3 Ventilatory parameters and blood gases in the low and high recruiter subgroups defined based on the median recruited volume (Rec_{mes}) measured on pressure-volume curves

	All patients $n = 30$	Low recruiters $n = 15$	High recruiters $n = 15$	*p* value
Ventilatory parameters				
Low PEEP (cmH_2O)	5 [5]	5 [5]	5 [5]	0.9
High PEEP (cmH_2O)	15 [13–16]	13 [12–15]	16.0 [14.5–16.5]	0.002
ΔPEEP (cmH_2O)	9 [7–10]	7 [6–9]	10 [9–11]	0.004
Pplat, low PEEP (cmH_2O)	19 [16–23]	22 [19–25]	16 [15–18]	0.001
Pplat, high PEEP (cmH_2O)	29 [29–31]	30 [29–32]	29 [29–30]	0.2
C_{stat}, low PEEP (mL/cmH_2O)	31.4 [24.1–38.6]	25.0 [23.5–32.4]	38.2 [30.2–40.5]	0.009
C_{stat}, high PEEP (mL/cmH_2O)	28.0 [23.4–31.9]	26.5 [20.9–27.9]	30.0 [27.7–32.8]	0.05
Blood gas values				
$PaCO_2$, low PEEP (mmHg)	39.5 [36.0–45.7]	43.0 [35.5–47.5]	39.0 [35.0–42.5]	0.3
$PaCO_2$, high PEEP (mmHg)	41.0 [35.2–45.7]	46.0 [38.0–51.5]	38.0 [36.5–41.5]	0.06
$\Delta PaCO_2$ (mmHg)	2.0 [−2.0 to 4.0]	2.0 [−0.5 to 4]	−2.0 [−4.0 to 2.5]	0.06
PaO_2/FiO_2, low PEEP (mmHg)	142 [106–176]	120 [103–150]	148 [113–185]	0.08
PaO_2/FiO_2, high PEEP (mmHg)	173 [126–215]	158 [116–208]	190 [143–276]	0.1

Values are median [interquartile range] unless otherwise indicated. Median recruitment was 272 mL [187–355]
The *p* values refer to the comparison of low and high recruiters

Table 4 Pulmonary volumes and strain in the low and high recruiter subgroups defined based on the median recruited volume (Rec_{mes}) measured on pressure-volume curves

	All patients $n = 30$	Low recruiters $n = 15$	High recruiters $n = 15$	p value
Volumes				
PEEP volume, low PEEP (mL)	170 [112–245]	157 [126–239]	184 [99–248]	0.8
PEEP volume, high PEEP (mL)	662 [463–961]	471 [356–644]	923 [726–1094]	0.001
ΔPEEP volume (mL)	501 [314–705]	322 [224–458]	713 [609–944]	0.0002
EELV, low PEEP (mL)	888 [658–1,078]	816 [629–1,023]	931 [776–1,067]	0.4
EELV, high PEEP (mL)	1,487 [987–1,803]	1,080 [885–1,504]	1,645 [1,487–2,000]	0.03
ΔEELV (mL)	444 [276–689]	373 [192–402]	658 [534–804]	0.0007
FRC[a] (mL)	685 [526–900]	582 [482–885]	743 [546–966]	0.5
ΔEELV/FRC (%)	73 [39–106]	55 [23–70]	110 [76–135]	0.001
FRC_{th}[b] (mL)	2,266 [1,896–2,540]	2,211 [1,841–2,814]	2,266 [2,089–2,512]	0.8
Minimum predicted increase in lung volume[c] (mL)	249 [182–393]	180 [145–237]	382 [289–432]	0.001
Rec_{mes} (mL)	272 [191–355]	187 [135–214]	355 [319–494]	<0.0001
Rec_{estim} (mL)	187 [67–297]	74 [22–215]	278 [145–475]	0.007
Strain, low PEEP[d]	0.27 [0.19–0.34]	0.29 [0.21–0.34]	0.25 [0.13–0.37]	0.47
Strain, high PEEP[e]	0.70 [0.53–0.83]	0.60 [0.48–0.77]	0.79 [0.66–0.91]	0.04
ΔStrain[f]	0.43 [0.31–0.55]	0.32 [0.28–0.40]	0.55 [0.46–0.60]	0.002

Values are median [interquartile range] unless otherwise indicated. Median recruitment was 272 mL [187–355]
The p values refer to the comparison of low and high recruiters
EELV End expiratory lung volume measured using the nitrogen washout/washin technique, *ΔEELV* difference between EELV values at high and low PEEP, *PEEP volume* volume trapped by PEEP, *ΔPEEP volume* difference between PEEP volumes at high and low PEEP, *ΔPEEP* calculated as the difference between high PEEP and low PEEP, *FRC* functional residual capacity
[a] FRC was calculated as the mean of estimated FRC at low and high PEEP, with estimated $FRC_{low\ PEEP} = (EELV_{low\ PEEP} - PEEP\ volume_{low\ PEEP})$ (Fig. 1)
[b] Theoretical FRC (FRC_{th}) was calculated using the formula proposed by Ibáñez and Raurish [16]
[c] Minimum predicted increase in lung volume was calculated as $C_{stat} \times \Delta PEEP$, where C_{stat} is static compliance [tidal volume/(Pplat measured at low PEEP − low PEEP)] and ΔPEEP is the difference between high PEEP and low PEEP
[d] Strain, low PEEP = (EELV at low PEEP − FRC at low PEEP)/FRC at low PEEP
[e] Strain, high PEEP = (EELV at high PEEP − FRC at high PEEP)/(FRC at high PEEP + Rec_{mes})
[f] ΔStrain = strain, high PEEP − strain, low PEEP

Lung volumes

Mean FRC (calculated from low and high PEEP) was 742 mL [546–890] (Table 4) and represented 31 ± 11% of FRCth [16]. Only four patients had FRC values close to FRCth at high PEEP (Fig. 2).

Comparison of measured and estimated PEEP-induced alveolar recruitment

The PV curve technique gave a value of Rec_{mes} of 272 mL [191–355]. The EELV technique gave a Rec_{estim} of 187 mL [67–297], well correlated to Rec_{mes} ($\rho = 0.68$; $p = 0.0002$) (Fig. 3). Bias between the two methods was 66 ± 145 mL with a 95% confidence interval for limits of agreement (dashed line in Fig. 3) of −223 to 357 mL (see ESM, Fig. E1).

Rec_{mes} was always lower than the observed ΔEELV and was correlated with ΔEELV ($\rho = 0.79$; $p < 0.0001$).

Compared to low recruiters, high recruiters had higher ΔEELV and ΔPEEP volume values. Also the ΔPEEP was larger in higher recruiters (10 cmH_2O [9–11] vs. 7 cmH_2O [6–9]; $p = 0.004$).

The ΔEELV/FRC ratio clearly differentiated high recruiters from low recruiters with little overlap (110% [76–135] vs. 55% [23–70]; $p = 0.001$) (Fig. 3). ROC curve for ΔEELV/FRC as a criterion for separating high recruiters from low recruiters had an area under curve of 0.84 (95% CI 0.67–0.95). The ΔEELV/FRC cutoff point giving the highest accuracy for separating high from low recruiters was 73% (sensitivity = 80%, specificity = 80%, positive likelihood ratio = 4.0, negative likelihood ratio = 0.25; Figs. E2, E3); (Fig. 4).

PEEP-induced strain

Alveolar strain induced by PEEP was 0.27 [0.19–0.34] at low PEEP and 0.70 [0.53–0.83] at high PEEP ($p < 0.0007$) (Fig. E4). PEEP increased the strain more in high than in low recruiters.

Discussion

In this study, we describe the value of a quantitative estimate (Rec_{estim}) and a semiquantitative physiological

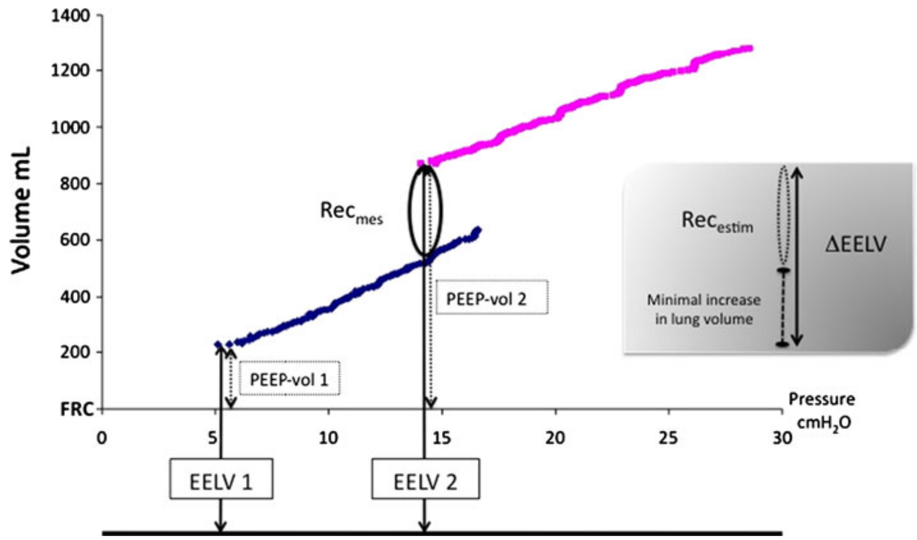
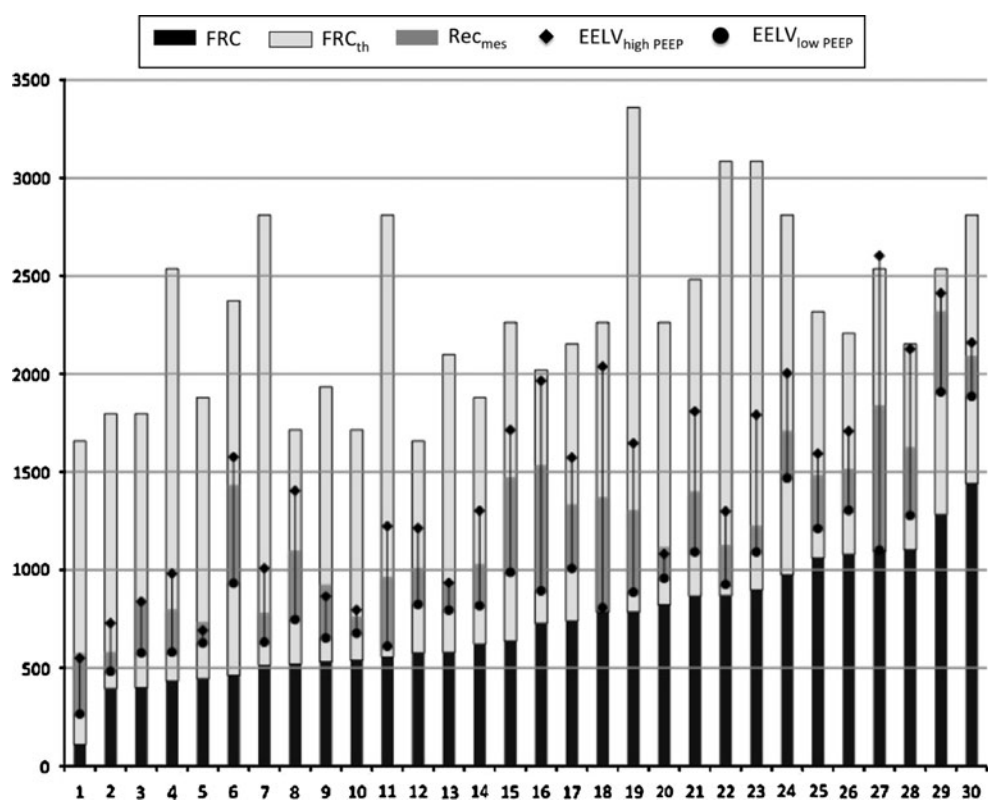


Fig. 1 Example of pressure-volume curves in a single patient, at both positive end-expiratory pressure (PEEP) levels studied (here low PEEP = 5 cmH_2O and high PEEP = 14 cmH_2O), repositioned on the same volume axis. The *solid line* indicates end-expiratory lung volume (EELV) measured using nitrogen washout/washin technique. EELV represents the aerated volume in the lungs at the end of expiration. *Dashed line* indicates the PEEP volume, i.e., expired volume from PEEP to elastic pressure measured using a prolonged exhalation to zero end expiratory pressure. FRC is estimated as the mean of ($EELV_{low\ PEEP}$ − PEEP $volume_{low\ PEEP}$) and ($EELV_{high\ PEEP}$ − PEEP $volume_{high\ PEEP}$). Rec_{mes} is the recruitment induced by PEEP change measured on the graph. Rec_{estim} is the recruitment calculated using ΔEELV − the minimum predicted increase in lung volume, which is the product of compliance and ΔPEEP. *Grey inset* is a schematic representation of Rec_{estim}

Fig. 2 Distribution of functional residual capacity (FRC), theoretical FRC (FRC_{th}), end-expiratory lung volume (EELV) measured at high and low PEEP, and measured lung recruitment (Rec_{mes}) in the 30 study patients



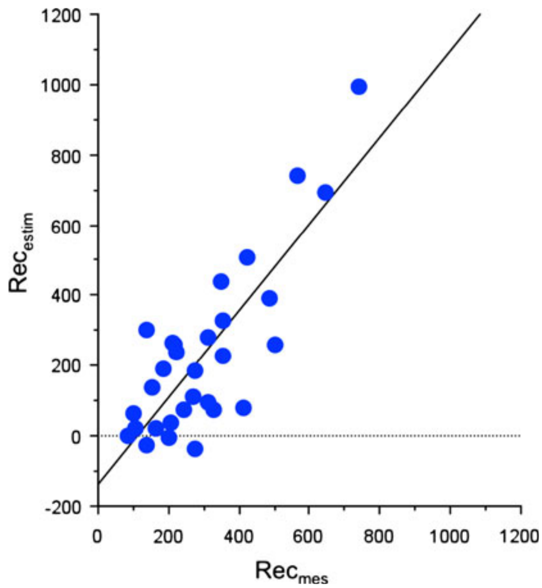


Fig. 3 Correlation between recruited volume measured on pressure-volume curves (measured recruitment, Rec_{mes}) and recruitment estimated using the nitrogen technique ($Rec_{estim} = \Delta EELV -$ minimum predicted increase in lung volume). $Rec_{estim} = -136 + 1.2(Rec_{mes})$; $\rho = 0.68$; $p = 0.0002$

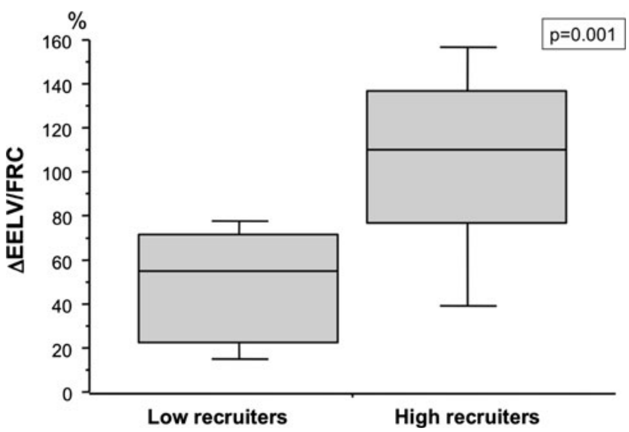


Fig. 4 ΔEELV/FRC in low recruiters (55% [23–70]) and high recruiters (110% [76–135]); $p = 0.001$

parameter (ΔEELV/FRC), based on lung volume measurements, for assessing PEEP-induced alveolar recruitment at the bedside without the need for multiple PV curves or CT scan. Measurement of EELV at two PEEP levels allows both an estimation of alveolar recruitment and a calculation of the PEEP-induced alveolar strain. The ΔEELV/FRC ratio performed well for differentiating low from high recruiters. As expected, alveolar strain was higher with higher PEEP levels.

A recent study using helium dilution showed that patients ventilated for surgical or nonpulmonary reasons had FRC values close to 80% of FRCth, whereas ARDS patients had much lower FRC values (42 ± 21% of FRCth) [21]. Here, using the same FRC estimation formula [16], we found extremely low FRC values (31 ± 11% of FRCth). These results emphasize the major aeration loss that occurs during ARDS as shown since the early descriptions of ARDS [22, 23].

High PEEP, even set to reach a safe Pplat [12], failed to decrease mortality in any of the individual multicenter trials, and some evidence suggests that PEEP should be set according to the potential lung recruitability [24]. Caironi et al. suggested that limiting the amount of opening and closing tissue prevailed over the potential harmful effect of increasing strain with high PEEP only in high recruiters. Since amounts of opening and closing lung tissue are greater in highly recruitable lung, evaluating the recruitment at the bedside could be of clinical interest. Here, we suggest simple, reproducible, bedside methods with few correcting parameters for quantitatively or qualitatively evaluating the alveolar recruitment induced by increasing the PEEP level. PV curves and radiological assessment of lung volume can be used to monitor PEEP-induced recruitment [5, 17, 25, 26]. A CT study showed wide variations in the percentage of potentially recruitable lung, defined as the increase in lung aeration when airway pressure increased from 5 to 45cmH_2O, in a large cohort of patients with ARDS or ALI [5]. The CT scan technique is, however, time-consuming and not applicable for clinical practice. Numerous studies showed good reproducibility and feasibility of PV curves for evaluating PEEP-induced recruitment, and a comparison with CT scans showed acceptable results for clinical practice [27]. Performing multiple PV curves as required for assessment of recruitment, although feasible, is difficult to introduce into clinical practice. Using bedside measurements (EELV, Cstat, and PEEP) all provided by an intensive care ventilator, we were able to separate high from low recruiters and to estimate PEEP-induced recruitment with imperfect but reasonable accuracy. Nitrogen (or oxygen) washout/washin correlates sufficiently well with helium dilution to be suitable for lung volume measurement in everyday practice [28, 29]. Other advantages of EELV are the lack of need for ventilator discontinuation and the PEEP stability during the measurement. Furthermore, light sedation may be sufficient to perform the measurement, in contrast to PV curves.

Strain can be evaluated with the same measurements. In an earlier study [21], the expected strain increase when PEEP increased from 5 to 15 cmH_2O was assessed using an estimate of recruitment to adjust the calculation of lung strain. Here, we used the measured recruitment to confirm these results. We found the highest strain for high recruiters at high PEEP, consistent with the results of Caironi et al., who found similar results for patients with high potentially recruitable lung [9].

From a technical standpoint, Patroniti et al. [30] suggested that the method used to estimate the PEEP volume above FRC with PEEP (long exhalation to ZEEP) may underestimate recruitment because the true FRC may be modified after the use of high PEEP. Therefore, our method might have slightly underestimated recruitment. In the study by Patroniti et al., the error was about 167 ± 78 ml between 5 and 15 cmH_2O of PEEP. Such underestimation would not invalidate our results, for the following reasons: (1) any underestimation of absolute recruitment would occur in all patients and, therefore, our method would still separate high and low recruiters; (2) we waited at least 15 s to reach FRC, which should have minimized any differences between the PEEP levels; and (3) low and high PEEP levels were tested in random order. Last, we calculated FRC from EELV and PEEP volume at the two PEEP levels; these two calculations showed no difference between low and high PEEP, suggesting that there was no substantial difference between the two PEEP levels in terms of true FRC.

From a clinical standpoint, we found that ΔEELV/FRC $\geq$ 73% was an accurate cut-off for separating low from high recruiters when titrating PEEP as described in the EXPRESS trial [16]. This result requires confirmation in a larger population but suggests that our method may hold promise for use at the bedside to help differentiate recruiters from nonrecruiters and, therefore, to better titrate PEEP.

Our study has several limitations. In patients with ALI/ARDS, PEEP-induced alveolar recruitment can be defined as the volume entering the poorly aerated and nonaerated alveolar structures following the PEEP increase. Compared to the reference CT method, the PV curve method has acceptable accuracy. However, the PV curve method can underestimate lung recruitment in patients with focal aeration loss [27]. Furthermore, in contrast to radiological techniques, our method cannot be used to measure end-inspiratory lung volume and, therefore, cannot evaluate intra-tidal strain. Last, our definition of low and high recruiters, based on the median value, was arbitrary and needs to be reevaluated with a large database.

In summary, we demonstrated that simple and relatively accurate bedside methods can be used to assess both alveolar recruitment and strain induced by PEEP. These methods may help to tailor PEEP and ventilation to the needs of individual patients based on the amount of potentially recruitable lung, whose estimation may predict the response to various ventilator settings.

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Conflict of interest Four authors and their institution are involved in a patent with General Electric describing the method used to estimate alveolar recruitment described in the manuscript. The following persons and their institutions are involved: Jean Dellamonica for CHU de Nice, Hôpital L’Archet, Université de Nice Sophia Antipolis, France; Alain Mercat for CHU Angers, Angers, France; Jean-Christophe M. Richard for CHU Charles Nicolle, Rouen, France; Laurent Brochard for Assistance Publique-Hopitaux de Paris, groupe hospitalier Henri Mondor, Créteil, France and Université Paris EST, Créteil, France. A grant was also received from General Electric for the conduct of the study. General Electric had no access to the data nor to the content of the manuscript. All authors kept full control of the analysis of the data and the writing of the manuscript.

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