ORIGINAL ARTICLE

Lung Recruitment Assessed by Electrical Impedance Tomography (RECRUIT)

A Multicenter Study of COVID-19 Acute Respiratory Distress Syndrome

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Abstract

Rationale: Defining lung recruitability is needed for safe positive end-expiratory pressure (PEEP) selection in mechanically ventilated patients. However, there is no simple bedside method including both assessment of recruitability and risks of overdistension as well as personalized PEEP titration.

Objectives: To describe the range of recruitability using electrical impedance tomography (EIT), effects of PEEP on recruitability, respiratory mechanics and gas exchange, and a method to select optimal EIT-based PEEP.

Methods: This is the analysis of patients with coronavirus disease (COVID-19) from an ongoing multicenter prospective physiological study including patients with moderate-severe acute respiratory distress syndrome of different causes. EIT, ventilator data, hemodynamics, and arterial blood gases were obtained during PEEP titration maneuvers. EIT-based optimal PEEP was defined as the crossing point of the overdistension and collapse curves during a decremental PEEP trial. Recruitability was defined as the amount of modifiable collapse when increasing PEEP from 6 to 24 cm H_2O ($\Delta Collapse_{24-6}$). Patients were classified as low, medium, or high recruiters on the basis of tertiles of $\Delta Collapse_{24-6}$.

Measurements and Main Results: In 108 patients with COVID-19, recruitability varied from 0.3% to 66.9% and was unrelated to acute respiratory distress syndrome severity. Median EIT-based PEEP differed between groups: 10 versus 13.5 versus 15.5 cm H_2O for low versus medium versus high recruitability ($P < 0.05$). This approach assigned a different PEEP level from the highest compliance approach in 81% of patients. The protocol was well tolerated; in four patients, the PEEP level did not reach 24 cm H_2O because of hemodynamic instability.

Conclusions: Recruitability varies widely among patients with COVID-19. EIT allows personalizing PEEP setting as a compromise between recruitability and overdistension.

Clinical trial registered with www.clinicaltrials.gov (NCT04460859).

Keywords: acute respiratory distress syndrome; lung recruitability; positive end-expiratory pressure; electrical impedance tomography; mechanical ventilation

Defining the potential for lung recruitment is crucial for a safe positive end-expiratory pressure (PEEP) selection in mechanically ventilated patients. The response to increasing pressure varies considerably among patients (1); however, no validated bedside method is available for identifying patients who may benefit versus incur harm by various levels of PEEP and for indicating the potential advantage of recruitment as well as the risks of overdistension (2). Oxygenation response is often used as a

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surrogate, but it has multiple limitations and often continues to increase with higher PEEP despite overdistension and negative hemodynamic impact (1, 3). PEEP/$F_{I_{O_2}}$ tables tend to select the highest PEEP in patients who do not respond in terms of oxygenation (4, 5), but some correlation with recruitability was reported previously (6). The absence of a reliable technique to titrate PEEP and assess both lung recruitability and risks of overdistension could explain why randomized clinical trials comparing higher versus lower PEEP failed to show improved survival of patients with acute respiratory distress syndrome (ARDS) (7). High PEEP application should fully exploit its benefits only in patients with high potential for alveolar recruitment (i.e., increase in aerated lung tissue by application of a reasonable range of PEEP) or in patients with airway closure (1, 8, 9). High PEEP may then reduce the repetitive cyclic opening and closing of alveoli and airways, limiting cyclic stretch, atelectrauma, and risks of atelectasis, and could relieve hypoxemia (1, 10). Conversely, in nonrecruitable or poorly recruitable lungs, excessive strain with high PEEP mainly induces harmful lung overdistension and cardiac impairment (11), and we have no reliable bedside method to directly assess overdistension.

Electrical impedance tomography (EIT) is a promising bedside technology to monitor the potential impact of PEEP on determinants of ventilator-induced lung injury. EIT is a noninvasive, radiation-free lung imaging tool that can continuously and in real time visualize the ventilation distribution and lung volume changes resulting from adaptations in ventilator settings or due to clinical evolution (12). In contrast to static anatomical computed tomography (CT) scans, EIT provides dynamic functional information: It assesses both regional alveolar recruitment and overdistension when studied across different PEEP levels. Bedside methods for assessing recruitability exist (e.g., recruitment-to-inflation [R/I] ratio [13], lung ultrasound score [14]), but they do not inform about the optimal PEEP and/or risk of overdistension. In contrast, EIT could be a useful tool for both bedside assessment of recruitability and personalized PEEP selection while finding the best compromise between (regional) recruitment and overdistension. Standardized EIT-derived parameters for this application are a subject of ongoing discussion. As such, with the Pleural Pressure Working Group, we designed a multicenter physiological study performing specific lung decremental PEEP steps with the main goal of verifying the feasibility of measuring the potential for lung recruitment in ARDS by EIT (RECRUIT [Recruitment Assessed by Electrical Impedance Tomography] study; ClinicalTrials.gov identifier NCT04460859). The clinical study is still ongoing in non–coronavirus disease (COVID-19) ARDS, and the current work presents insights obtained in COVID-19 ARDS. These patients exhibit complex physiological abnormalities affecting both ventilation and perfusion, likely making them vulnerable to harm from inappropriate PEEP (15–17). The objectives are to describe the range of recruitability; the effects of PEEP on recruitability, respiratory mechanics, and gas exchange; and the results of methods for EIT-based PEEP selection, particularly using the crossing point of the overdistension and collapse curves as a compromise for PEEP selection (18).

Methods

Design

This is the analysis of patients with COVID-19 from an ongoing multicenter prospective physiological study (NCT04460859) looking at patients with ARDS of different causes. The study was approved by each center's research ethics board. The patient's substitute decision maker provided informed consent before enrollment. The selection of centers was based on their previous use and knowledge of the EIT technique, and all agreed that EIT

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

At a Glance Commentary

Scientific Knowledge on the Subject: Defining lung recruitability is needed for a safe positive end-expiratory pressure (PEEP) selection in mechanically ventilated patients with acute respiratory failure. However, no simple bedside method is available for identifying patients who may benefit (recruitment) versus incur harm (hyperinflation) by various levels of PEEP and for indicating the potential advantage of recruitment as well as the risks of overdistension.

What This Study Adds to the Field: In a large cohort of patients with coronavirus disease (COVID-19) with moderate-severe acute respiratory distress syndrome ($N = 108$), we show that electrical impedance tomography (EIT) is a feasible bedside technique for defining the potential of lung recruitment over a clinical range of PEEP, provided a derecruitment titration maneuver is performed. The PEEP value at the crossing point of the collapse and overdistension curves obtained with a decremental PEEP trial indicates the level where collapse and overdistension are jointly minimized. This EIT-based PEEP was associated with comparable respiratory mechanics across all degrees of recruitability and yielded an optimal PEEP level that was different from the highest respiratory compliance method. EIT differentiates patients with different responses to PEEP and supports setting a personalized PEEP according to a compromise between distension and recruitment.

measurements during PEEP titration maneuvers could be included in their current practice but in the form of a formalized protocol.

Patients

Intubated patients with COVID-19 admitted to the ICU were enrolled within the first week of ARDS diagnosis. Inclusion criteria were *1*) age >18 years, *2*) moderate-severe ARDS (Pa_{O_2}/FI_{O_2} <200 mm Hg) (19), and *3*) controlled ventilation under continuous sedation with or without paralysis. Exclusion criteria were *1*) bronchopleural fistula, *2*) pure chronic obstructive pulmonary disease exacerbation, *3*) contraindication for EIT monitoring (e.g., pacemaker, burns, or wounds limiting electrode placement), *4*) hemodynamic instability (i.e., systolic blood pressure [SBP] <75 mm Hg or mean arterial pressure [MAP] <60 mm Hg despite vasopressor use and/or heart rate <55 beats per minute), and *5*) attending physician considering the transient application of high pressures to be unsafe.

Data Collection

At enrollment, we collected information regarding sex, age, body mass index (BMI), Sequential Organ Failure Assessment score, Simplified Acute Physiology Score II, and ARDS severity (Pa_{O_2}/FI_{O_2} at ICU admission). Follow-up data included ventilation duration, ICU length of stay, ICU mortality, and ventilator-free days at Day 28.

EIT Monitoring

Continuous EIT monitoring was performed with a belt placed at the fourth to fifth intercostal space and using the EIT device present at each institution (Enlight 1800 and 2100, Timpel; PulmoVista 500, Dräger Medical GmbH; Swisstom BB2 device, Swisstom). Synchronized recordings of EIT, airway pressure, and/or flow were stored for offline analysis.

Study Procedures

Study steps, including safety measures, are presented in Figure 1. All measurements were performed with the patient in supine position.

- *Baseline:* Controlled ventilation with a passive patient (Richmond Agitation-Sedation Scale score less than or equal to −3 as a condition to perform PEEP titration maneuvers and to evaluate and compare static mechanics) was ensured by adapting sedation levels and/or providing neuromuscular blockade if necessary. Automated mattress movements, fluid boluses, and excessive diuresis were avoided to limit EIT signal interference. Hemodynamic stability (MAP >70 mm Hg) was ensured; volume status was adapted if necessary as per a VT challenge (20). Clinical ventilation settings were recorded for 10 minutes, after which respiratory mechanics (plateau pressure, total PEEP), hemodynamics (oxygen saturation as measured by pulse oximetry, SBP, MAP, heart rate), and arterial blood gases (ABGs) were obtained. Throughout the protocol, respiratory rate was set to aim for similar $\dot{V}E$ as at baseline and to minimize auto-PEEP, and FI_{O_2} was kept constant.
- *Step 1*: Step 1 was a relatively simple incremental PEEP step allowing measurement of ABG. In volume-controlled ventilation with a VT of 6 ml/kg predicted body weight, the potential for lung recruitment was tested by applying PEEP 6 (5 min), 16 (5 min), and 6 (2 min) cm H_2O. At PEEP 6 cm H_2O, airway closure and the airway opening pressure (AOP) were assessed with a low-flow inflation maneuver (8, 21). Respiratory mechanics, hemodynamics, and ABG were obtained at the end of each 5-minute step. Alveolar derecruitment was assessed with a single-breath maneuver during the PEEP drop from 16 to 6 cm H_2O to measure R/I ratio (13).
- *Step 2*: Step 2 was a detailed decremental PEEP trial without measurement of gas exchange and was made as safe as possible. First, in pressure-controlled ventilation with a driving pressure of 15 cm H_2O, PEEP was progressively increased to ensure and test the patient's tolerance up to 24 cm H_2O (or lower, depending on step-by-step clinical tolerance). This progressive increase was chosen because of its better tolerance than abrupt increases in pressure (likely allowing time for vascular adaptation [22]). The maximum pressure reached was 39 cm H_2O (a classical recruitment pressure used is ∼40 cm H_2O; importantly, this level was much lower than in the ART trial [Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial], where clinical tolerance was an important concern [23]). Then, ventilator mode was switched to volume-controlled ventilation with the VT lowered to

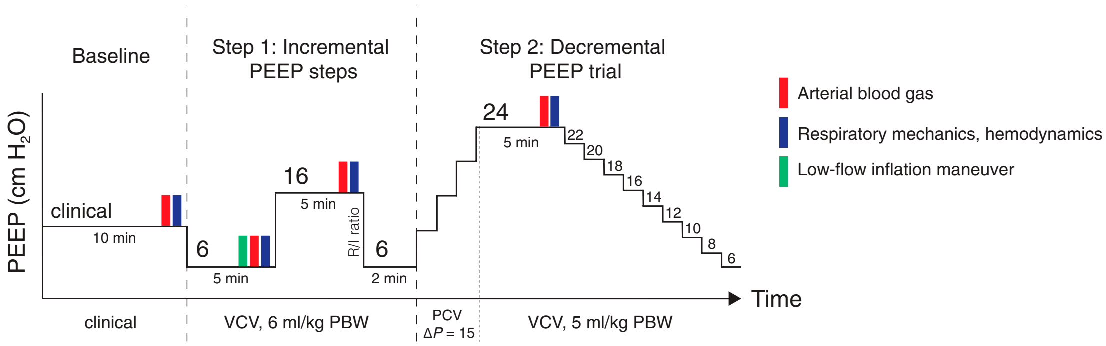


Figure 1. Study protocol with applied positive end-expiratory pressure (PEEP) steps. For further details, *see* the Methods section. Ventilator mode is mentioned below the *x*-axis. Continuous monitoring of electrical impedance tomography and airway pressure and/or flow was performed throughout the protocol. Arterial blood gas and measurements of respiratory mechanics (short 0.2- to 0.3-s end-inspiratory and end-expiratory occlusions) and hemodynamics were obtained at baseline clinical PEEP level and for PEEP steps with a duration of 5 minutes. R/I ratio was assessed during a single-breath maneuver when decreasing PEEP from 16 to 6 cm H_2O (Step 1). In Step 2, before applying the decremental PEEP trial, PEEP was increased from 6 to 24 cm H_2O (or lower if not tolerated) in small steps (10 to 15 to 20 to 24 cm H_2O) of 1–2 minutes to test the patient's tolerance; this was done in PCV mode with a driving pressure (ΔP) of 15 cm H_2O, an inspiratory to expiratory (I:E) ratio of 1:1, yielding a maximum peak airway pressure of 39 cm H_2O that was allowed. At PEEP 24 cm H_2O in VCV mode with a V_T lowered to 5 ml/kg PBW to minimize tidal recruitment effects, a maximum plateau pressure of 40 cm H_2O was accepted (V_T values were lowered if necessary). The following safety criteria were in place to ensure the patient's tolerance: interruption of the protocol (back to preceding PEEP value) at any time if aforementioned values could not be maintained for at least 30 seconds without a drop in blood pressure (by 15 mm Hg for systolic blood pressure) or oxygen saturation as measured by pulse oximetry (Sp_{O_2}) <85%. If stability was obtained at the previous step, the rest of the measurements were performed starting from the last PEEP level associated with stability. The protocol was aborted (back to clinical baseline settings), and the patient was classified as failure to perform the test in case of sustained hypotension (drop in mean arterial pressure, >15 mm Hg) or sustained hypoxemia (Sp_{O_2} <85% for at least 1 min). PBW = predicted body weight; PCV = pressure-controlled ventilation; R/I = recruitment-to-inflation; VCV = volume-controlled ventilation.

5 ml/kg predicted body weight (to minimize effects of tidal recruitment) to measure respiratory mechanics, hemodynamics, and ABG after 5 minutes. Next, PEEP was decreased from 24 to 6 cm H_2O in steps of 2 cm H_2O with a duration of at least 10 breaths or 30 seconds at each step. Experimental and clinical data from the laboratory of Prof. Marcelo Amato showed that this time is sufficient for a reasonably accurate estimate of the change in compliance because the occurrence of airway closure is very fast (24). If a PEEP of 24 cm H_2O was not tolerated, we allowed the decremental PEEP trial to be done starting from a lower than maximal PEEP.

The patient's ventilatory management was then resumed as per local clinical protocol while data were analyzed offline.

Offline Analysis

EIT data were processed using dedicated software (Timpel: software in LabVIEW and validated against CT in animal studies [25–27]; Dräger: PV500 Data Analysis SW130; Swisstom: Ibex V6 [Sentec] and MATLAB R2020b [MathWorks]); computations were made as consistent as possible for different EIT devices. Because EIT-based parameters are derived from the calculus of relative changes in pixel compliance (after computing the maximum pixel compliance observed along the whole titration as the 100% reference for each pixel), reported percentages of collapse refer to the percentage loss of pixel compliance over the range of applied PEEP from 24 (or lower if not tolerated) to 6 cm H_2O. This computation means that *1*) any remaining collapse at PEEP 24 cm H_2O (as per CT scan) is not visible on EIT for this calculation, and *2*) the percentage of recruitable collapse at any PEEP step depends on this reference PEEP used. Conversely, the minimal PEEP level (6 cm H_2O) was considered as having 0% of overdistension, and percentages of overdistension at higher PEEP refer to the overdistension that disappeared at this low PEEP. Therefore, the reported percentages of collapse and overdistension refer to relative percentages of modifiable collapse and overdistension. Last, to allow within-patient comparison along the whole study protocol, PEEP steps outside of the decremental PEEP trial (baseline, incremental step) were also used for comparison.

Recruitability definition and groups. Recruitability was defined as the absolute reduction in the percentage of collapse when comparing PEEP 6 cm H_2O at the start of the protocol with PEEP 24 cm H_2O (or to the highest tolerated PEEP); we refer to this parameter as ΔCollapse$_{24–6}$. Note that the computation of collapse requires the whole decremental PEEP trial (*see above*). To facilitate the presentation, equal-size groups of patients with low, medium, or high recruitability were made using tertiles of ΔCollapse$_{24–6}$.

Optimal PEEP compromise during the decremental trial. Optimum EIT-based PEEP was first defined as the crossing point of the collapse and overdistension curves along the decremental PEEP trial (18); if the crossing point was between two PEEP levels, values were rounded up to the nearest integer. For comparison, we obtained the PEEP level associated with the highest respiratory system compliance (thus lowest driving pressure) during the decremental PEEP trial and the PEEP level associated with the nondependent/dependent tidal

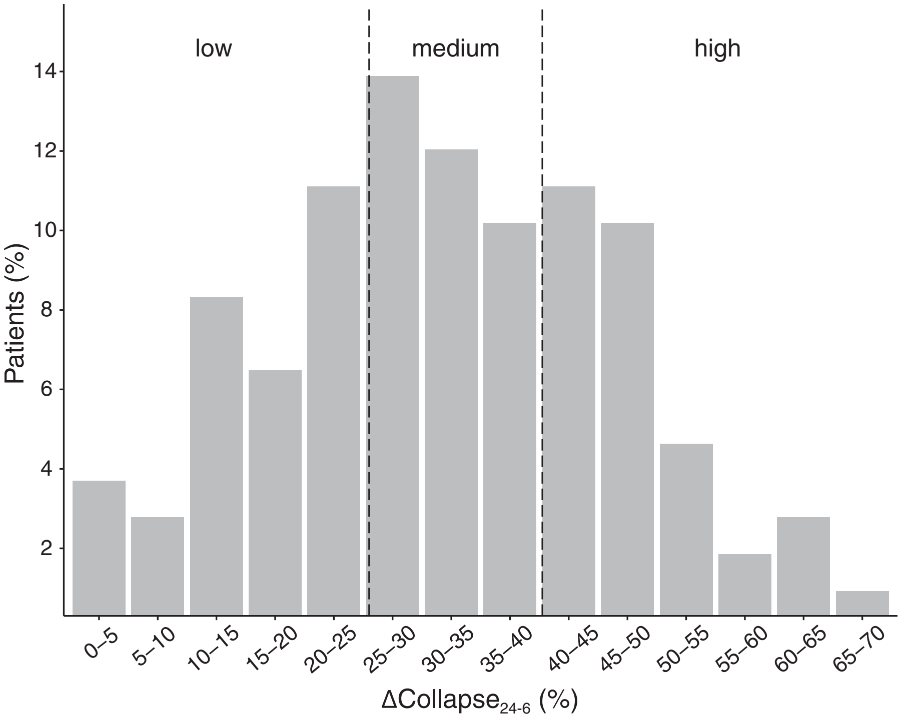


Figure 2. Distribution of recruitability as defined by the decrease in the collapse on electrical impedance tomography when increasing positive end-expiratory pressure from 6 cm H_2O (Step 1 of protocol) to 24 cm H_2O (ΔCollapse$_{24–6}$). Groups of low, medium, and high recruitability were made using the tertiles of ΔCollapse$_{24–6}$: low (<25.3%), medium (25.4–39.6%), and high (>39.6%) recruitability.

ventilation distribution ratio closest to 1 (indicating most homogeneous ventilation) (28).

Regional distribution. We hypothesized that collapse would be present primarily in the posterior dependent lung regions and overdistension would be present in the anterior nondependent regions. EIT images were thus horizontally divided into two equal regions (to allow within- and between-patient comparisons), and we computed the percentages of collapse and overdistension separately for both regions. In addition, we computed the regional distribution of tidal ventilation separately for the dependent and nondependent regions, as well as for the left and right lungs.

R/I ratio, respiratory mechanics, hemodynamics, and gas exchange. R/I ratio was calculated during the single-breath maneuver (PEEP 16 to 6 cm H_2O) and taking into account AOP if present (13). An EIT-based R/I ratio was developed using the same breaths but with changes in end-expiratory lung impedance from PEEP 16 to 6 cm H_2O and tidal impedance at PEEP 6 cm H_2O to determine the predicted change in impedance during the maneuver. At each PEEP step, we report hemodynamics and calculated driving pressure, compliance, and normalized elastance. For steps with ABG available, we calculated the Pa_{O_2}/FI_{O_2} and ventilatory ratios (29).

Sample Size

In the original main study proposal, which was supposed to enroll patients with ARDS of multiple causes, the planned sample size was 171 patients. This report includes all patients with COVID-19 ARDS enrolled. The decision to perform this interim analysis was triggered by the significant drop in the number of intubated mechanically ventilated patients with COVID-19 and the much slower enrollment of patients without COVID-19 who had ARDS.

Statistical Analysis

Descriptive data are presented as mean ± SD or median [interquartile range] according to the normality of data checked using the Shapiro-Wilk test. We did not impute missing data. Repeated measurements at different PEEP steps were compared with linear mixed-effects models with fixed effects of PEEP and a random effect of subject; estimated means were compared after Tukey correction. These models were extended with fixed effects of recruitability group and group by PEEP interaction to test for their interaction effect (i.e., to test if the change in repeated measurements was different between the recruitability groups). The Kruskal-Wallis test with *post hoc* comparison after Dunn's correction was applied to test for differences in parameters between recruitability groups. Relationships between continuous parameters were tested with linear regression analysis. *P* values <0.05 were considered statistically significant. Analyses were performed using R version 1.3 (RStudio).

Results

A total of 108 patients with COVID-19 were enrolled (May 2020–December 2021). The protocol was well tolerated; in four patients, the PEEP level of 24 cm H_2O was not reached because of hemodynamic instability (*see* safety criteria in Figure 1); their highest tolerated PEEP ranged from 16 to 20 cm H_2O, and, by design, the protocol allowed the decremental PEEP trial to be started from this lower than maximal pressure. The protocol was not aborted in any patient.

Recruitability across Patients and Characteristics of Groups

Recruitability distribution (ΔCollapse$_{24–6}$) varied from 0.3% to 66.9% and is displayed in Figure 2. Three equal-size groups were defined as low recruiters having a ΔCollapse$_{24–6}$ $<$ 25.3%, with moderate recruiters being between 25.4% and 39.6% and high recruiters being $>$39.6%. Their characteristics and respiratory mechanics at study baseline are presented in Table 1. Patients did not differ in terms of ARDS severity and general severity on ICU admission. High recruiters were younger and had higher BMI. Airway closure at $>$6 cm H_2O PEEP was present in 45 (41%) patients (per group: $n = 11$, 16, and 18 patients with low, medium, and high recruitability, respectively); their AOP was low (7 [7, 7] cm H_2O; only one patient presented with AOP $>$10 cm H_2O) and did not differ between groups ($P = 0.528$). R/I ratio correlated

Table 1. Patient Characteristics

Characteristics	Total Population ($N = 108$)	Low Recruitability ($n = 36$)	Medium Recruitability ($n = 36$)	High Recruitability ($n = 36$)	*P* Value
Sex, M/F	65/42	23/13	22/14	20/15	0.8530
BMI, kg/m^2	30.4 [25.9; 32.9]	28.4 [24.8; 31.5]	30.1 [26.6; 31.9]	$32.9^{*\dagger}$ [27.2; 39.4]	**0.0134**
Age, yr	61 [51; 68]	65 [57.6; 70]	61 [54; 65]	55* [46; 63.5]	**0.0051**
Pa_{O_2}/Fi_{O_2} ratio at ICU admission, mm Hg	114 [98; 140]	113 [97; 134]	120 [100; 142]	113 [99; 141]	0.9070
SAPS II	52.5 [45; 59]	53 [47; 60]	50 [45; 62]	53 [42.8; 56]	0.4792
SOFA score at study enrollment	6 [4; 8]	7 [4; 8]	5 [4; 8]	5 [4; 8]	0.5678
Days ventilated before study, d	2 [1; 3]	2 [1; 3]	1 [1; 2]	2 [1; 4]	0.1299
Total ventilation duration, d	15 [9; 24.8]	17 [12; 31]	13 [7; 23]	13 [8.5; 24.3]	0.1112
ICU length of stay, d	23 [12; 38]	29 [16; 39]	20 [12; 33]	15.5 [10; 36.5]	0.0878
ICU mortality,[‡] %	39% ($n = 38$ of 98)	45% ($n = 15$ of 33)	36% ($n = 12$ of 33)	33% ($n = 11$ of 32)	0.2167
VFD Day 28, d	5 [0; 18]	0 [0; 13]	11 [0; 20]	11 [0; 17.3]	0.1410
Respiratory mechanics at study baseline (clinical settings)					
Total PEEP, cm H_2O	11 [10; 14]	11 [10; 14]	11 [10; 14]	11 [10; 13.8]	0.5604
Driving pressure, cm H_2O[§]	13 [11; 16]	15 [12; 18]	14 [11.5; 16]	12* [11; 13.8]	**0.0196**
Crs, ml/cm H_2O	27.4 [22.4; 34.8]	24.6 [18.9; 31.7]	28.4 [23.3; 37.0]	28.1 [23.6; 32.9]	0.0817
Normalized elastance, cm H_2O/(ml/kg PBW)	2.20 [1.85; 2.68]	2.42 [1.99; 3.15]	2.20 [2.0; 2.64]	2.04* [1.76; 2.27]	**0.0211**
Pa_{O_2}/Fi_{O_2} ratio, mm Hg	114 [92; 140]	115.4 [98.7; 138.3]	108.5 [89.2; 145.6]	115.3 [89.4; 140.6]	0.8592
Ventilatory ratio	1.75 [1.52; 2.02]	1.89 [1.67; 2.18]	1.57* [1.38; 1.85]	1.75 [1.55; 2.00]	**0.0175**
Recruitability					
$\Delta Collapse_{24\text{-}6}$, %	32.0 (min-max, 0.3–66.9)	16.9 [11.1; 22.2]	32.0 [27.3; 34.9]	46.4 [42.5; 51.6]	—
R/I ratio (ventilator based)	0.71 [0.51; 0.94] ($n = 98$)	0.59 [0.43; 0.70] ($n = 33$)	0.79 [0.54; 0.95]* ($n = 35$)	0.83 [0.68; 1.05]* ($n = 30$)	**0.0012**
R/I ratio (EIT based)	0.94 [0.79; 1.17] ($n = 77$)	0.82 [0.59; 1.09] ($n = 24$)	0.90 [0.84; 1.10] ($n = 31$)	1.08 [0.95; 1.35]* ($n = 22$)	**0.0055**

Definition of abbreviations: $\Delta Collapse_{24\text{-}6}$ = amount of modifiable collapse when increasing PEEP from 6 to 24 cm H_2O; BMI = body mass index; Crs = respiratory system compliance; EIT = electrical impedance tomography; PBW = predicted body weight; PEEP = positive end-expiratory pressure; R/I = recruitment to inflation; SAPS II = Simplified Acute Physiology Score II; SOFA = Sequential Organ Failure Assessment; VFD = ventilator-free days.

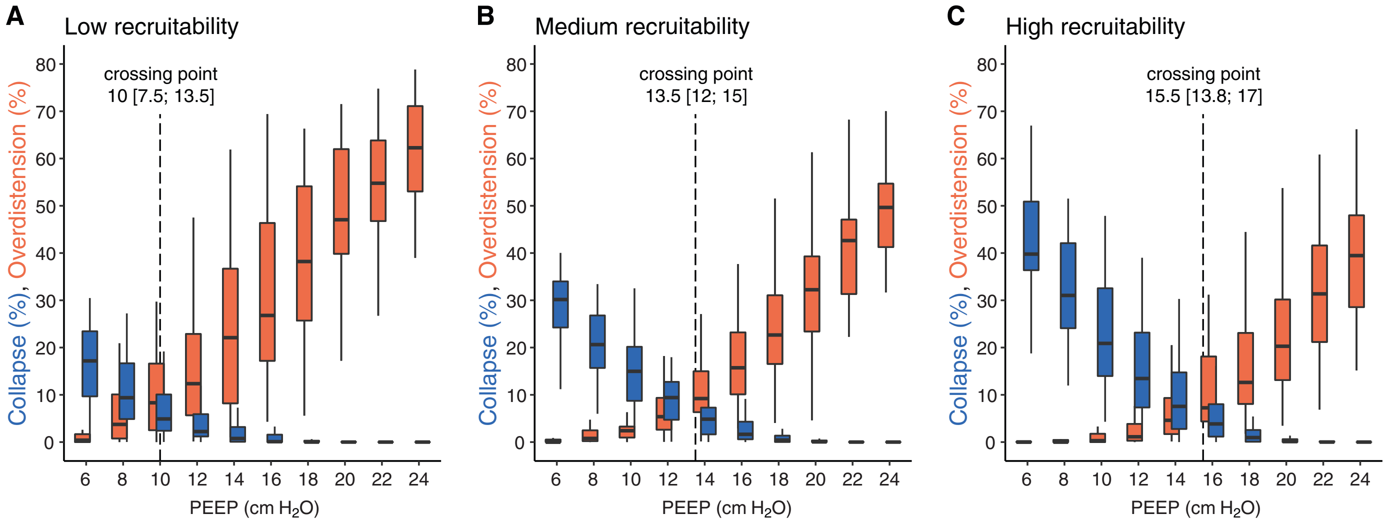
Data within brackets are presented as median [interquartile range].

*$P < 0.05$ difference from lower recruitability.

[†] $P < 0.05$ difference from medium recruitability. *P* values are based on a three-group comparison with the Kruskal-Wallis test and *post hoc* comparison with Dunn correction. *P* values in bold indicate significance.

[‡] Follow-up data on ICU mortality and clinical outcomes were missing for some patients (e.g., due to transfer); mortality percentages are based on the number of known outcomes.

[§] Driving pressure as measured via short inspiratory and expiratory occlusions.



PEEP effect (within group): collapse, $P < 0.001$; overdistention, $P < 0.001$
PEEP x group interaction effect: collapse, $P < 0.001$; overdistention, $P < 0.001$

Figure 3. Distribution of collapse (blue) and overdistension (orange) during the decremental positive end-expiratory pressure (PEEP) trial for the three groups of recruitability (*A*: low recruitability, *B*: medium recruitability, *C*: high recruitability). The dotted lines indicate the group median [interquartile range] PEEP level as per the crossing point of the collapse and overdistension curves.

moderately with $\Delta\text{Collapse}_{24-6}$ ($r = 0.49$ for EIT-based R/I ratio; $P < 0.001$) and was significantly higher in patients with medium and higher recruitability (Table 1).

Decremental PEEP Trial

Collapse and overdistension crossing point. Percentages of collapse and overdistension during the decremental PEEP trial for the recruitability groups are shown in Figure 3, resulting in different optimal PEEP levels as per the crossing point method: median [interquartile range] of 10 [7.5; 13.5] versus

Table 2. Mechanics during Decremental Positive End-Expiratory Pressure Trial and at Crossing Point

	Low Recruitability	Medium Recruitability	High Recruitability	*P* Value
Crossing point PEEP level, cm H_2O	10 [7.5; 13.5]	13.5* [12; 15]	15.5*† [13.8; 17]	**<0.001**
PEEP level with highest Crs, cm H_2O	9 [6; 12]	12* [10; 14]	16*† [12; 18]	**<0.001**
PEEP level with most homogeneous ventilation distribution, cm H_2O	18 [13.8; 22]	16 [13.5; 22]	16 [11.8; 20.5]	0.615
Mechanics at the crossing point PEEP				
Crs, ml/cm H_2O	29.2 [24.4; 38.4]	37.4 [28.2; 46.6]	35.6 [30.8; 39.5]	0.054
ΔPaw, cm H_2O‡	8.2 [7.5; 9.7]	8.6 [7.1; 10.1]	8.4 [7.1; 10.9]	0.923
Collapse, %	4.8 [3.1; 7.2]	6.0 [4.4; 7.3]	4.5 [3.2; 5.8]	0.216
Overdistension, %	8.3 [4.9; 9.9]	8.0 [7.0; 10.1]	6.3 [4.8; 7.9]	0.053
Normalized elastance, cm H_2O/(ml/kg PBW)	1.87 [1.61; 2.53]	1.71 [1.42; 2.04]	1.56 [1.40; 1.87]	0.158
Drop in ΔPaw vs. PEEP 6 cm H_2O (end PEEP trial), cm H_2O	−0.4 [0.0; −0.9]	−1.4* [−0.7; −2.5]	−2.7*† [−1.7; −4.0]	**<0.001**
RR during PEEP trial, breaths/min	25 [23.5; 26]	24 [21.5; 25]	23 [20; 25]	0.0645
Set VT during PEEP trial, ml	258 [239; 319]	319 [271; 348]*	297 [260; 331]	**0.0268**

Definition of abbreviations: ΔPaw = airway driving pressure; Crs = respiratory system compliance; PBW = predicted body weight; PEEP = positive end-expiratory pressure; RR = respiratory rate.
Data within brackets are presented as median [interquartile range].
*$P < 0.05$ difference from lower recruitability.
†$P < 0.05$ difference from medium recruitability. *P* values are based on a three-group comparison with the Kruskal-Wallis test and *post hoc* comparison with Dunn correction. *P* values in bold indicate significance.
‡Driving pressure while VT was set at 5 ml/kg PBW during the PEEP trial to minimize tidal recruitment effects; driving pressure was calculated using the compliance and set VT at PEEP 24 cm H_2O. Compliance at each step was obtained using the plateau pressure at a 0.2- or 0.3-second short inspiratory pause that was set, or based on a linear regression model to estimate plateau pressure.

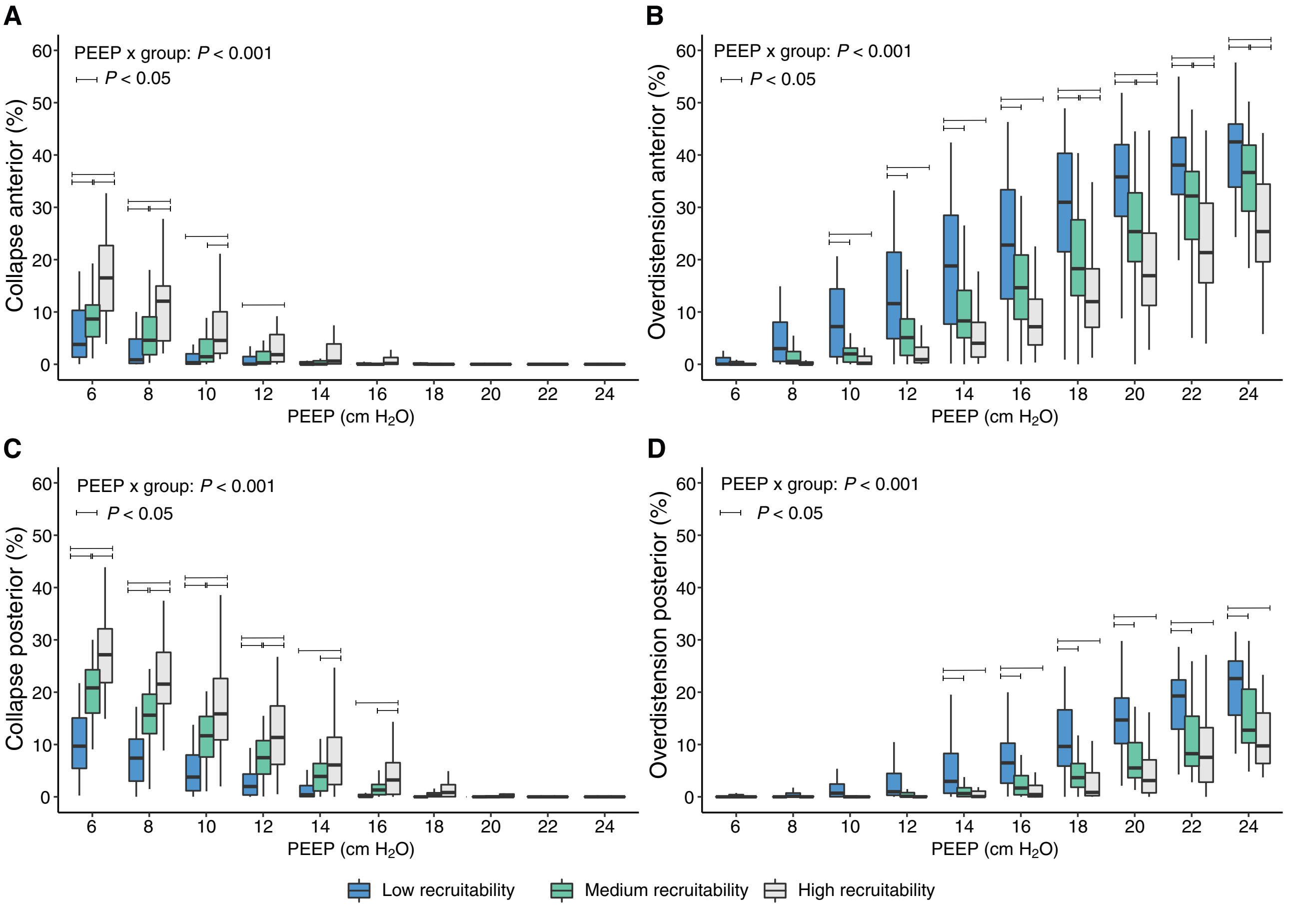


Figure 4. Regional distribution of collapse (left, panels *A* and *C*) and overdistension (right, panels *B* and *D*) for the anterior (upper graphs, panels *A* and *B*) and posterior (lower graphs, panels *C* and *D*) lung and separated for the three recruitability groups. Collapse was present mainly in the dependent lung and highest for the higher recruitable patients (per our definition). Overdistension occurred primarily in the nondependent lung, with highest values found for lower recruitable patients and already at low PEEP levels. PEEP = positive end-expiratory pressure.

13.5 [12; 15] versus 15.5 [13.8; 17] cm H_2O for patients with low, medium, and high recruitability, respectively ($P < 0.001$). For patients with airway closure, this optimal PEEP level was a median [interquartile range] of 7 [4; 8] cm H_2O above AOP; only one patient presented an AOP of 1 cm H_2O above the crossing point PEEP. At the crossing point, collapse, overdistension, and respiratory mechanics were similar between groups. There was a trend toward lower compliance for patients with low recruitability ($P = 0.054$) (Table 2). The crossing point PEEP level had a positive moderate correlation to BMI ($r = 0.57$; $P < 0.001$).

Regional distribution of collapse and overdistension. Recruitable collapse was present mainly in the dependent lung, whereas overdistension occurred primarily in the nondependent lung, but with large variability between and within groups (Figure 4).

Comparison with the highest compliance. Although the optimal PEEP level per the crossing point approach was related to the PEEP associated with the highest compliance during the decremental PEEP trial ($R^2 = 0.72$; $P < 0.05$), both methods did not assign the same PEEP for all patients: Low and medium recruitability groups had a higher crossing point PEEP than the PEEP with the highest compliance ($P < 0.05$), whereas no difference was found for the highly recruitable group ($P = 0.070$) (Table 2, Figure 5). In only 20 (19%) patients, both methods assigned the same PEEP (Figure 5; median [range] of differences for the total population, 1 [−4 to 6] cm H_2O).

For 24 patients, the crossing point PEEP was between two fixed PEEP steps. Because this would by design influence the comparison with the PEEP associated with the highest compliance (which was calculated only at the fixed PEEP steps), a sensitivity analysis also evaluated the comparison between both PEEP selection approaches when taking either *1*) the nearest higher fixed PEEP step or *2*) the nearest lower fixed PEEP step for patients where the crossing point PEEP was between two fixed PEEP steps. This did not change the overall correlation between the crossing point PEEP versus optimal compliance PEEP ($R^2 = 0.69$ and 0.71, respectively). Taking the higher fixed PEEP step resulted in more separation between both approaches, with a crossing point PEEP that was higher than the optimal compliance PEEP (median difference, 2 cm H_2O; range, 4, −6 cm H_2O), whereas no overall difference was found between both approaches when taking the lower fixed PEEP step (median difference, 0 cm H_2O; range, 4, −6 cm H_2O). In only 31 (29%) and 41 (38%) of 108 patients, both methods assigned the same PEEP level when taking the higher or lower fixed PEEP step,

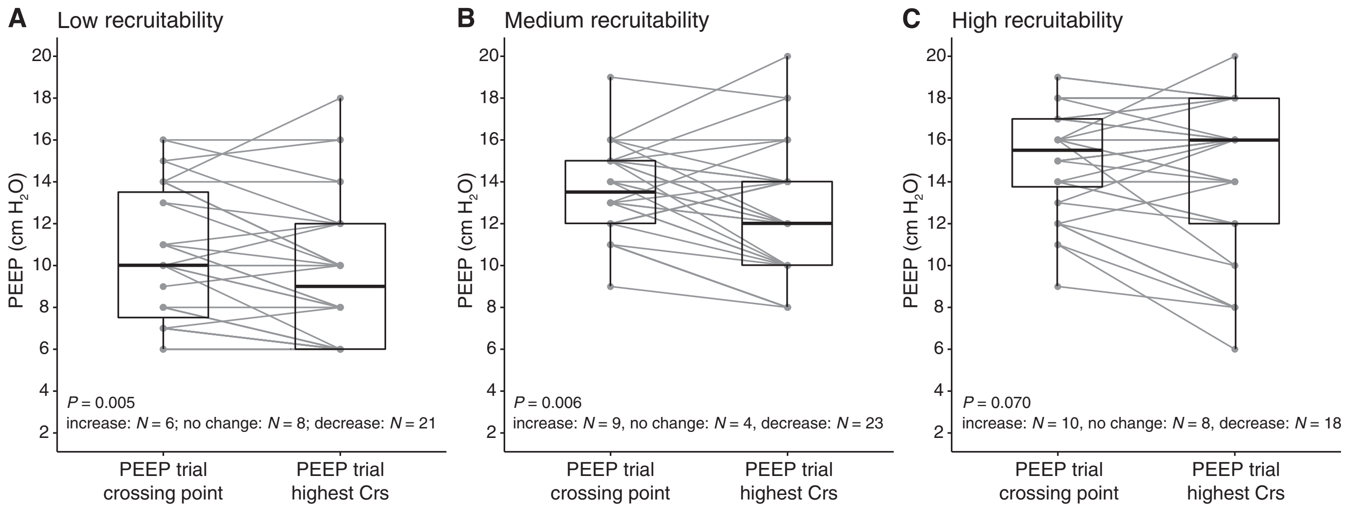


Figure 5. Comparison of the optimal positive end-expiratory pressure (PEEP) according to the crossing point of the collapse and overdistension curves (PEEP trial crossing point) and the PEEP level with the highest respiratory system compliance (PEEP trial highest Crs) obtained during the decremental PEEP trial and separated for the three recruitability groups (*A*: low recruitability, *B*: medium recruitability, *C*: high recruitability). Individual comparison and the median with interquartile range are provided.

respectively. Compliance throughout the decremental PEEP trial, analyzed per group, is shown in Figure E1 in the online supplement.

Regional distribution of ventilation. Figure 6 shows the ventilation distribution for the dependent and nondependent lung during the decremental PEEP trial. The PEEP level associated with a nondependent/dependent tidal ventilation ratio closest to 1 did not differ between groups ($P = 0.615$) (Table 2) and was higher than PEEP levels based on the crossing point or highest compliance approach ($P < 0.001$). The distribution of ventilation separated for the left and right lungs is shown in Figure E2.

Incremental PEEP Steps

There were only three incremental PEEP steps, and respiratory mechanics, hemodynamics, and gas exchange at these 5-minute incremental PEEP steps of 6, 16, and 24 cm H_2O are shown in Table 3 and Figure 7. At these steps, the effect of PEEP on collapse and overdistension varied significantly between groups (Figure E3). Driving pressure increased from PEEP 6 to 16 cm H_2O in low and medium recruitability groups, but not in high recruiters (Table 3).

Pa_{O_2}/FI_{O_2} and Pa_{O_2} increased in all groups with higher PEEP, as well as Pa_{CO_2} (Figure 7). Multiple linear models revealed that changes (improvements) in oxygenation at incremental PEEP steps of 6, 16, and 24 cm H_2O were driven mainly by progressively lower levels of collapse

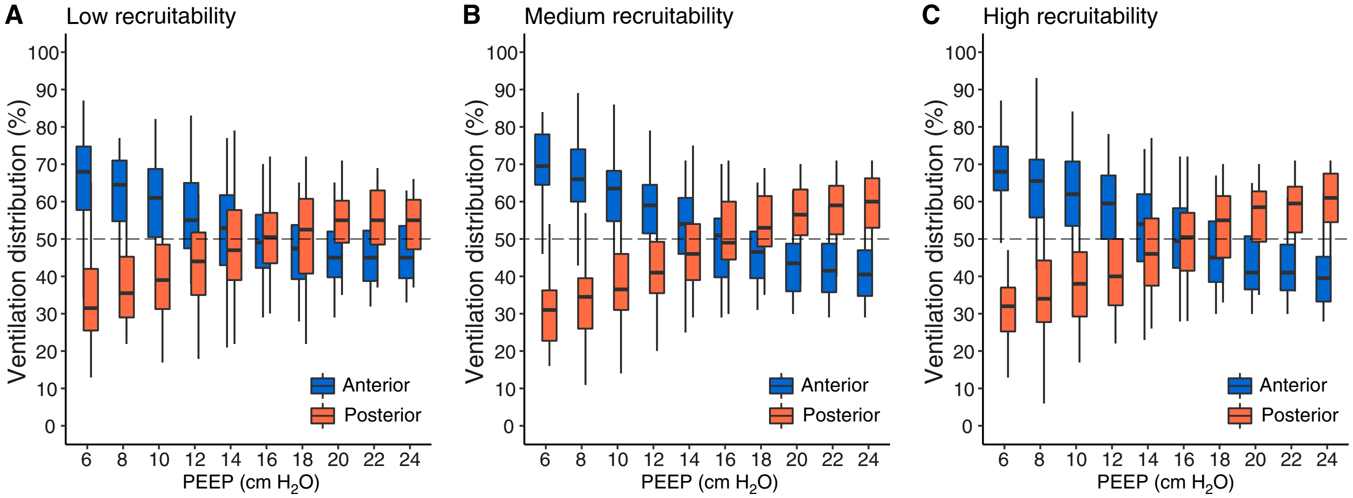


Figure 6. Distribution of tidal ventilation for the posterior dependent (orange) and anterior nondependent (blue) lung, as obtained during the decremental positive end-expiratory pressure (PEEP) trial and separated for the three recruitability groups (*A*: low recruitability, *B*: medium recruitability, *C*: high recruitability). The PEEP level associated with a nondependent/dependent tidal ventilation ratio closest to 1 (i.e., the PEEP level where the *y*-axis is 50%) did not differ between groups. At increasing levels of PEEP, more tidal ventilation to the posterior lung is observed, which is suggestive of overdistension of the anterior lung.

Table 3. Mechanics, Hemodynamics, and Gas Exchange during Incremental 5-Minute Positive End-Expiratory Pressure Steps

	Low Recruitability			Medium Recruitability			High Recruitability			
	PEEP 6 cm H_2O	PEEP 16 cm H_2O	PEEP 24 cm H_2O	PEEP 6 cm H_2O	PEEP 16 cm H_2O	PEEP 24 cm H_2O	PEEP 6 cm H_2O	PEEP 16 cm H_2O	PEEP 24 cm H_2O	*P* Value PEEP × Group Interaction
Crs, ml/cm H_2O	26.9 [22.1; 33.5]	22.4 [18.8; 31.8]	15.4*† [11.1; 19.9]	29.1 [22.5; 35.9]	31.8* [24.0; 43.3]	22.6*† [19.1; 30.9]	23.6 [21.7; 31.6]	28.6* [23.4; 33.2]	24.7† [20.4; 28.5]	**0.001**
ΔPaw, cm H_2O	13 [11; 16]	17* [13; 22]	18* [15.5; 21]	13 [11; 15]	15* [12; 17]	14 [12; 16]	14 [12; 16]	14 [11; 15.5]	14 [10; 15.3]	**<0.001**
Heart rate, beats/min	91 [77; 100]	90 [70; 100]	94*† [84; 112]	90 [75; 104]	89 [73; 103]	88 [74; 106]	84 [77; 94]	79 [71; 95]	81 [69; 93]	**0.012**
SBP, mm Hg	127 [117; 150]	121 [109; 129]	127 [103; 151]	128 [105; 149]	118 [104; 134]	127 [112; 146]	122 [115; 143]	122 [114; 136]	122 [108; 133]	0.631
MAP, mm Hg	89 [80; 98]	84* [77; 89]	84* [70; 95]	83 [74; 102]	79 [74; 94]	88† [79; 97]	86 [78; 95]	81 [77; 91]	85 [79; 93]	0.255
Pa_{O_2}, mm Hg	84 [66; 106]	90 [71; 135]	111*† [84; 192]	72 [62; 93]	112* [72; 173]	223*† [150; 330]	67 [56; 91]	105* [79; 125]	246*† [97; 322]	**<0.001**

Definition of abbreviations: ΔPaw = airway driving pressure; Crs = respiratory system compliance; MAP = mean arterial pressure; PEEP = positive end-expiratory pressure; SBP = systolic blood pressure.

Data within brackets are presented as median [interquartile range].

*$P < 0.05$ difference from PEEP 6 cm H_2O.

†$P < 0.05$ difference from PEEP 16 cm H_2O.

P values are based on linear mixed-effects models with fixed effects of PEEP, group, PEEP by group interaction, and a random effect of subject; within-group comparisons of estimated means were made with the Tukey method. *P* values in bold indicate significance.

($P < 0.001$), whereas higher levels of Pa_{CO_2} observed at higher PEEP were driven mainly by higher levels of overdistension (without any correlation with lung collapse). In the particular condition of 24 cm H_2O PEEP, oxygenation was correlated to both: Oxygenation was maximized when the reduction in collapse was largest, but it was lower with higher levels of overdistension ($P < 0.001$).

Discussion

The main findings of this study in patients with COVID-19 with moderate-severe ARDS are as follows: *1*) EIT is a feasible bedside technique for defining the potential of lung recruitment over a clinical range of PEEP in patients with moderate-severe ARDS; *2*) recruitability varies widely and is not related to ARDS severity or general severity; *3*) the PEEP value at the crossing point of the collapse and overdistension curves obtained with a decremental PEEP trial indicates the level where collapse and overdistension are jointly minimized and associated with comparable respiratory mechanics independent of the level of recruitability; *4*) the crossing point method does not assign the same PEEP as with the highest compliance or the most homogeneous ventilation approach for the majority of patients; and *5*) EIT allows the differentiation of patients with different responses to PEEP, including regional information (dependent and nondependent lung) that cannot be assessed by respiratory mechanics and/or oxygenation response solely. EIT therefore could allow personalized PEEP selection at the bedside as a compromise between recruitment and overdistension.

Definition and Heterogeneity of Recruitability

We defined recruitability based on EIT as the amount of collapse that can be reopened by higher PEEP by comparing the collapse reduction from the lowest (6 cm H_2O) to the highest (24 cm H_2O or lower if not tolerated) PEEP level. Inherent to the computational method of collapse as a relative percentage, it, therefore, does not inform about the precise amount of anatomical collapse, such as with a CT scan. For the purpose of clinical application, it estimates the amount of recruitable collapse in relation to the size of the lung at the highest PEEP (24 cm H_2O or

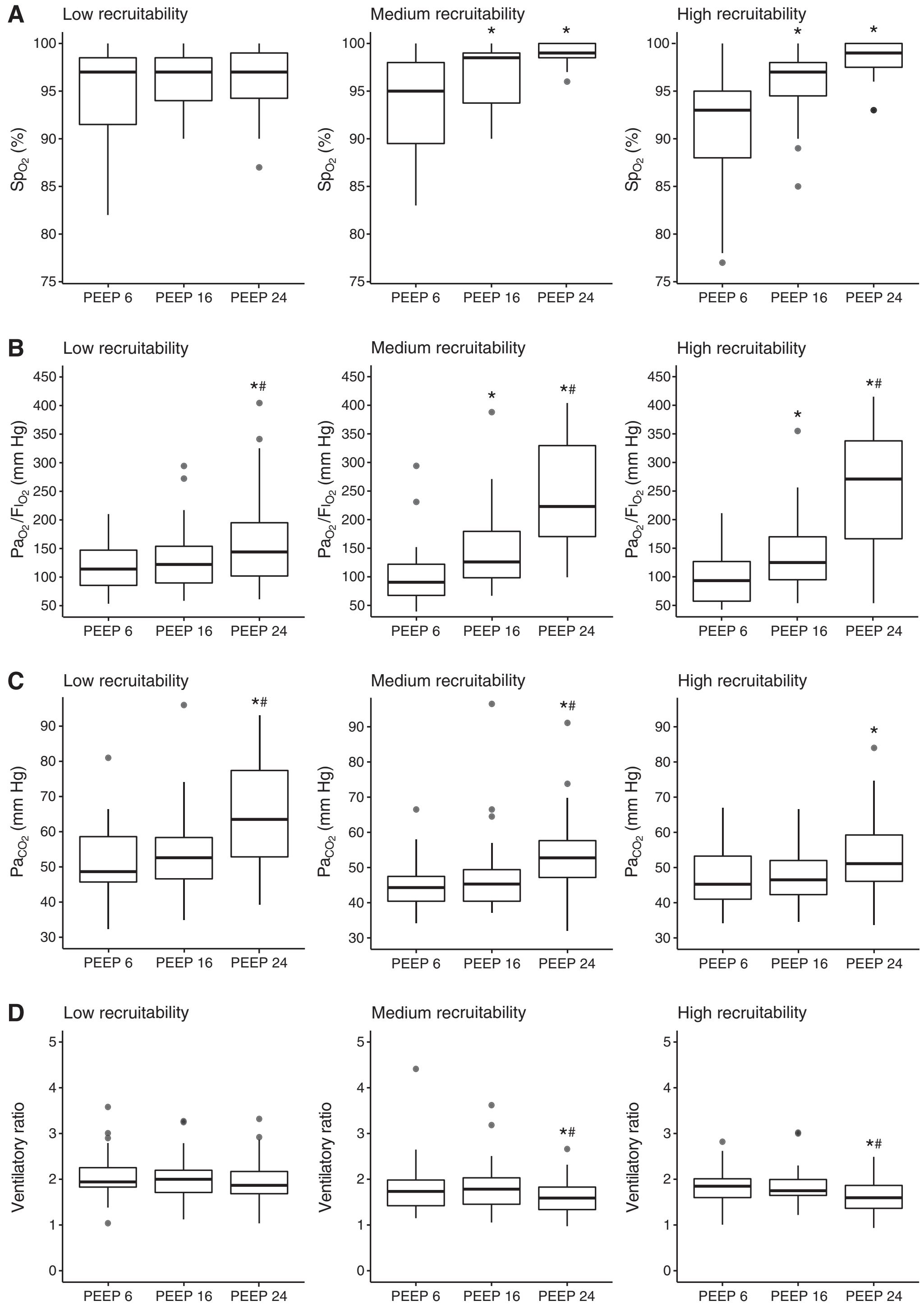


Figure 7. Mechanics, hemodynamics, and gas exchange during incremental 5-minute positive end-expiratory pressure (PEEP) steps and separated per recruitability group. (*A*) Oxygen saturation as measured by pulse oximetry (Sp_{O_2}) at fixed FI_{O_2}. (*B*) Pa_{O_2} to FI_{O_2} ratio. (*C*) Pa_{CO_2}. (*D*) Ventilatory ratio. $^*P < 0.05$ difference from PEEP 6 cm H_2O; $^\#P < 0.05$ difference from PEEP 16 cm H_2O. *P* values are based on linear mixed-effects models with fixed effects of PEEP, group, PEEP by group interaction, and a random effect of subject; within-group comparisons of estimated means were made with the Tukey method. Interaction effects of PEEP by group interaction were as follows: Sp_{O_2}, $P < 0.001$; Pa_{O_2}/FI_{O_2}, $P < 0.001$; Pa_{CO_2}, $P < 0.001$; Ventilatory ratio, $P = 0.425$.

lower if not tolerated). Quantification of collapse based on EIT correlates very well with CT scan when computing the mass of pixels that collapse from the highest PEEP down (18).

As previously shown by Gattinoni and colleagues in "classical ARDS" using CT scans (1), recruitability varied widely in our COVID-19 ARDS cohort as well, in line with studies done earlier during the pandemic using EIT and/or R/I ratio in small cohorts (15, 30–33) or using respiratory parameters (34). Recruitability was also higher than reported recently by Protti and colleagues (33) using CT scans and with recruitability estimated in relation to the lung mass at low PEEP, similar to Gattinoni and colleagues (1) (for comparison, *see* Figure E4). Differences with Protti and colleagues (33) may be related to a different definition of recruitability, a more extensive maneuver (5-min PEEP 24 cm H_2O with plateau pressure $\sim$40 cm H_2O [Figure 1] vs. continuous positive airway pressure 45 cm H_2O for 10–15 s [33]) and a higher proportion of obese patients in our cohort, most of them demonstrating higher recruitability. The higher PEEP crossing point with higher BMI is consistent with recent findings (35, 36).

EIT-based PEEP Selection: Crossing Point Method

The large variability in recruitability and PEEP crossing point strengthens the need for an individualized PEEP setting. Although we defined recruitability during the increment of PEEP, decremental PEEP trials are generally used to determine the PEEP level required for optimal lung behavior after first recruiting the lung. What the optimal EIT-based PEEP should be after a decremental PEEP trial is debated. We chose the crossing point method because this approach allows a compromise between minimizing both alveolar collapse and overdistension. This approach, initially proposed by Costa and colleagues in two patients (18), can be applied directly at the bedside and has been described in few studies (30, 35, 37). However, it assumes that both overdistension and collapse are equally harmful (38). Recruiting collapse is essential for lowering the shunt and increasing the size of the aerated baby lung (1). How the amount of overdistension relates to markers of lung inflammation and subsequent lung injury are yet to be studied. Nevertheless, the risks of overdistension cannot be estimated by other bedside techniques, such as R/I ratio, multiple pressure–volume curves method, or lung ultrasound; importantly, these techniques do not precisely allow titration of the PEEP level.

For all but one patient, the crossing point PEEP was above the AOP. Given that AOP is typically a quasi-static phenomenon of the inspiratory limb and the crossing point PEEP is a description of the lung at the expiratory limb, hysteresis could explain why it is possible, though rare, to find an AOP slightly higher than the crossing point PEEP.

An important result of this study was that, independent of the amount of recruitability, respiratory mechanics at the crossing point PEEP were comparable between patients and associated with consistently low values for overdistension ($<$10%) and collapse ($<$5%) for most patients. Experimental data also suggest that the crossing point PEEP coincides with a slightly positive end-expiratory transpulmonary pressure (25 and personal observations of the authors), and a study in asymmetrical lung injury also suggested that a transpulmonary pressure around zero indicated the best compromise between recruitment and distension (39). This concept is in line with the idea of keeping the recruitable lung open without applying excessive pressures. Whether this improves clinical outcomes, however, should be evaluated prospectively.

Comparison with the Highest Compliance

An individualized PEEP setting using the highest respiratory system compliance during a PEEP trial has been proposed and seems attractive because it can also yield the lowest driving pressure (40). First, and as suggested by our results, it is important to stress that incremental and decremental PEEP trials can give very different values, in part because of the impact of intratidal recruitment and opening versus closing pressures. Furthermore, the overall compliance can poorly reflect the regional mechanics in different parts of the lungs (41). We demonstrate that the crossing point PEEP does not match the PEEP related to the highest compliance in 81% of patients, despite a correlation between the two methods. This is consistent with findings in a cohort of patients with severe ARDS treated with extracorporeal membrane oxygenation (37). The relationship between recruitment and compliance is impacted by regional differences between dependent and nondependent lungs (41) and by intratidal recruitment, which makes this relationship more complex than is often considered (13, 42, 43). The highest compliance approach selected different individual PEEP levels, on average slightly lower than the crossing point method. It is important to stress that EIT can inform when (regional) distension is excessive, thereby avoiding the possibility to lose the potential benefit of recruitment. Risks for overdistension cannot be assessed by measuring changes in global compliance. Indeed, we found that blindly increasing PEEP from 6 to 16 cm H_2O can create a large amount of overdistension (up to 80%; Figure E2) not reflected by changes in compliance. This was previously shown experimentally in a model of acute lung injury where most compliance changes reflected the dependent lung in the supine position and not the distension of the nondependent lung (41). Furthermore, the assessment of recruitability by EIT helps to identify those patients in whom an individualized PEEP setting produces the largest possible reduction in driving pressure, as we demonstrated by the significant and larger drop in driving pressure at the crossing point PEEP (vs. at PEEP 6 cm H_2O) for higher recruitable patients (Table 2). In contrast, a fixed increment in PEEP from 6 to 16 cm H_2O did not demonstrate the same beneficial effect in terms of driving pressure (Table 3). Tidal recruitment may also contribute to the discrepancy between both approaches, and we aimed to minimize these effects by lowering V_T values during the PEEP titration.

Effect of Overdistension on Oxygenation

The negative correlation between overdistension and Pa_{O_2}/FI_{O_2} was surprising and possibly unique to COVID-19 pathophysiology including endothelial vascular damage with lung perfusion impairments. In most previous ARDS studies, oxygenation was determined mainly by the amount of collapsed tissue, directly responsible for shunt production (44, 45). Unlike classical ARDS, lung regions in patients with COVID-19 ARDS should be less prone to changes in airway pressure on the distribution of regional blood flow. Our observation in COVID-19 ARDS suggests that higher pressures generate diversion of pulmonary perfusion from well-aerated lung areas (suffering compression of intraalveolar capillaries) and transiently direct perfusion to dependent, still collapsed zones of the lung (not suffering from capillary compression), thereby increasing shunt fraction (46). This inverse correlation highlights the danger of using PEEP/$F_{I_{O_2}}$ tables: Any increase in PEEP may lead to lower oxygenation, triggering a vicious circle of new increases in PEEP and further overdistension.

Strengths and Limitations

The strengths of this physiological study are the multicenter prospective design with protocolized PEEP steps performed in a large cohort and during different waves of the COVID-19 pandemic and the description of a possible compromise between recruitment and distension selected individually. The multicenter nature of the study was an important aspect of assessing generalizability and feasibility of performing PEEP titration maneuvers. To date, this is the largest study in COVID-19 ARDS that presents a comprehensive EIT analysis and physiological assessment over a wide range of PEEP levels that were well tolerated by all patients. Although we performed all analyses offline for research purposes, information on the tidal ventilation distribution and collapse and overdistension at all PEEP steps, including the crossing point PEEP, is directly available at the bedside (within 1 min once the PEEP trial has been finished for Dräger and Timpel devices). This confirms the feasibility of performing EIT assessment during a decremental PEEP trial at the bedside as well as its potential to integrate information directly into the clinical workflow. Of note, the crossing point method can also be performed clinically with a decremental PEEP trial starting at lower pressures (our fixed PEEP steps allowed between-patient comparisons). Comparisons with non–COVID-19 ARDS and analysis of all study endpoints (NCT04460859) will be performed after completing enrollment of the ongoing main study.

Limitations of EIT include the risk of measuring changes in blood volume that could affect the computation of pixel compliance and hence the results of recruitability. These effects were minimized by avoiding fluid loading and induced diuresis during the study. Second, measurements were performed with the patient in supine position on a single day early during the first week of ARDS diagnosis. It could differ in prone position and later stages of the disease. Third, measurements of lung perfusion were not part of the protocol. This would have been of interest because of the $\dot{V}/\dot{Q}$ mismatch reported in patients with COVID-19 (15–17); however, this also would have added to the complexity of the protocol. Fourth, PEEP-related displacement of the diaphragm and heart relative to the location of EIT electrodes might be misinterpreted as changes in recruitment, but this is inherent to the EIT technique of measuring in only one horizontal plane. We minimized this risk by placing the belt systematically within the fourth to fifth intercostal space (below the armpits). The limitation is that it does not cover the whole lung. Fifth, different EIT devices were used according to the availability within each center. Although different image reconstruction algorithms exist, the method for quantification of collapse and overdistension is the same and corresponds to its first description (18), and analysis methods were made as consistent as possible to contribute to the generalizability of findings. Last, we cannot comment on the impact on outcome. Clinicians could see the results of the EIT examination for the decremental PEEP trial, but there was no recommendation for setting the clinical PEEP, and it is yet uncertain if the crossing point method provides the optimal PEEP setting. In the absence of precise knowledge about the relative importance of recruiting the lung versus generating overdistension, this is a method offering a reasonable compromise. No difference was observed for clinical outcomes among the three recruitability groups, in contrast with previous description (1). It is difficult to know if this could be explained by a titration of PEEP adjusted to the results of the trial or to specific features of COVID-19.

Conclusions

Recruitability varies widely among patients with COVID-19. EIT is feasible for assessing recruitability and to support setting a personalized PEEP according to the best compromise between distension and recruitment. The impact of this approach on clinical outcomes must be studied. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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