Lung RecruitmEnt assessed by eleCtRical Impedance Tomography (RECRUIT): a multicenter study of COVID-19 ARDS

Running title: *Lung recruitability in COVID-19 ARDS*

Annemijn H. Jonkman[1,2,3*], Glasiele C. Alcala[4*], Bertrand Pavlovsky[5,6], Oriol Roca[7,8], Savino Spadaro[9,10], Gaetano Scaramuzzo[9,10], Lu Chen[1,2], Jose Dianti[2,11], Mayson L. de A. Sousa[1,2,4], Michael C. Sklar[1,2], Thomas Piraino[1,2], Huiqing Ge[12], Guang-Qiang Chen[13], Jian-Xin Zhou[13], Jie Li[14], Ewan C. Goligher[2,11,15], Eduardo Costa[4], Jordi Mancebo[16†], Tommaso Mauri[17#], Marcelo Amato[4#] & Laurent J. Brochard[1,2#+] for the Pleural Pressure Working Group (PLUG)

List of Collaborators:
Tobias Becher, Giacomo Bellani, Francois Beloncle, Gilda Cinnella, Carla Fornari, Inéz Frerichs, Claude Guerin, Ahmed Mady, Fabiana Madotto, Alain Mercat, Ibrahim Nagwa, Stefano Nava, Paolo Navalesi, Elena Spinelli, Daniel Talmor

[*] *Co-first authors,* [#] *Co-senior authors*

[†] Deceased on August 6, 2022

[+] Deputy Editor of the AJRCCM (participation complies with American Thoracic Society requirements for recusal from review and decisions for authored work)

Author affiliations:

1. Keenan Research Centre, Li Ka Shing Knowledge Institute, St. Michael’s Hospital, Unity Health Toronto, Toronto, Canada
2. Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada
3. Department of Intensive Care Medicine, Erasmus Medical Center, Rotterdam, the Netherlands
4. Pulmonology Division, Cardiopulmonary Department, Heart Institute, University of Sao Paulo, São Paulo, Brazil.
5. Department of Anesthesia, Critical Care and Emergency, Institute for Treatment and Research, Ca' Granda Maggiore Policlinico Hospital Foundation, Milan, Italy.
6. University Hospital of Angers, Angers, France
7. Parc Taulí Hospital Universitari, Institut de Investigació i Innovació Parc Taulí (I3PT), Sabadell, Spain.
8. Ciber Enfermedades Respiratorias (CIBERES), Health Institute Carlos III, Madrid, Spain.
9. Anesthesia and Intensive Care Medicine, Azienda Ospedaliero Universitaria Di Ferrara, Ferrara, Italy.
10. Department of Translational Medicine, University of Ferrara, Ferrara, Italy.
11. Division of Respirology, Department of Medicine, University Health Network, Toronto, Canada.

AJRCCM Articles in Press. Published April 25, 2023 as 10.1164/rccm.202212-2300OC

12. Department of Respiratory and Critical Care Medicine, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang Province, People's Republic of China.
13. Department of Critical Care Medicine, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
14. Department of Cardiopulmonary Sciences, Division of Respiratory Care, Rush University, Chicago, IL, USA.
15. Toronto General Hospital Research Institute, Toronto, Ontario, Canada
16. Intensive Care Department, Hospital Universitari de La Santa Creu I Sant Pau, Barcelona
17. Department of Anesthesia, Intensive Care and Emergency, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Correspondence to: Laurent J. Brochard, M.D., Li Ka Shing Knowledge Institute, 209 Victoria Street, Room 4-08, Toronto, ON, M5B 1T8 Canada.
E-mail: Laurent.brochard@unityhealth.to

Author contributions: Concept: JM, TM, MA, LB for the PLUG (writing committee) and DT, EG, SN, CG, GB, GC, IF, TB, JXZ, TP, AM (scientific committee) and FM, CF (statistical advisors); Design: AJ, GA, EG, TM, MA, LB; Data acquisition: AJ, GA, BP, OR, SS, GS, LC, JD, MLAS, MS, TP, EG, TM, MA, LB; Data analysis: AJ, GA, BP, GS, TM, MA, LB; Data interpretation: AJ, GA, JM, TM, MA, LB; Manuscript drafting: AJ, GA, TM, MA, LB; Manuscript revising for intellectual content and final approval: all authors and contributors.

Funding: Supported in part by Timpel (Sao Paulo, Brazil) and Drager Medical GmbH (Lubeck, Germany). Funders played no role in the design and conduct of the study; interpretation of the data; preparation, review, or approval of the manuscript; nor in the decision to submit the manuscript for publication. The opinions, results and conclusions reported in this paper are those of the authors.

Key words: acute respiratory distress syndrome, lung recruitability, positive end-expiratory pressure, electrical impedance tomography, mechanical ventilation

Word count: 4987

At a Glance Commentary

Current 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) vs. 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 COVID-19 patients with moderate-severe ARDS (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 differentiate patients with different responses to PEEP and support setting a personalized PEEP according to a compromise between distension and recruitment.

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

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 COVID-19 patients , from an ongoing multicenter prospective physiological study including patients with moderate-severe ARDS 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 cmH_2O ($=\Delta Collapse_{24-6}$). Patients were classified as low, medium or high recruiters based on the tertiles of $\Delta Collapse_{24-6}$.

Measurements and Main Results. In 108 COVID-19 patients, recruitability varied from 0.3% to 66.9% and was unrelated to ARDS severity. EIT-based PEEP differed between groups: 10 vs. 13.5 vs. 15.5 cmH_2O for low vs. medium vs. high recruitability ($p<0.05$). This approach assigned a different PEEP level than the highest compliance approach in 81% of patients. The protocol was well tolerated; in 4 patients the PEEP level did not reach 24 cmH_2O due to hemodynamic instability.

AJRCCM Articles in Press. Published April 25, 2023 as 10.1164/rccm.202212-2300OC

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

Word count: 255

INTRODUCTION

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 vs. 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 surrogate but has multiple limitations and often continues to increase with higher PEEP despite overdistension and negative hemodynamic impact[1, 3]. PEEP/FiO_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 vs. lower PEEP failed to show improved survival of patients with the 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/closing of alveoli and airways, limiting cyclic stretch, atelectrauma and risks of atelectasis, and could relieve hypoxemia[1, 10]. Conversely, in non- 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.

AJRCCM Articles in Press. Published April 25, 2023 as 10.1164/rccm.202212-2300OC

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 non-invasive, radiation-free lung imaging tool that can continuously and in real-time visualize the ventilation distribution and lung volume changes owing to adaptations in ventilator settings or to clinical evolution[12]. In contrast to static anatomical 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 ratio (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 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 study, NCT04460859). The clinical study is still ongoing in non-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 COVID-19 patients 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 prior to enrolment. The selection of centers was based on their previous use and knowledge of the EIT technique and all agreed that EIT measurements during PEEP titration maneuvers could be included in their current practice but in the form of a formalized protocol.

Patients

Intubated COVID-19 patients admitted to the ICU were enrolled within the first week of ARDS diagnosis. Inclusion criteria were: (1) age >18 years; (2) moderate-severe ARDS (PaO_2/FiO_2 <200mmHg)[19]; (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/wounds limiting electrode placement); (4) hemodynamic instability (i.e., systolic blood pressure (SBP) <75mmHg or mean arterial pressure (MAP) <60mmHg despite vasopressor use and/or heart rate <55min^{-1}); (5) attending physician considering the transient application of high pressures to be unsafe.

Data collection

At enrollment, we collected sex, age, body mass index (BMI), Sequential Organ Failure Assessment score, Simplified Acute Physiology Score II, and ARDS severity (PaO_2/FiO_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 4th-5th intercostal space and using the EIT device present at each institution (Enlight 1800 and 2100, Timpel, Sao Paulo, Brazil; PulmoVista 500, Draeger Medical GmbH, Lubeck, Germany; Swisstom BB2 device, Swisstom, Lanquart, Switzerland). 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 (RASS ≤-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 mattresses movements, fluid boluses and excessive diuresis were avoided to limit EIT signal interference. Hemodynamic stability (MAP >70mmHg) was ensured; volume status was adapted if necessary as per a tidal volume challenge[20]. Clinical ventilation settings were recorded for 10 minutes after which respiratory mechanics (plateau pressure, total PEEP), hemodynamics (SpO_2, systolic and mean arterial pressures (SBP, MAP), heart rate), and arterial blood gases (ABG) were obtained. Throughout the protocol, respiratory rate was set to aim for similar minute ventilation as at baseline and to minimize auto-PEEP, and FiO_2 was kept constant.

- *Step 1* was a relatively simple incremental PEEP step allowing measurement of ABG. In volume-controlled ventilation (VCV) with a tidal volume 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) cmH_2O. At PEEP 6 cmH_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 cmH_2O to measure R/I ratio[13].
- *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 cmH_2O, PEEP was progressively increased, to ensure and test the patient's tolerance, up to 24 cmH_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 cmH_2O (a classical recruitment pressure used is around 40 cmH_2O; importantly, this level was much lower than in the ART trial where clinical tolerance was an important concern[23]). Then, ventilator mode was switched

to VCV with the tidal volume lowered to 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 cmH_2O in steps of 2 cmH_2O with a duration of at least 10 breaths or 30 seconds at each step. Experimental and clinical data from the laboratory of Pr. Marcelo Amato showed that this time is sufficient for a reasonably accurate estimate of the change in compliance because the occurrence airway closure is very fast (Doctorate Thesis available on demand). If a PEEP of 24 cmH_2O was not tolerated, we allowed to do the decremental PEEP trial 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[24–26]; Draeger: PV500 Data Analysis SW130; Swisstom: Ibex V6 (Sentec, Switzerland) and Matlab R2020b (MathWorks, USA)); computations were made as consistent as possible for different EIT devices. Since 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 percent loss of pixel compliance over the range of applied PEEP from 24 (or lower if not tolerated) to 6 cmH_2O. This computation means that (1) any remaining collapse at PEEP 24 cmH_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 cmH_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.

Lastly, 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 cmH_2O at the start of the protocol to PEEP 24 cmH_2O (or to the highest tolerated PEEP); we refer to this parameter as $\Delta Collapse_{24\text{-}6}$. Note that 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 $\Delta Collapse_{24\text{-}6}$.

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 in 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 non-

AJRCCM Articles in Press. Published April 25, 2023 as 10.1164/rccm.202212-2300OC

dependent/dependent tidal ventilation distribution ratio closest to 1 (indicating most homogeneous ventilation)[27].

Regional distribution

We hypothesized that collapse would be primarily present in the posterior dependent lung regions and overdistension in the anterior non-dependent 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 separated for both regions. In addition, we computed the regional distribution of tidal ventilation separated for the dependent and non-dependent regions, as well as for the left and right lung.

R/I ratio, respiratory mechanics, hemodynamics, and gas exchange

R/I ratio was calculated during the single-breath maneuver (PEEP 16 to 6 cmH_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 cmH_2O, and tidal impedance at PEEP 6 cmH_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 PaO_2/FiO_2 and ventilatory ratio[28].

Sample size

In the original main study proposal, which was supposed to enroll patients with ARDS from multiple causes, the planned sample size is 171 patients. This report includes all COVID-19

ARDS patients enrolled. The decision to perform this interim analysis was triggered by the significant drop in the number of intubated mechanically ventilated COVID-19 patients and the much slower enrolment of non-COVID-19 ARDS patients.

Statistical analysis

Descriptive data are presented as mean ± standard deviation or median [interquartile range] according to the normality of data checked through 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 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 following 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 COVID-19 patients were enrolled (May 2020-December 2021). The protocol was well tolerated; infour patients the PEEP level of 24 cmH_2O was not reached due to hemodynamic instability (see safety criteria Figure 1); their highest tolerated PEEP ranged from

AJRCCM Articles in Press. Published April 25, 2023 as 10.1164/rccm.202212-2300OC

16 to 20 cmH_2O and by design the protocol allowed to start the decremental PEEP trial from this lower than maximal pressure. The protocol was not aborted in any patient.

Recruitability across patients and characteristics of groups

Recruitability distribution ($\Delta Collapse_{24\text{-}6}$) varied from 0.3% to 66.9% and is displayed in Figure 2. Three equal-size groups were defined as low recruiters having a $\Delta Collapse_{24\text{-}6}$ <25.3%, moderate recruiters between 25.4–39.6%, and high recruiters >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 cmH_2O PEEP was present in 45 (41%) patients (per group: n=11, 16, 18 patients with low, medium, and high recruitability, respectively); their AOP was low (7 [7; 7] cmH_2O; only 1 patient presented AOP >10 cmH_2O) and did not differ between groups (p=0.528). R/I ratio correlated moderately with $\Delta Collapse_{24\text{-}6}$ (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: 10 [7.5; 13.5] vs. 13.5 [12; 15] vs. 15.5 [13.8; 17] cmH_2O for patients with low, medium, and high recruitability, respectively (p<0.001). For patients with airway closure, this optimal PEEP level was 7 [4; 8] cmH_2O above AOP; only one patient presented an AOP of 1

AJRCCM Articles in Press. Published April 25, 2023 as 10.1164/rccm.202212-2300OC

cmH_2O above the crossing point PEEP. At the crossing point, collapse, overdistension and respiratory mechanics were similar between groups. There was a trend towards 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 mainly present in the dependent lung, while overdistension primarily occurred in the non-dependent 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 compared to the PEEP with the highest compliance ($p<0.05$), while 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 – 6) cmH_2O).

For n=24 patients the crossing point PEEP was in between two fixed PEEP steps. Because this would by design influence the comparison with the PEEP associated with the highest compliance (which was only calculated 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 in between two fixed PEEP steps. This did not change the overall correlation between the crossing point PEEP vs. optimal compliance PEEP (R^2 of 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 cmH_2O, range: 4, -6 cmH_2O), whereas no overall difference was found between both approaches when taking the lower fixed PEEP step (median difference: 0 cmH_2O, range: 4, -6 cmH_2O). In only 31/108 (29%) and 41/108 (38%) both methods assigned the same PEEP level when taking the higher or lower fixed PEEP step, respectively.

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

Regional distribution of ventilation

Figure 6 shows the ventilation distribution for the dependent and non-dependent lung during the decremental PEEP trial. PEEP level associated with a non-dependent/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). Distribution of ventilation separated for the left and right lung is demonstrated in Supplemental Figure E2.

Incremental PEEP steps

There were only three incremental PEEP steps and respiratory mechanics, hemodynamics, and gas exchange at these 5-min incremental PEEP steps of 6, 16 and 24 cmH_2O are shown in Table 3 and Figure 7. At these steps, the effect of PEEP on collapse and overdistension varied significantly between groups (Supplemental Figure E3). Driving pressure increased from PEEP 6 to 16 cmH_2O in low and medium recruitability groups but not in high recruiters (Table 3).

PaO_2/FiO_2 and PaO_2 increased in all groups with higher PEEP, as well as $PaCO_2$ (Figure 7). Multiple linear models revealed that changes (improvements) in oxygenation at incremental PEEP steps of 6, 16 and 24 cmH_2O were mainly driven by progressively lower levels of collapse ($p<0.001$), whereas higher levels of $PaCO_2$ observed at higher PEEP were mainly driven by higher levels of overdistension (without any correlation with lung collapse). In the particular condition of 24 cmH_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 COVID-19 patients with moderate-severe ARDS are: (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 homogenous ventilation approach for the majority of patients; and (5) EIT allows to differentiate patients with different responses to PEEP including regional information (dependent and non-dependent lung) which 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 on EIT as the amount of collapse that can be reopened by higher PEEP, by comparing the collapse reduction from the lowest (6 cmH_2O) to the highest (24 cmH_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 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 cmH_2O or lower if not tolerated). Quantification of collapse 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 et al. in ‘classical ARDS’ using CT scan[1], recruitability varied widely in our COVID-19 ARDS cohort as well, in line with studies earlier during the pandemic using EIT and/or R/I ratio in small cohorts[15, 29–32] or using respiratory parameters[33]. Recruitability was also higher than reported recently by Protti et al.[32] using CT scan and with recruitability estimated in relation to the lung mass at low PEEP, similar to Gattinoni et al.[1] (for comparison, see Supplemental Figure E4). Differences with Protti et al.[32] may be related to a different definition of recruitability, a more extensive maneuver (5-min PEEP

24 cmH_2O with Pplat ~40 cmH_2O (Figure 1) vs. CPAP 45 cmH_2O for 10-15 seconds[32]) 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[34, 35].

EIT-based PEEP selection: crossing point method

The large variability in recruitability and PEEP crossing point strengthens the need for an individualized PEEP setting. While 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 post a decremental PEEP trial is debated. We chose the crossing point method since this approach allows a compromise between minimizing both alveolar collapse and overdistension. This approach, initially proposed by Costa et al. in two patients[18], can be applied directly at the bedside and has been described in few studies[29, 34, 36]. However, it assumes that both overdistension and collapse are equally harmful[37]. 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 to titrate 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 a

AJRCCM Articles in Press. Published April 25, 2023 as 10.1164/rccm.202212-2300OC

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[24] (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[38]. This concept is in line with the idea to keep the recruitable lung open without applying excessive pressures. Whether this improves clinical outcomes, however, should be evaluated prospectively.

Comparison with the highest compliance

Individualized PEEP setting using the highest respiratory system compliance during a PEEP trial has been proposed and looks attractive since it can also yield the lowest driving pressure[39]. 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 due to the impact of intra-tidal recruitment and opening vs. closing pressures. Furthermore, the overall compliance can poorly reflect the regional mechanics in different parts of the lungs[40]. 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 severe ARDS patients treated with extracorporeal membrane oxygenation[36]. The relationship between recruitment and compliance is impacted by regional differences between dependent and non-dependent lungs[40] and by intra-tidal recruitment, which makes this relationship more complex than often considered[13, 41, 42]. 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) distention is excessive, thereby avoiding 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 cmH_2O can create a large amount of overdistension (up to 80%, Supplemental 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 non-dependent lung[40]. Furthermore, the assessment of recruitability by EIT helps to identify those patients in which 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 cmH_2O) for higher recruitable patients (Table 2). In contrast, a fixed increment in PEEP from 6 to 16 cmH_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 tidal volumes during the PEEP titration.

Effect of overdistension on oxygenation

The negative correlation between overdistension and PaO_2/FiO_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 mainly determined by the amount of collapsed tissue, directly responsible for shunt production[43, 44]. Unlike classical ARDS, lung regions in COVID-19 ARDS patients 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 intra-alveolar capillaries), and transiently direct perfusion to dependent, still collapsed zones of the lung (not suffering from capillary compression), thereby increasing shunt fraction[45]. This inverse correlation highlights the danger of using PEEP/FiO$_2$ 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 pandemic, and describing a possible compromise between recruitment and distension selected individually. The multicenter nature of the study was an important part for assessing generalizability and feasibility of performing PEEP titrations 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 was well tolerated by all patients. While 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 one minute once the PEEP trial has been finished; for Drager 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 for between-patient comparisons). Comparisons with non-COVID-19 ARDS and analysis of all study endpoints (NCT04460859) will be performed after completing enrolment 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 results of recruitability. These effects were minimized by avoiding fluid loading and induced diuresis during the study. Second, measurements were performed 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 ventilation/perfusion mismatch reported in COVID-19 patients[15–17], however this would have also 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 4th-5th 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, at 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.

Conclusion

Recruitability varies widely among COVID-19 patients. 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 has to be studied.

AJRCCM Articles in Press. Published April 25, 2023 as 10.1164/rccm.202212-2300OC

Table 1. Patient characteristics

	Total population (n=108)	Low recruitability (n=36)	Medium recruitability (n=36)	High recruitability (n=36)	p-value
Gender, 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]	$32.9^{*\#}$ [27.2; 39.4]	**0.0134**
Age, years	61 [51; 68]	65 [57.6; 70]	61 [54; 65]	55* [46; 63.5]	**0.0051**
PaO_2/FiO_2 ratio at ICU admission, mmHg	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 at study enrolment	6 [4; 8]	7 [4; 8]	5 [4; 8]	5 [4; 8]	0.5678
Days ventilated before study, days	2 [1; 3]	2 [1; 3]	1 [1; 2]	2 [1; 4]	0.1299
Total ventilation duration, days	15 [9; 24.8]	17 [12; 31]	13 [7; 23]	13 [8.5; 24.3]	0.1112
ICU length-of-stay, days	23 [12; 38]	29 [16; 39]	20 [12; 33]	15.5 [10; 36.5]	0.0878
ICU mortality[1], %	39% (n=38/98)	45% (n=15/33)	36% (n=12/33)	33% (n=11/32)	0.2167
VFD day 28, days	5 [0; 18]	0 [0; 13]	11 [0; 20]	11 [0; 17.3]	0.1410
Respiratory mechanics at study baseline (clinical settings)					
Total PEEP, cmH_2O	11 [10; 14]	11 [10; 14]	11 [10; 14]	11 [10; 13.8]	0.5604
Driving pressure, cmH_2O[2]	13 [11; 16]	15 [12; 18]	14 [11.5; 16]	12* [11; 13.8]	**0.0196**
Crs, mL/cmH_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, $cmH_2O/(mL/kgPBW)$	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**
PaO_2/FiO_2 ratio, mmHg	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					
$\Delta Collapse_{24-6}$, %	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**

---

*$p<0.05$ 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. [1]Follow-up data on ICU mortality and clinical outcomes missing for some patients (e.g., due to transfer), mortality percentages are based on the number of known outcomes; [2]Driving pressure as measured via short inspiratory and expiratory occlusions. Abbreviations: Crs, respiratory system compliance; BMI, body mass index; EIT, electrical impedance tomography; FiO_2, fraction inspired oxygen; ICU, intensive care unit; PaO_2, arterial oxygen partial pressure; PEEP, positive end-expiratory pressure; PBW, predicted body weight; R/I, recruitment-to-inflation; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment score; VFD, ventilator-free days.

AJRCCM Articles in Press. Published April 25, 2023 as 10.1164/rccm.202212-2300OC

Table 2. Mechanics during the decremental PEEP trial and at the crossing point

	Low recruitability	Medium recruitability	High recruitability	**p-value**
Crossing point PEEP level (cmH_2O)	10 [7.5; 13.5]	13.5* [12; 15]	15.5*# [13.8; 17]	**<0.001**
PEEP level with highest Crs (cmH_2O)	9 [6; 12]	12* [10; 14]	16*# [12; 18]	**<0.001**
PEEP level with most homogenous ventilation distribution (cmH_2O)	18 [13.8; 22]	16 [13.5; 22]	16 [11.8; 20.5]	0.615
Mechanics at the crossing point PEEP				
Crs, mL/cmH_2O	29.2 [24.4; 38.4]	37.4 [28.2; 46.6]	35.6 [30.8; 39.5]	0.054
ΔPaw, cmH_2O^1	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, $cmH_2O/(mL/kgPBW)$	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 (end PEEP trial)	-0.4 [0.0; -0.9]	-1.4* [-0.7; -2.5]	-2.7*# [-1.7; -4.0]	**<0.001**
RR during PEEP trial, /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**

*$p<0.05$ 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. [1] Driving pressure while tidal volume 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 tidal volume at PEEP 24 cmH_2O. Compliance at each step was obtained using the Pplat at a 0.2 or 0.3 short inspiratory pause that was set, or based on a linear regression model to estimate Pplat. Abbreviations: Crs, respiratory system compliance; ΔPaw, airway driving pressure; PEEP, positive end-expiratory pressure; PBW, predicted body weight; RR, respiratory rate; Vt, tidal volume.

AJRCCM Articles in Press. Published April 25, 2023 as 10.1164/rccm.202212-2300OC

Table 3. Mechanics, hemodynamics and gas exchange during incremental 5-minute PEEP steps

	Low recruitability			**Medium recruitability**			**High recruitability**			
	PEEP 6	**PEEP 16**	**PEEP 24**	**PEEP 6**	**PEEP 16**	**PEEP 24**	**PEEP 6**	**PEEP 16**	**PEEP 24**	**p-value PEEP x group interaction**
Crs, mL/cmH$_2$O	**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, cmH$_2$O	**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, min^{-1}	**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, mmHg	**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, mmHg	**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
PaO$_2$, mmHg	**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**

AJRCCM Articles in Press. Published April 25, 2023 as 10.1164/rccm.202212-2300OC

Figure legends

Figure 1. Study protocol with applied PEEP steps. For further details, see Methods. Ventilator mode is mentioned below the x-axis. Continuous monitoring of EIT 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 sec 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. Recruitment-to-inflation (R/I) ratio was assessed during a single-breath maneuver when decreasing PEEP from 16 to 6 cmH_2O (Step 1). In Step 2, before applying the decremental PEEP trial, PEEP was increased from 6 to 24 cmH_2O (or lower if not tolerated) in small steps (10 – 15 – 20 – 24 cmH_2O) of 1-2 minutes to test the patient's tolerance; this was done in PCV mode with a driving pressure (ΔP) of 15 cmH_2O, an I:E ratio of 1:1, yielding a maximum peak airway pressure of 39 cmH_2O that was allowed. At PEEP 24 in volume-controlled ventilation mode with a tidal volume lowered to 5 mL/kg PBW to minimize tidal recruitment effects, a maximum plateau pressure of 40 cmH_2O was accepted (tidal volumes 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 mmHg for systolic blood pressure) or SpO_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 mmHg) or sustained hypoxemia (SpO_2 <85% for at least one minute).

Figure 2. Distribution of recruitability as defined by the decrease in the collapse on EIT when increasing PEEP from 6 cmH_2O (Step 1 of protocol) to 24 cmH_2O (= $\Delta Collapse_{24\text{-}6}$). Groups of low, medium and high recruitability were made using the tertiles of $\Delta Collapse_{24\text{-}6}$: low (<25.3%), medium (25.4–39.6%) and high (>39.6%.) recruitability.

Figure 3. Distribution of collapse (blue) and overdistension (orange) during the decremental PEEP trial for the three groups of recruitability. The dotted lines indicate the group median

[interquartile range] PEEP level as per the crossing point of the collapse and overdistension curves.

Figure 4. Regional distribution of collapse (left) and overdistension (right) for the anterior (upper graphs) and posterior (lower graphs) lung and separated for the three recruitability groups. Collapse was mainly present in the dependent lung and highest for the higher recruitable patients (per our definition). Overdistension primarily occurred in the non-dependent lung with highest values found for lower recruitable patients and already at low PEEP levels.

Figure 5. Comparison of the optimal 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. Individual comparison as well as the median with interquartile range is provided.

Figure 6. Distribution of tidal ventilation for the posterior dependent (orange) and anterior non-dependent (blue) lung, as obtained during the decremental PEEP trial and separated for the three recruitability groups. The PEEP level associated with a non-dependent/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.

Figure 7. Mechanics, hemodynamics and gas exchange during incremental 5-minute PEEP steps and separated per recruitability group. A) Oxygen saturation (SpO_2) at fixed fraction inspired oxygen (FiO_2); B) arterial oxygen partial pressure (PaO_2) to FiO_2 ratio; C) arterial carbon dioxide partial pressure ($PaCO_2$); D) Ventilatory ratio. *$p<0.05$ difference from PEEP 6; $^{\#}p<0.05$ difference from PEEP 16. 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: SpO_2, $p<0.001$; PaO_2/FiO_2, $p<0.001$; $PaCO_2$, $p<0.001$; ventilator ratio, $p=0.425$.

References

1. Gattinoni L, Caironi P, Cressoni M, et al (2006) Lung Recruitment in Patients with the Acute Respiratory Distress Syndrome. New England Journal of Medicine 12

2. Jonkman AH, Ranieri VM, Brochard L (2022) Lung recruitment. Intensive Care Med 48:936–938. https://doi.org/10.1007/s00134-022-06715-z

3. Chiumello D, Marino A, Brioni M, et al (2016) Lung Recruitment Assessed by Respiratory Mechanics and Computed Tomography in Patients with Acute Respiratory Distress Syndrome. What Is the Relationship? Am J Respir Crit Care Med 193:1254–1263. https://doi.org/10.1164/rccm.201507-1413OC

4. Grasso S, Stripoli T, De Michele M, et al (2007) ARDSnet Ventilatory Protocol and Alveolar Hyperinflation: Role of Positive End-Expiratory Pressure. Am J Respir Crit Care Med 176:761–767. https://doi.org/10.1164/rccm.200702-193OC

5. Terragni PP, Rosboch G, Tealdi A, et al (2007) Tidal Hyperinflation during Low Tidal Volume Ventilation in Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 175:160–166. https://doi.org/10.1164/rccm.200607-915OC

6. Chiumello D, Cressoni M, Carlesso E, et al (2014) Bedside Selection of Positive End-Expiratory Pressure in Mild, Moderate, and Severe Acute Respiratory Distress Syndrome*: Critical Care Medicine 42:252–264. https://doi.org/10.1097/CCM.0b013e3182a6384f

7. Walkey AJ, Del Sorbo L, Hodgson CL, et al (2017) Higher PEEP versus Lower PEEP Strategies for Patients with Acute Respiratory Distress Syndrome. A Systematic Review and Meta-Analysis. Annals ATS 14:S297–S303. https://doi.org/10.1513/AnnalsATS.201704-338OT

8. Chen L, Del Sorbo L, Grieco DL, et al (2018) Airway Closure in Acute Respiratory Distress Syndrome: An Underestimated and Misinterpreted Phenomenon. Am J Respir Crit Care Med 197:132–136. https://doi.org/10.1164/rccm.201702-0388LE

9. Caironi P, Cressoni M, Chiumello D, et al (2010) Lung Opening and Closing during Ventilation of Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 181:578–586. https://doi.org/10.1164/rccm.200905-0787OC

10. Hedenstierna G, Chen L, Brochard L (2020) Airway closure, more harmful than atelectasis in intensive care? Intensive Care Med 46:2373–2376. https://doi.org/10.1007/s00134-020-06144-w

11. Slutsky AS, Ranieri VM (2013) Ventilator-Induced Lung Injury. N Engl J Med 369:2126–2136. https://doi.org/10.1056/NEJMra1208707

12. Frerichs I, Amato MBP, van Kaam AH, et al (2017) Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus

statement of the TRanslational EIT developmeNt stuDy group. Thorax 72:83–93. https://doi.org/10.1136/thoraxjnl-2016-208357

13. Chen L, Del Sorbo L, Grieco DL, et al (2020) Potential for Lung Recruitment Estimated by the Recruitment-to-Inflation Ratio in Acute Respiratory Distress Syndrome. A Clinical Trial. Am J Respir Crit Care Med 201:178–187. https://doi.org/10.1164/rccm.201902-0334OC

14. Bouhemad B, Brisson H, Le-Guen M, et al (2011) Bedside Ultrasound Assessment of Positive End-Expiratory Pressure–induced Lung Recruitment. Am J Respir Crit Care Med 183:341–347. https://doi.org/10.1164/rccm.201003-0369OC

15. Mauri T, Spinelli E, Scotti E, et al (2020) Potential for Lung Recruitment and Ventilation-Perfusion Mismatch in Patients With the Acute Respiratory Distress Syndrome From Coronavirus Disease 2019: Critical Care Medicine 1. https://doi.org/10.1097/CCM.0000000000004386

16. Lang M, Som A, Mendoza DP, et al (2020) Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. The Lancet Infectious Diseases 20:1365–1366. https://doi.org/10.1016/S1473-3099(20)30367-4

17. Busana M, Giosa L, Cressoni M, et al (2021) The impact of ventilation–perfusion inequality in COVID-19: a computational model. Journal of Applied Physiology 130:865–876. https://doi.org/10.1152/japplphysiol.00871.2020

18. Costa ELV, Borges JB, Melo A, et al (2009) Bedside estimation of recruitable alveolar collapse and hyperdistension by electrical impedance tomography. Intensive Care Med 35:1132–1137. https://doi.org/10.1007/s00134-009-1447-y

19. The ARDS Definition Task Force (2012) Acute Respiratory Distress Syndrome: The Berlin Definition. JAMA 307:. https://doi.org/10.1001/jama.2012.5669

20. Myatra SN, Monnet X, Teboul J-L (2017) Use of 'tidal volume challenge' to improve the reliability of pulse pressure variation. Crit Care 21:60. https://doi.org/10.1186/s13054-017-1637-x

21. Chen L, Chen G-Q, Shore K, et al (2017) Implementing a bedside assessment of respiratory mechanics in patients with acute respiratory distress syndrome. Crit Care 21:84. https://doi.org/10.1186/s13054-017-1671-8

22. Katira BH, Engelberts D, Otulakowski G, et al (2018) Abrupt Deflation after Sustained Inflation Causes Lung Injury. Am J Respir Crit Care Med 198:1165–1176. https://doi.org/10.1164/rccm.201801-0178OC

23. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators, Cavalcanti AB, Suzumura ÉA, et al (2017) Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients

With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. JAMA 318:1335. https://doi.org/10.1001/jama.2017.14171

24. Fumagalli J, Berra L, Zhang C, et al (2017) Transpulmonary Pressure Describes Lung Morphology During Decremental Positive End-Expiratory Pressure Trials in Obesity*: Critical Care Medicine 45:1374–1381. https://doi.org/10.1097/CCM.0000000000002460

25. Mori ARR (2017) Impacto de duas estratégias de titulação da PEEP em modelo suíno de síndrome do desconforto respiratório agudo: guiada por pressão esofágica versus guiada por tomografia de impedância elétrica. Doutorado Direto em Pneumologia, Universidade de São Paulo

26. Santiago RR de S (2016) Quantificação à beira do leito do potencial de recrutamento alveolar através da tomografia de impedância elétrica em modelo experimental síndrome do desconforto respiratório agudo. Doutorado Direto em Pneumologia, Universidade de São Paulo

27. Mauri T, Bellani G, Confalonieri A, et al (2013) Topographic Distribution of Tidal Ventilation in Acute Respiratory Distress Syndrome: Effects of Positive End-Expiratory Pressure and Pressure Support*. Critical Care Medicine 41:1664–1673. https://doi.org/10.1097/CCM.0b013e318287f6e7

28. Sinha P, Calfee CS, Beitler JR, et al (2019) Physiologic Analysis and Clinical Performance of the Ventilatory Ratio in Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 199:333–341. https://doi.org/10.1164/rccm.201804-0692OC

29. Perier F, Tuffet S, Maraffi T, et al (2020) Electrical impedance tomography to titrate positive end-expiratory pressure in COVID-19 acute respiratory distress syndrome. Crit Care 24:678. https://doi.org/10.1186/s13054-020-03414-3

30. Haudebourg A-F, Perier F, Tuffet S, et al (2020) Respiratory Mechanics of COVID-19– versus Non–COVID-19–associated Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 202:287–290. https://doi.org/10.1164/rccm.202004-1226LE

31. Beloncle FM, Pavlovsky B, Desprez C, et al (2020) Recruitability and effect of PEEP in SARS-Cov-2-associated acute respiratory distress syndrome. Ann Intensive Care 10:55. https://doi.org/10.1186/s13613-020-00675-7

32. Protti A, Santini A, Pennati F, et al (2022) Lung Response to a Higher Positive End-Expiratory Pressure in Mechanically Ventilated Patients With COVID-19. Chest 161:979–988. https://doi.org/10.1016/j.chest.2021.10.012

33. Filippini DFL, Di Gennaro E, van Amstel RBE, et al (2022) Latent class analysis of imaging and clinical respiratory parameters from patients with COVID-19-related ARDS identifies recruitment subphenotypes. Crit Care 26:363. https://doi.org/10.1186/s13054-022-04251-2

34. Somhorst P, van der Zee P, Endeman H, Gommers D (2022) PEEP-FiO2 table versus EIT to titrate PEEP in mechanically ventilated patients with COVID-19-related ARDS. Crit Care 26:272. https://doi.org/10.1186/s13054-022-04135-5

35. Dargvainis M, Ohnesorge H, Schädler D, et al (2022) Recruitable alveolar collapse and overdistension during laparoscopic gynecological surgery and mechanical ventilation: a prospective clinical study. BMC Anesthesiol 22:251. https://doi.org/10.1186/s12871-022-01790-7

36. Franchineau G, Bréchot N, Lebreton G, et al (2017) Bedside Contribution of Electrical Impedance Tomography to Setting Positive End-Expiratory Pressure for Extracorporeal Membrane Oxygenation–treated Patients with Severe Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 196:447–457. https://doi.org/10.1164/rccm.201605-1055OC

37. Gattinoni L, Quintel M, Marini JJ (2018) Volutrauma and atelectrauma: which is worse? Crit Care 22:264, s13054-018-2199–2. https://doi.org/10.1186/s13054-018-2199-2

38. Bastia L, Engelberts D, Osada K, et al (2021) Role of Positive End-Expiratory Pressure and Regional Transpulmonary Pressure in Asymmetrical Lung Injury. Am J Respir Crit Care Med 203:969–976. https://doi.org/10.1164/rccm.202005-1556OC

39. Amato MBP, Meade MO, Slutsky AS, et al (2015) Driving Pressure and Survival in the Acute Respiratory Distress Syndrome. N Engl J Med 372:747–755. https://doi.org/10.1056/NEJMsa1410639

40. Katira BH, Osada K, Engelberts D, et al (2021) Positive End-Expiratory Pressure, Pleural Pressure, and Regional Compliance during Pronation. An Experimental Study. Am J Respir Crit Care Med 203:1266–1274. https://doi.org/10.1164/rccm.202007-2957OC

41. Grasso S, Stripoli T, Sacchi M, et al (2009) Inhomogeneity of Lung Parenchyma during the Open Lung Strategy: A Computed Tomography Scan Study. Am J Respir Crit Care Med 180:415–423. https://doi.org/10.1164/rccm.200901-0156OC

42. Del Sorbo L, Tonetti T, Ranieri VM (2019) Alveolar recruitment in acute respiratory distress syndrome: should we open the lung (no matter what) or may accept (part of) the lung closed? Intensive Care Med 45:1436–1439. https://doi.org/10.1007/s00134-019-05734-7

43. Reske AW, Costa ELV, Reske AP, et al (2013) Bedside Estimation of Nonaerated Lung Tissue Using Blood Gas Analysis*: Critical Care Medicine 41:732–743. https://doi.org/10.1097/CCM.0b013e3182711b6e

44. Borges JB, Okamoto VN, Matos GFJ, et al (2006) Reversibility of Lung Collapse and Hypoxemia in Early Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 174:268–278. https://doi.org/10.1164/rccm.200506-976OC

45. Musch G, Bellani G, Vidal Melo MF, et al (2008) Relation between Shunt, Aeration, and Perfusion in Experimental Acute Lung Injury. Am J Respir Crit Care Med 177:292–300. https://doi.org/10.1164/rccm.200703-484OC

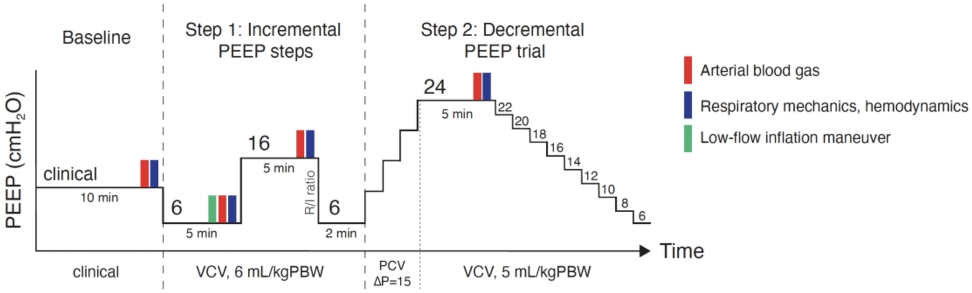

Figure 1. Study protocol with applied PEEP steps. For further details, see Methods. Ventilator mode is mentioned below the x-axis. Continuous monitoring of EIT and airway pressure and/or flow was performed throughout the protocol. Arterial blood gas and measurements of respiratory mechanics (short 0.2 to 0.3 sec 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. Recruitment-to-inflation (R/I) ratio was assessed during a single-breath maneuver when decreasing PEEP from 16 to 6 cmH2O (Step 1). In Step 2, before applying the decremental PEEP trial, PEEP was increased from 6 to 24 cmH2O (or lower if not tolerated) in small steps (10 – 15 – 20 – 24 cmH2O) of 1-2 minutes to test the patient's tolerance; this was done in PCV mode with a driving pressure (ΔP) of 15 cmH2O, an I:E ratio of 1:1, yielding a maximum peak airway pressure of 39 cmH2O that was allowed. At PEEP 24 in volume-controlled ventilation mode with a tidal volume lowered to 5 mL/kg PBW to minimize tidal recruitment effects, a maximum plateau pressure of 40 cmH2O was accepted (tidal volumes 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 mmHg for systolic blood pressure) or SpO2 <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 mmHg) or sustained hypoxemia (SpO2 <85% for at least one minute).

472x147mm (144 x 144 DPI)

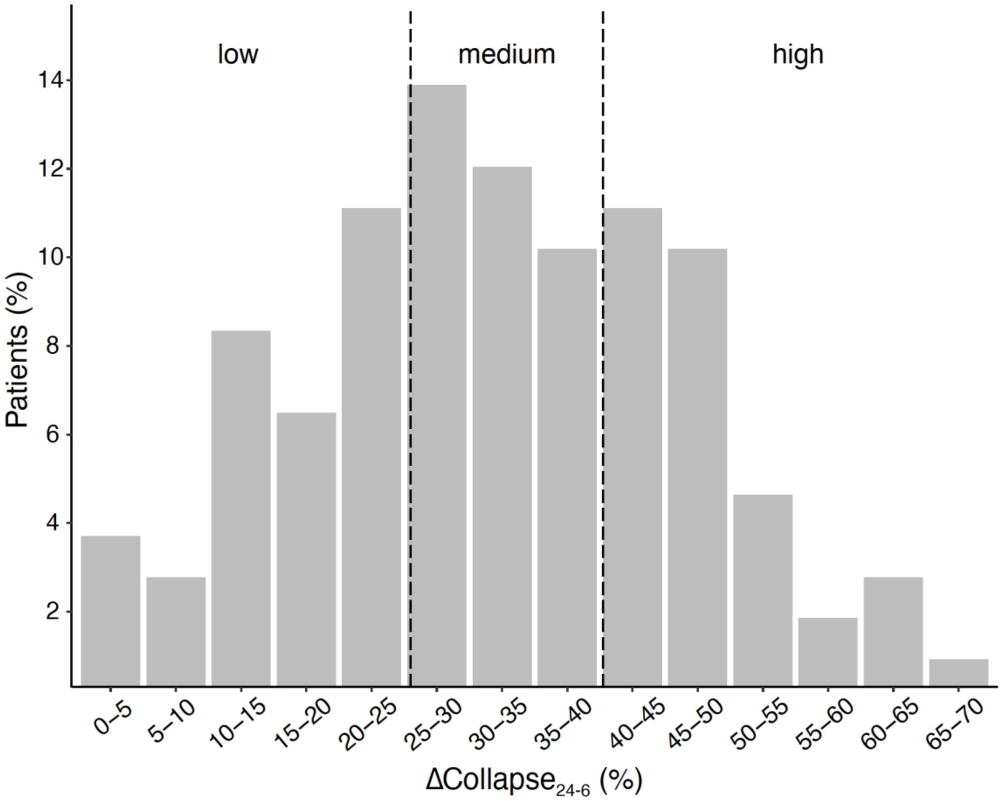

Figure 2. Distribution of recruitability as defined by the decrease in the collapse on EIT when increasing PEEP from 6 cmH2O (Step 1 of protocol) to 24 cmH2O (= ΔCollapse24-6). Groups of low, medium and high recruitability were made using the tertiles of ΔCollapse24-6: low (<25.3%), medium (25.4–39.6%) and high (>39.6%.) recruitability.

312x249mm (144 x 144 DPI)

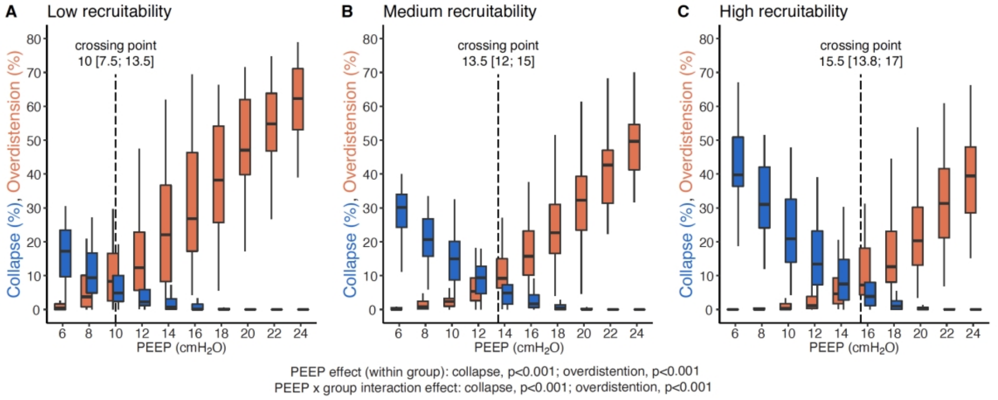

Figure 3. Distribution of collapse (blue) and overdistension (orange) during the decremental PEEP trial for the three groups of recruitability. The dotted lines indicate the group median [interquartile range] PEEP level as per the crossing point of the collapse and overdistension curves.

440x176mm (144 x 144 DPI)

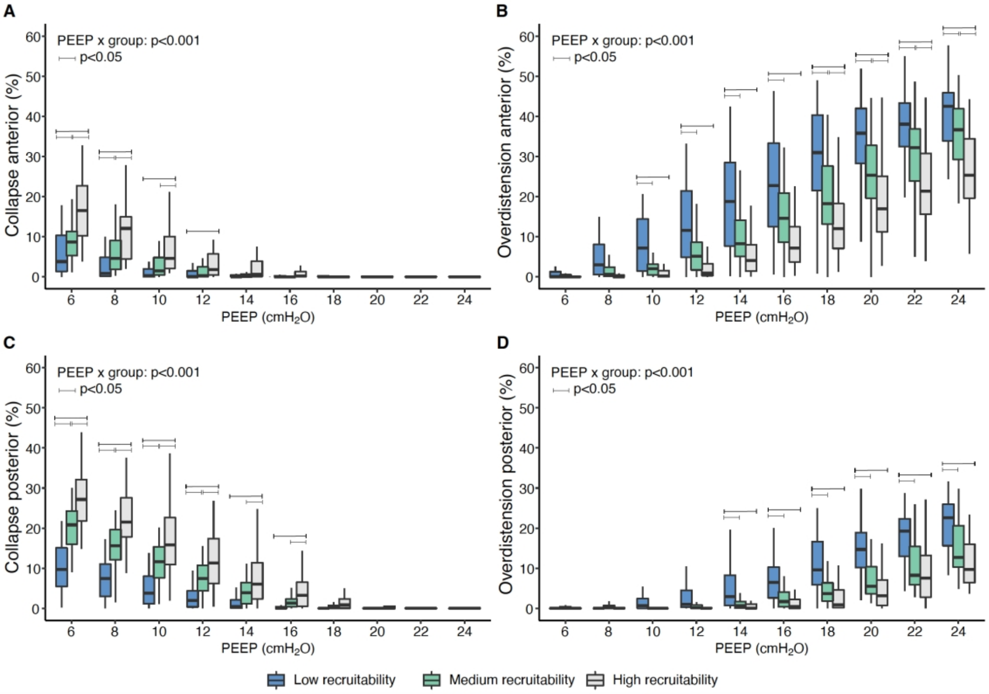

Figure 4. Regional distribution of collapse (left) and overdistension (right) for the anterior (upper graphs) and posterior (lower graphs) lung and separated for the three recruitability groups. Collapse was mainly present in the dependent lung and highest for the higher recruitable patients (per our definition). Overdistension primarily occurred in the non-dependent lung with highest values found for lower recruitable patients and already at low PEEP levels.

409x285mm (144 x 144 DPI)

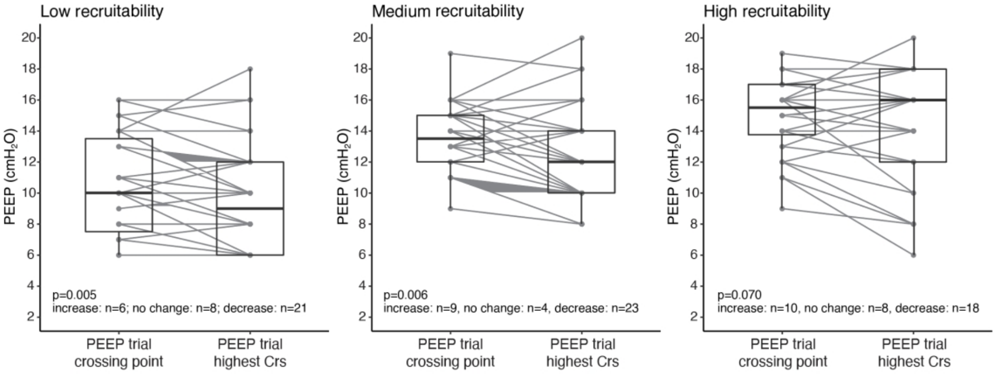

Figure 5. Comparison of the optimal PEEP according to the crossing point of the collapse and overdistension curves (PEEP trial crossing point) and the PEEP level with the highest respiratory system compliance (PEEP trial highest Crs) obtained during the decremental PEEP trial. Individual comparison as well as the median with interquartile range is provided.

385x147mm (144 x 144 DPI)

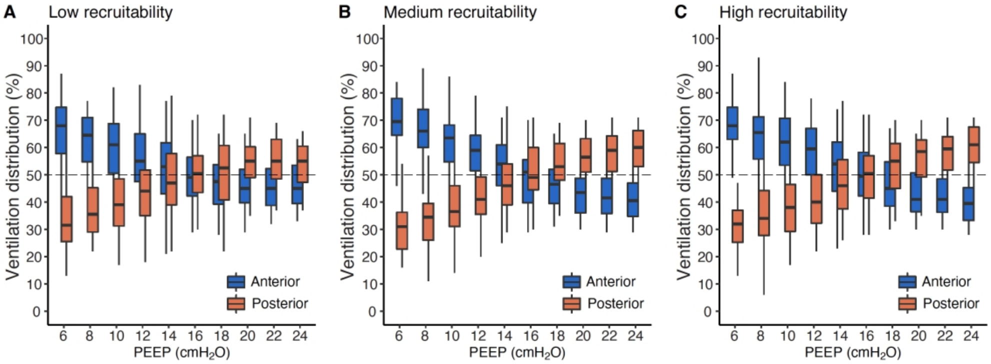

Figure 6. Distribution of tidal ventilation for the posterior dependent (orange) and anterior non-dependent (blue) lung, as obtained during the decremental PEEP trial and separated for the three recruitability groups. The PEEP level associated with a non-dependent/dependent tidal ventilation ratio closest 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.

489x180mm (144 x 144 DPI)

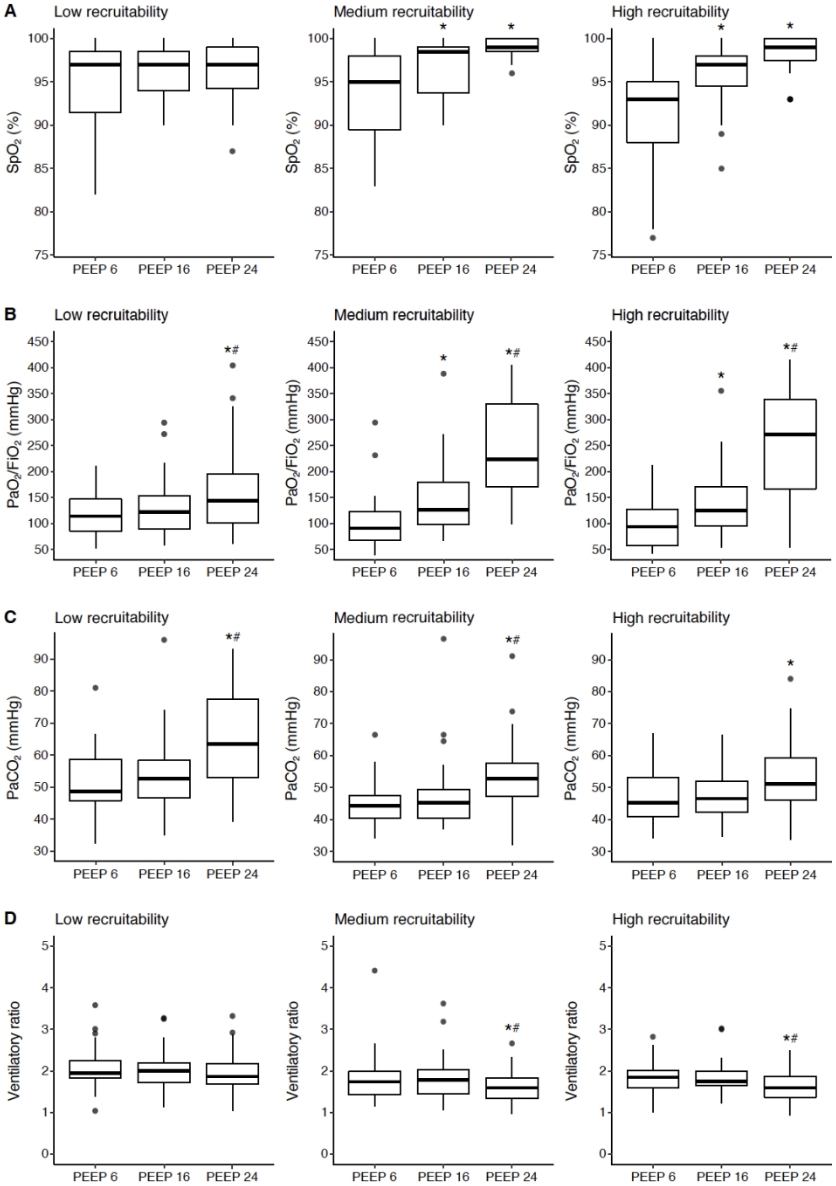

Figure 7. Mechanics, hemodynamics and gas exchange during incremental 5-minute PEEP steps and separated per recruitability group. A) Oxygen saturation (SpO2) at fixed fraction inspired oxygen (FiO2); B) arterial oxygen partial pressure (PaO2) to FiO2 ratio; C) arterial carbon dioxide partial pressure (PaCO2); D) Ventilatory ratio. *p<0.05 difference from PEEP 6; #p<0.05 difference from PEEP 16. 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: SpO2, p<0.001; PaO2/FiO2, p<0.001; PaCO2, p<0.001; ventilator ratio, p=0.425.

197x281mm (144 x 144 DPI)

Lung RecruitmEnt Assessed by eleCtRical Impedance Tomography (RECRUIT): a multicenter study of COVID-19 ARDS

Annemijn H. Jonkman, Glasiele C. Alcala, Bertrand Pavlovsky, Oriol Roca, Savino Spadaro, Gaetano Scaramuzzo, Lu Chen, Jose Dianti, Mayson L. de A. Sousa, Michael C. Sklar, Thomas Piraino, Huiqing Ge, Guang-Qiang Chen, Jian-Xin Zhou, Jie Li, Ewan C. Goligher, Eduardo Costa, Jordi Mancebo, Tommaso Mauri, Marcelo Amato & Laurent J. Brochard, for the PLUG working group

List of Collaborators:
Tobias Becher, Giacomo Bellani, Francois Beloncle, Gilda Cinnella, Carla Fornari, Inéz Frerichs, Claude Guerin, Fabiana Madotto, Ahmed Mady, Alain Mercat, Ibrahim Nagwa, Stefano Nava, Paolo Navalesi, Elena Spinelli, Daniel Talmor

ONLINE DATA SUPPLEMENT

AJRCCM Articles in Press. Published April 25, 2023 as 10.1164/rccm.202212-2300OC

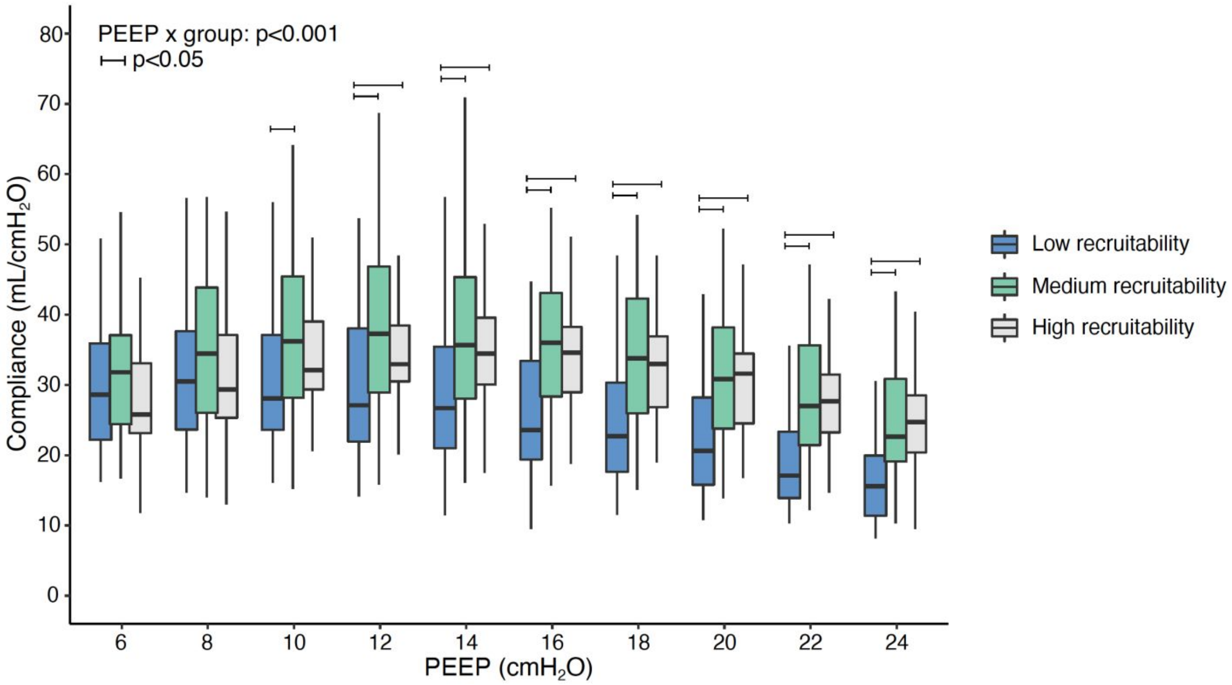

Figure E1. Respiratory system compliance throughout the decremental PEEP trial, separated for recruitability groups.

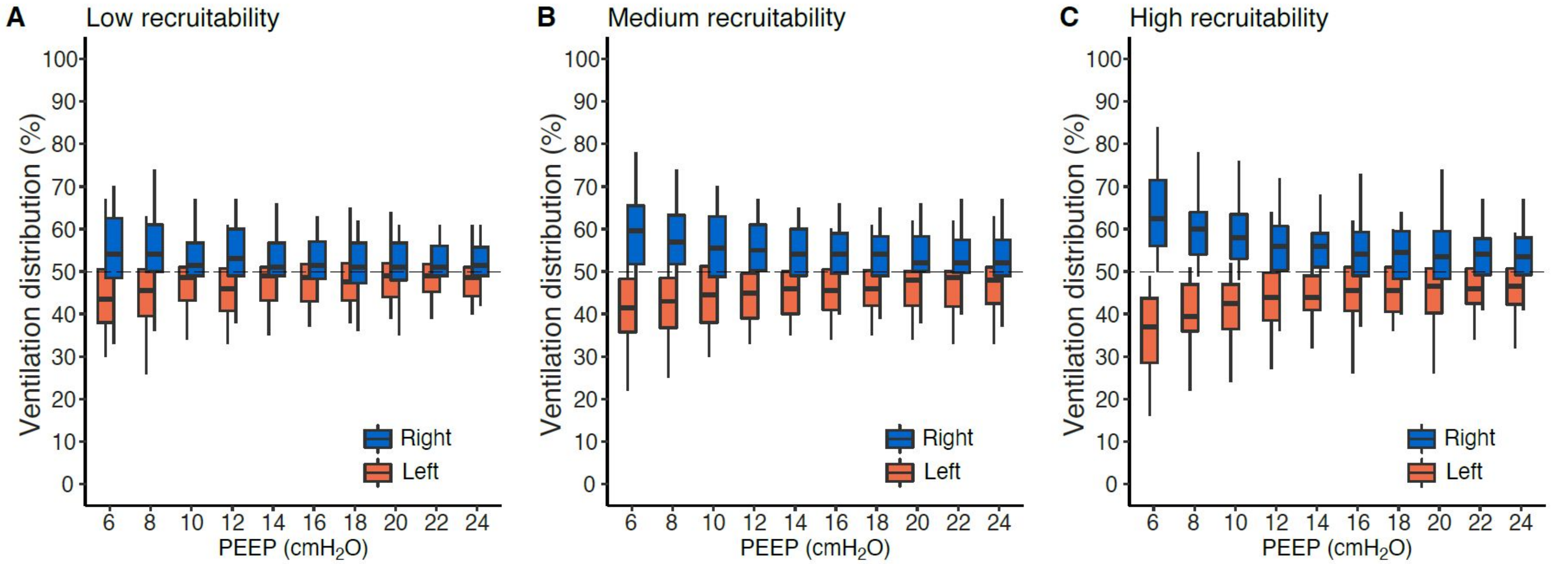

Figure E2. Distribution of tidal ventilation for the left (orange) and right (blue) lung, as obtained during the decremental PEEP trial and separated for the three recruitability groups. Due to the smaller size of the left lung, tidal ventilation is slightly higher in the right lung. At increasing levels of PEEP more homogeneous ventilation is observed; however, this is consistent with an overdistended lung.

AJRCCM Articles in Press. Published April 25, 2023 as 10.1164/rccm.202212-2300OC

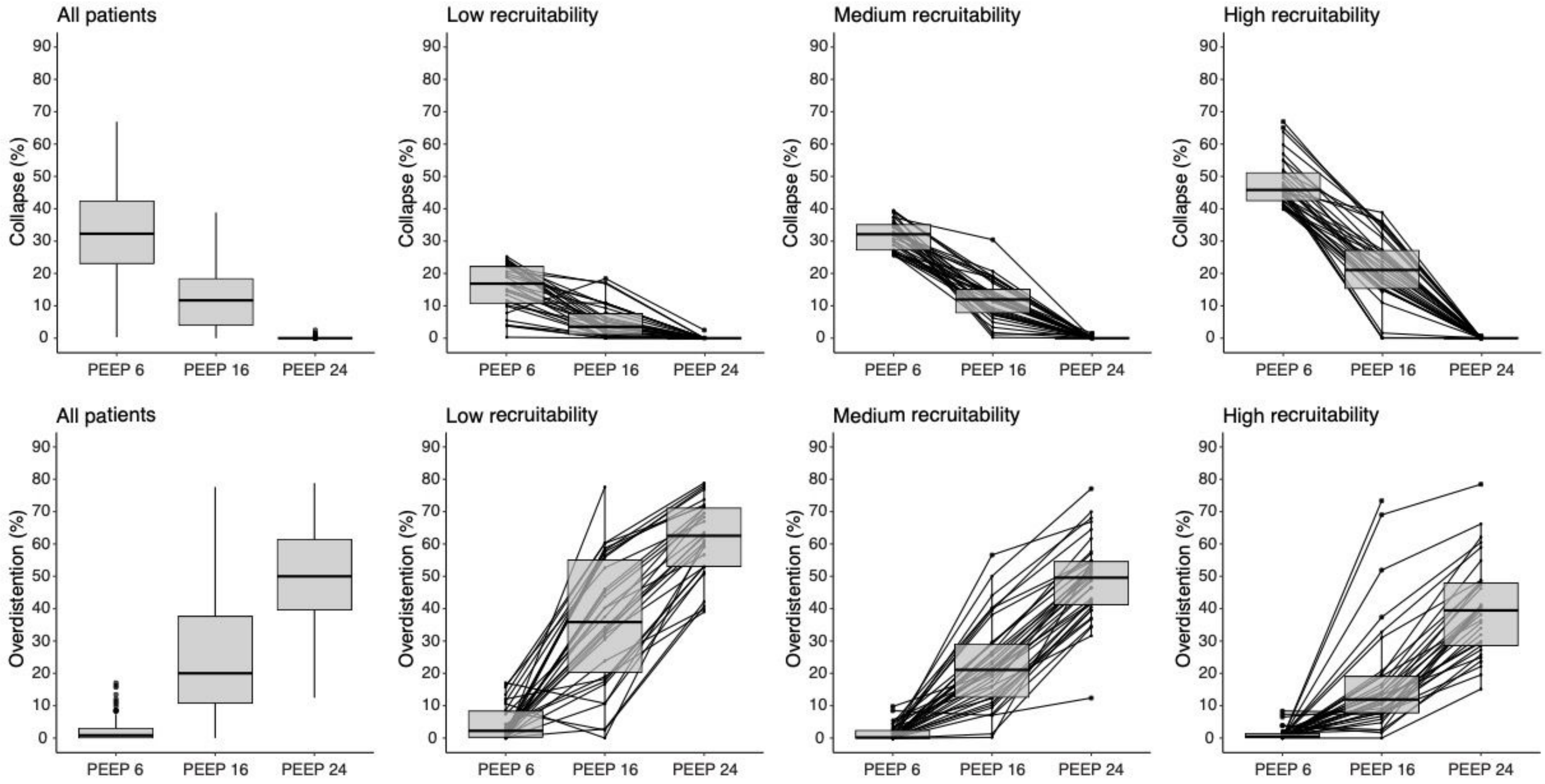

Figure E3. The effect of PEEP on collapse (upper graphs) and overdistention (lower graphs) for the total population and separated for recruitability groups. For both collapse and overdistention, there was a significant difference ($p<0.001$) between all PEEP levels for the total population as well as within each group. Note that the overdistention values at PEEP 6 cmH_2O do not reach 0% for all patients, since lower values could have been obtained at another PEEP 6 step during the study protocol which then served as reference for the calculation of relative overdistention at other steps.

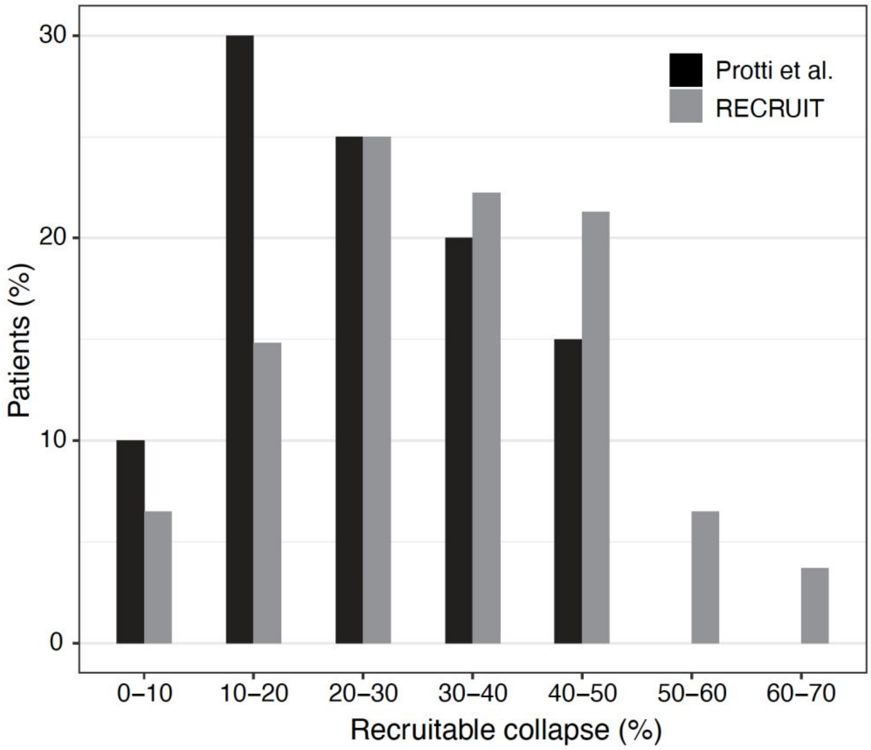

Figure E4. Comparison of recruitability in COVID-19 ARDS patients as presented in the current RECRUIT study and as reported by Protti et al. [E1].

References

E1. Protti A, Santini A, Pennati F, et al (2022) Lung Response to a Higher Positive End-Expiratory Pressure in Mechanically Ventilated Patients With COVID-19. Chest 161:979–988. https://doi.org/10.1016/j.chest.2021.10.012

AJRCCM Articles in Press. Published April 25, 2023 as 10.1164/rccm.202212-2300OC