To the Editor:

Coronavirus disease (COVID-19) spreads rapidly and has already resulted in severe burden to hospitals and ICUs worldwide. Early reports described progression to acute respiratory distress syndrome (ARDS) in 29% of cases (1).

It is unknown how to titrate positive end-expiratory pressure (PEEP) in patients with ARDS. Patient survival improved if higher PEEP successfully recruited atelectatic lung tissue (2). However, excessive PEEP caused alveolar overdistention, resulting in reduced patient survival (3). Therefore, PEEP should be personalized to maximize alveolar recruitment and minimize the amount of alveolar overdistention. Electrical impedance tomography (EIT) provides a reliable bedside approach to detect both alveolar overdistention and alveolar collapse (4).

We describe a case series of patients with COVID-19 and moderate to severe ARDS in whom EIT was applied to personalize PEEP based on the lowest relative alveolar overdistention and collapse. Subsequently, we compared this PEEP level with the PEEP that could have been set according to the lower or higher PEEP–FiO$_2$ table from the ALVEOLI trial (5). These early experiences may help clinicians to titrate PEEP in patients with COVID-19 and ARDS.

Methods

Study design and inclusion criteria. We conducted this case series between March 1, 2020, and March 31, 2020, in our tertiary referral ICU (Erasmus Medical Center, Rotterdam, the Netherlands). All consecutive mechanically ventilated patients admitted to the ICU with COVID-19 and moderate to severe ARDS (according to the Berlin definition of ARDS) were included in this study. COVID-19 was defined as a positive result on a PCR of sputum, nasal swab, or pharyngeal swab specimen. The local medical ethical committee approved this study. Informed consent was obtained from all patients’ legal representatives.

Study protocol. A PEEP trial was performed daily in all patients according to our local mechanical ventilation protocol. Patients were fully sedated with continuous intravenous infusion of propofol, midazolam, and opiates. Persisting spontaneous breathing efforts were prevented with increased sedation or neuromuscular blockade. Arterial blood pressure was measured continuously. Noradrenaline was titrated to maintain a mean arterial blood pressure above 65 mm Hg at the start of the PEEP trial. All patients were ventilated in pressure-control mode. FiO$_2$ was titrated to obtain a peripheral oxygen saturation between 92% and 95%. The other mechanical ventilation parameters (i.e., PEEP driving pressure, respiratory rate, and inspiratory/expiratory ratio) remained unchanged. Plateau airway pressure and total PEEP were measured during a zero-flow state with an inspiratory and expiratory hold procedure, respectively. Absolute transpulmonary pressures were measured with an esophageal balloon catheter (CooperSurgical or NutriVent). The position and balloon inflation status were tested with chest compression during an expiratory hold maneuver.

We monitored bedside ventilation distribution with EIT (Pulmovista 500; Dräger or Enlight 1800; Timpel). An EIT belt was placed around the patient’s thorax in the transversal plane corresponding with the fourth to fifth intercostal parasternal space. The belt was placed daily (Pulmovista) or once in 3 days (Enlight), according to manufacturer’s instructions. EIT data were visualized on screen during the entire study protocol without repositioning the EIT belt.

Subsequently, we performed a decremental PEEP trial. The PEEP was increased stepwise until the PEEP was 10 cm H$_2$O above the baseline PEEP with a minimum PEEP of 24 cm H$_2$O (PEEP$_{high}$), corresponding with the maximum PEEP advised by the PEEP–FiO$_2$ table. The PEEP trial was limited to a lower PEEP level in case of hypotension (mean arterial blood pressure <60 mm Hg) or desaturation (peripheral oxygen saturation <88%). PEEP$_{high}$ was maintained for at least 1 minute. From PEEP$_{high}$, the PEEP was reduced in 2–cm H$_2$O steps of 30 seconds until the EIT showed evident collapse. The PEEP was reduced an additional 2 cm H$_2$O to confirm a further increase in collapse. The EIT devices provided percentages of relative alveolar overdistention and collapse at every PEEP step. Lastly, the total PEEP was set (PEEP$_{set}$) at the PEEP level above the intersection of the curves representing relative alveolar overdistention and collapse (Figure 1) (6).

Baseline characteristics and laboratory analyses were retrieved from the patient information system. Diffuse or focal ARDS was established with chest X-ray or lung computed tomography (CT) scan, similar to the LIVE (Lung Imaging for Ventilatory Setting in ARDS) study (7).

Statistical analysis. Data were presented as medians and interquartile ranges (IQRs). Only PEEP$_{set}$, as determined by the first PEEP trial, of each patient was used for analyses. The absolute distance in cm H$_2$O between PEEP$_{set}$ and the closest PEEP level that could have been set based on the lower PEEP–FiO$_2$ table or the higher PEEP–FiO$_2$ table from the ALVEOLI trial was calculated (5). The Wilcoxon signed-rank test was used to test the difference between PEEP$_{set}$ and the absolute distance to either the PEEP–FiO$_2$ table and to test the difference in PEEP$_{set}$ between the first and last PEEP trial (up to Day 7). Correlations were assessed using Spearman’s rank correlation coefficient ($\rho$).

Results

Study population. We included 15 patients with COVID-19–related ARDS (Table 1). Patients had a body mass index (BMI) of 30 kg/m$^2$ (IQR, 27–34 cm H$_2$O). All patients had high concentrations of C-reactive protein and required vasopressors during the first
week after ICU admission. In addition, 14 (93%) patients had or progressed to diffuse ARDS on their chest X-ray or lung CT scan.

**PEEP** set in **COVID-19**–related ARDS. We conducted a total of 63 PEEP trials, of which 52 were performed in the supine position. The median amount of PEEP trials per patient was 3 (IQR, 2–4.5). PEEP set based on EIT was 21 cm H₂O (IQR, 16–22 cm H₂O). Driving pressure was below 13 cm H₂O in all patients (Table 1). In one PEEP trial (1.6%), we did not reach a PEEP high of 10 cm H₂O above the baseline PEEP because of hemodynamic instability (mean arterial blood pressure <60 mm Hg). No pneumothoraces were observed. At 28 days, four patients died (26.7%), three patients were weaning from mechanical ventilation (20.0%), and eight patients were discharged from the ICU (53.3%).

PEEP set was 2 cm H₂O (IQR, 0–5 cm H₂O) above the PEEP set by the higher PEEP–FI₉O₂ table and 10 cm H₂O (IQR, 7–14 cm H₂O) above the PEEP set by the lower PEEP–FI₉O₂ table (P = 0.01 for the absolute difference) (Figure 2A). There was no correlation between PEEP set and FI₉O₂ (P = 0.11; P = 0.69). However, we did find a significant correlation between PEEP set and BMI (P = 0.76; P = 0.001) (Figure 2B). PEEP set did not change significantly over time (Figure 2C).

**Discussion**

In 15 patients with COVID-19–related ARDS, personalized PEEP at the level of lowest relative alveolar overdistention and collapse, as measured with EIT, resulted in high PEEP. These PEEP levels did not result in high driving pressure or transpulmonary pressure. In addition, PEEP trials did not result in relevant hemodynamic instability or pneumothorax. PEEP set corresponded better with the higher PEEP–FI₉O₂ table than the lower PEEP–FI₉O₂ table and was positively correlated with BMI.

In COVID-19–related ARDS, both a low lung recruitability (L-type) and a high lung recruitability phenotype (H-type) have been described based on lung compliance and the amount of nonaerated lung tissue on lung CT scans (8). Especially in patients with the
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**Definition of abbreviations:** APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; BMI = body mass index; CRP = C-reactive protein; CW = chest wall; DP = driving pressure; Exp = expiratory; Insp = inspiratory; MV = mechanical ventilation; N/A = not available; PEEP = positive end-expiratory pressure; PL = transpulmonary pressure; RS = respiratory system.

\textsuperscript{a}Lowest within 24 hours after ICU admission in our center.

\textsuperscript{b}Baseline PEEP level at the moment of PaO\textsubscript{2}/F\textsubscript{I}O\textsubscript{2} ratio measurement; baseline PEEP was set at the discretion of the attending clinician.

\textsuperscript{c}Number of days on MV at the day of the first PEEP trial.

\textsuperscript{d}Received at least one session of prone positioning.

\textsuperscript{g}Highest measured value (in cm H\textsubscript{2}O) in the first 7 days of admission; DP was calculated as the difference between plateau pressure and total PEEP.

\textsuperscript{**}Highest measured concentration in the first 3 days of admission.

\textsuperscript{††}Unavailable because of loss of data.

\textsuperscript{‡‡}Not available because of an unsuccessful attempt to place esophageal balloon catheter.
L-type, low PEEP was advised because higher PEEP would only result in alveolar overdistention without the benefit of alveolar recruitment. In 12 patients with COVID-19–related ARDS, Pan and colleagues (9) used the recruitment-to-inflation ratio and found that lung recruitability was low as well. However, in our first 15 patients with COVID-19–related ARDS, personalized PEEP at the level of lowest relative alveolar overdistention and collapse, as measured with EIT, resulted in high PEEP. Perhaps we included only patients with the H-type, but it is more likely that both phenotypes are the extremes of a recruitability continuum. The recruitability continuum represents the amount of nonaerated lung tissue resulting from edema.Gattinoni and colleagues (8) already described that one patient with COVID-19–related ARDS could progress from the L-type to the H-type as the amount of nonaerated lung tissue increased. If these results can be generalized, most patients with COVID-19 will become recruitable to some extent. The potential changes in recruitability over time make a personalized PEEP titration approach very interesting, although we did not observe a significant change in PEEP over time.

In addition, a secondary analysis of the ALVEOLI trial found that higher PEEP improved survival in patients with a hyperinflammatory ARDS phenotype (10). The hyperinflammatory phenotype could be predicted accurately using IL-6, tumor necrosis factor receptor, and vasopressors. Given the very high C-reactive protein concentrations and the use of vasopressors in all our patients, we assumed that the majority of patients in our study were in a hyperinflammatory state.

The LIVE trial predicted PEEP response based on lung morphology and found that patients with focal ARDS benefited from lower PEEP and that patients with diffuse ARDS benefited from higher PEEP (7). In our study, the majority of patients had or progressed to diffuse ARDS, based on chest X-ray or lung CT scan. As a consequence, these patients with COVID-19 were likely to respond to higher PEEP.

We realize that the availability of EIT is limited in ICUs worldwide. In clinical practice, the PEEP–FiO2 table is often used because it is a simple approach to titrate PEEP. This study showed that PEEP at the level of lowest relative alveolar overdistention and collapse, as measured with EIT, corresponded better with the higher PEEP–FiO2 table in 15 patients with COVID-19–related ARDS. However, the patients in our study had a high BMI, resulting in a lower transpulmonary pressure and increased PEEP requirement. Higher PEEP should be used with caution in patients with focal ARDS or low BMI. Moreover, response to higher PEEP should always be monitored in terms of driving pressure (2) or oxygenation (11).

Acknowledgment: The authors thank all ICU personnel who enabled us to perform this study.

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*These authors contributed equally to this work.

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

References


3. Cavalcanti AB, Suzumura EA, Laranjeira LN, Paisani DM, Damiani LP, Guimarães HP, et al; Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs...
Bronchoscopic examination included orotracheal tube positioning check, direct inspection of tracheal and bronchial mucosa, suctioning of secretions, and mucoactive agent instillation if necessary (hypertonic saline combined with hyaluronic acid), and mucosa, suctioning of secretions, and mucoactive agent instillation if necessary (hypertonic saline combined with hyaluronic acid), and mucosal protective gown including head and neck cover. Recommended (2), level III of personal protective equipment was used, including N95 or FPP3 mask, goggles, double gloves, and a plastic protective gown including head and neck cover.

Bronchoscopic examination included orotracheal tube positioning check, direct inspection of tracheal and bronchial mucosa, suctioning of secretions, and mucoactive agent instillation if necessary (hypertonic saline combined with hyaluronic acid), and in 63 cases, a mini-BAL with 60-ml saline aliquots at room temperature was performed just before the end of procedure. This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (http://creativecommons.org/licenses/by-nc-nd/4.0/). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rcmr.202004-0945LE on May 15, 2020