Electrical Impedance Tomography for Positive End-Expiratory Pressure Titration in COVID-19–related Acute Respiratory Distress Syndrome

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–FI_{O_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. Noradrenalin 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. FI_{O_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_2O above the baseline PEEP with a minimum PEEP of 24 cm H_2O ($PEEP_{high}$), corresponding with the maximum PEEP advised by the PEEP–FI_{O_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_2O steps of 30 seconds until the EIT showed evident collapse. The PEEP was reduced an additional 2 cm H_2O 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_2O between $PEEP_{set}$ and the closest PEEP level that could have been set based on the lower PEEP–FI_{O_2} table or the higher PEEP–FI_{O_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–FI_{O_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 (ρ).

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_2O). All patients had high concentrations of C-reactive protein and required vasopressors during the first

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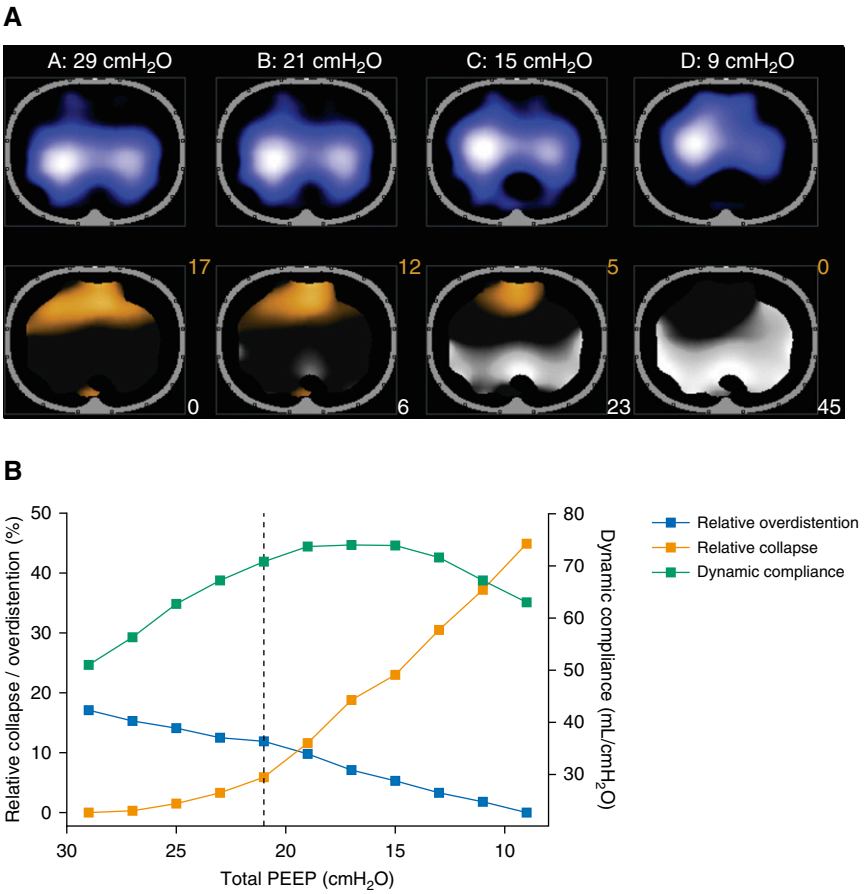

Figure 1. Total set positive end-expiratory pressure (PEEP) based on electrical impedance tomography. (*A*) Ventilation distribution at four levels of PEEP. The top row shows the ventilation distribution in blue, whereas the bottom row shows relative alveolar overdistention in orange and relative alveolar collapse in white. The percentages of relative alveolar overdistention and collapse are presented as well. At a total PEEP of 29 cm H_2O, the dorsal areas of the lung are mainly ventilated, whereas the ventral parts are not ventilated because of overdistention. At a total PEEP of 9 cm H_2O, the ventral parts are mainly ventilated (with more ventilation in the right lung than the left lung), and the dorsal parts are not ventilated because of alveolar collapse. At a total PEEP between 15 and 21 cm H_2O, ventilation is mainly distributed to the center. (*B*) Relative alveolar overdistention, collapse, and dynamic compliance. Relative alveolar overdistention and collapse and the dynamic compliance of the respiratory system are shown during a decremental PEEP trial. At 29 cm H_2O PEEP, there is relative alveolar overdistention but no relative collapse, whereas at 9 cm H_2O PEEP, there is relative alveolar collapse but no relative overdistention. The total PEEP was set at the PEEP level above the intersection of the curves representing relative alveolar overdistention and collapse, in this case 21 cm H_2O (6). Images: Pulmovista 500, Dräger.

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 H_2O (IQR, 16–22 cm H_2O). Driving pressure was below 13 cm H_2O in all patients (Table 1). In one PEEP trial (1.6%), we did not reach a $PEEP_{high}$ of 10 cm H_2O above the baseline PEEP because of hemodynamic instability (mean arterial blood pressure <60 mm Hg). No pneumothoraxes 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 H_2O (IQR, 0–5 cm H_2O) above the PEEP set by the higher PEEP–FI_{O_2} table and 10 cm H_2O (IQR, 7–14 cm H_2O) above the PEEP set by the lower PEEP–FI_{O_2} table ($P = 0.01$ for the absolute difference) (Figure 2A). There was no correlation between $PEEP_{set}$ and FI_{O_2} ($\rho = 0.11$; $P = 0.69$). However, we did find a significant correlation between $PEEP_{set}$ and BMI ($\rho = 0.76$; $P = 0.001$) (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–FI_{O_2} table than the lower PEEP–FI_{O_2} 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

Table 1. Patient Characteristics

Sex	Age (*yr*)	BMI (kg/m^2)	APACHE IV Score	Pa_{O_2}/Fi_{O_2} Ratio (*mm Hg*)*	Baseline PEEP (*cm* H_2O)†	Duration of MV (*d*)‡	Prone Positioning§	DP (*cm* H_2O)‖	P_L (*cm* H_2O)¶		Compliance (*ml/cm* H_2O)			CRP (*mg/L*) **	ARDS Morphology
									Exp	Insp	Lung	CW	RS		
F	49	42	79	68	18	8	Yes	12	2	13	104	53	35	530	Diffuse
M	56	33	113	171	20	8	Yes	8	0	8	90	165	58	349	Diffuse
M	65	27	94	54	16	2	Yes	10	2	19	89	103	47	681	Diffuse
M	16	22	74	158	15	1	No	N/A††	6	19	52	92	33	157	Focal to diffuse
M	72	26	99	163	16	1	No	8	4	12	114	175	69	673	Diffuse
F	59	28	73	116	18	1	Yes	10	5	14	54	189	42	563	Diffuse
F	73	18	125	105	16	0	No	8	2	10	82	134	51	401	Focal to diffuse
F	54	31	94	132	16	2	Yes	13	3	16	43	180	35	526	Diffuse
M	53	31	67	186	16	1	Yes	7	9	14	101	148	60	401	Diffuse
F	62	30	98	134	12	1	No	10	N/A‡‡	N/A‡‡	N/A‡‡	N/A‡‡	61	350	Focal to diffuse
M	66	36	124	118	18	1	No	4	4	13	77	88	41	638	Focal
M	68	34	94	134	18	2	Yes	6	−1	14	124	77	47	280	Diffuse
M	56	34	101	148	18	2	Yes	7	N/A‡‡	N/A‡‡	N/A‡‡	N/A‡‡	69	331	Diffuse
M	61	29	124	140	18	1	Yes	7	9	14	94	95	47	336	Diffuse
M	65	27	112	100	16	3	Yes	7	5	9	102	146	60	386	Diffuse

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; P_L = transpulmonary pressure; RS = respiratory system.

*Lowest within 24 hours after ICU admission in our center.

†Baseline PEEP level at the moment of Pa_{O_2}/Fi_{O_2} ratio measurement; baseline PEEP was set at the discretion of the attending clinician.

‡Number of days on MV at the day of the first PEEP trial.

§Received at least one session of prone positioning.

‖Highest measured value (in cm H_2O) in the first 7 days of admission; DP was calculated as the difference between plateau pressure and total PEEP.

¶Lowest measured end-expiratory value and highest measured end-inspiratory value (in cm H_2O) in the first 7 days of admission; absolute transpulmonary pressure was calculated as the difference between airway pressure and esophageal pressure. Note: the expiratory and inspiratory values are not necessarily measured at the same time and do not reflect transpulmonary driving pressure.

**Highest measured concentration in the first 3 days of admission.

††Unavailable because of loss of data.

‡‡Not available because of an unsuccessful attempt to place esophageal balloon catheter.

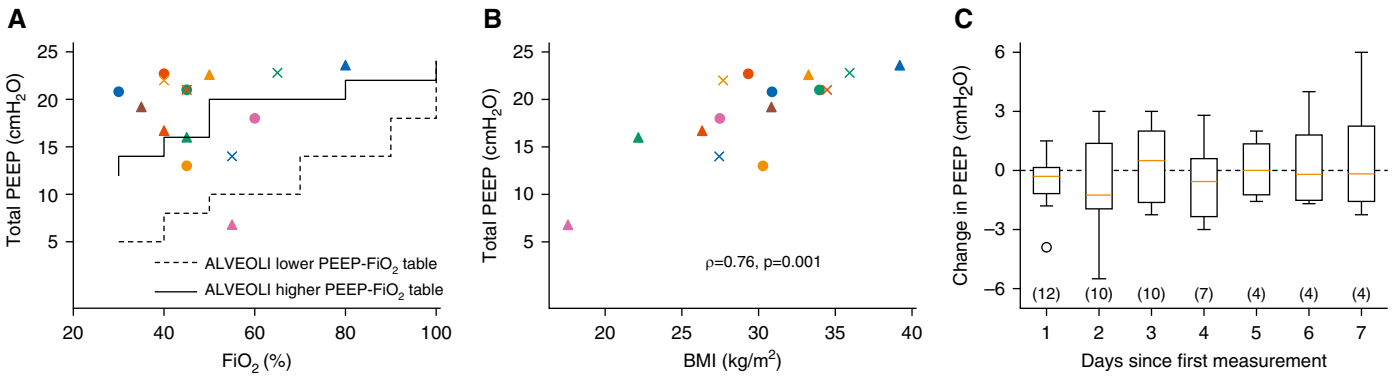

Figure 2. (*A*) Total set positive end-expiratory pressure ($PEEP_{set}$) versus higher and lower PEEP–FI_{O_2} tables. The solid and dashed lines represent the PEEP–FI_{O_2} combination to be used according to the lower and higher PEEP–FI_{O_2} tables from the ALVEOLI trial. Each marker represents $PEEP_{set}$ at the level of lowest relative alveolar overdistention and collapse as measured with electrical impedance tomography. Only the first PEEP trial of each patient is presented. The crosses indicate subjects who died within 28 days following ICU admission. There was no correlation between $PEEP_{set}$ and FI_{O_2} ($\rho = 0.11$; $P = 0.69$). (*B*) $PEEP_{set}$ versus body mass index (BMI). The correlation between BMI and $PEEP_{set}$ after the first PEEP trial for each patient is shown. Spearman's rank correlation coefficient $\rho = 0.76$ with $P = 0.001$. Similar markers in Figures 2A and 2B represent the same patient. (*C*) Change in PEEP compared with the first PEEP trial. The change in $PEEP_{set}$ compared with the first PEEP trial is represented by the median (orange lines), interquartile ranges (boxes), and minimum and maximum values (whiskers). $PEEP_{set}$ did not change significantly over time. The number between parentheses represents the number of patients measured at that day.

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 $PEEP_{set}$ 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–FI_{O_2} table is often used because it is a simple approach to titrate PEEP. This study showed that $PEEP_{set}$ at the level of lowest relative alveolar overdistention and collapse, as measured with EIT, corresponded better with the higher PEEP–FI_{O_2} 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). ■

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Bronchoscopy in Patients with COVID-19 with Invasive Mechanical Ventilation: A Single-Center Experience

To the Editor:

Severe coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leads to acute respiratory distress syndrome and hypoxemic respiratory failure (1).

The University Hospital de la Santa Creu i Sant Pau serves an area of downtown Barcelona, Spain, of about 420,000 citizens. The first case of COVID-19 at our hospital was detected on March 17, 2020. The first two cases in the ICU were detected on March 13, and the number of beds dedicated to intensive care multiplied by four, with 163 new ICU admissions and 139 patients requiring mechanical ventilation between March 13 and April 4. During this period, 59 patients were discharged, 23 died, and 81 were still in the ICU.

BAL, bronchial wash, and protected specimen brush are bronchoscopic procedures used to provide microbiological samples from lower respiratory airways. However, because of the risk of viral transmission, bronchoscopy is not routinely indicated for the diagnosis of COVID-19 (2).

Bronchoscopy in critically ill patients with COVID-19 has been required to manage complications (atelectasis, hemoptysis, etc.) as well as to obtain samples for microbiological cultures and to assist in the management of artificial airways (guide intubation and percutaneous tracheostomy) (3).

Because no series of intubated patients with COVID-19 submitted to bronchoscopy has been published so far, we describe our experience in performing flexible bronchoscopies in patients with COVID-19 with severe acute hypoxemic respiratory failure requiring invasive mechanical ventilation during the first 3 weeks of the epidemic outbreak.

Between March 16 and April 4, 2020, a total of 101 bronchoscopies were performed in 93 patients with COVID-19. Eight patients required two bronchoscopies.

Indications for bronchoscopy were as follows: radiological and/or clinical deterioration suggesting possible superinfection (63/101) as well as airway secretion management with/without atelectasis (38/101). Intensivists indicated procedures 6.6 days (range, 1–17) after intubation. At the time of indication, the median $F_{I_{O_2}}$ was 0.8 (interquartile range [IQR], 0.67–0.82), the median positive end-expiratory pressure was 10 cm H_2O (IQR, 9–11), and the median $Pa_{O_2}/F_{I_{O_2}}$ ratio was 111 (IQR, 103–125).

Procedures were performed in either supine (74/101) or prone (27/101) position, under usual intravenous sedation and with pressure-controlled ventilation mode. Disposable scopes were used in all cases (Ambu aScope 4 Broncho, Large 5.8/2.8. Ambu A/S), and minimal staff attended the procedure bedside (one expert bronchoscopist occasionally accompanied by a staff intensivist). One out of two bronchoscopists got infected with SARS-CoV-2 and developed COVID-19. As a consequence, our colleague had to be replaced by another bronchoscopist during the third week.

Before the procedure, all the necessary equipment and materials were prepared outside the patient room, including saline, syringes, mucoactive drugs, microbiological recipients, connections, and bronchoscopy system (scope and screen). A negative-pressure room was not always available for the procedures owing to the variety of locations adapted for intensive care support. As 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 for microbiological sampling. The bronchial segment to

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