Electrical Impedance Tomography for Positive End-expiratory Pressure Titration in COVID-19 Related ARDS

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Conception of the work: Van der Zee, Somhorst, Endeman, Gommers

Data acquisition and analysis: Van der Zee, Somhorst

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To the editor:

Coronavirus disease 2019 (COVID-19) spreads rapidly and already resulted in severe burden to hospitals and intensive care units (ICU) 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 in order 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 COVID-19 patients with moderate to severe ARDS, in whom EIT was applied to personalize PEEP based on 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 COVID-19 patients with ARDS.

Methods

Study design and inclusion criteria

We conducted this case series between March 1 and March 31 2020 in our tertiary referral ICU (Erasmus MC, 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 polymerase chain reaction of sputum, nasal swab,

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or pharyngeal swab specimen. The local Medical Ethical Committee approved this study. Informed consent was obtained from all patient's 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 mmHg at the start of the PEEP trial.

All patients were ventilated in pressure control mode. FiO_2 was titrated in order to obtain a peripheral oxygen saturation (SpO_2) between 92-95%. 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, USA or NutriVent, Sidam, Italy). 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, Germany or Enlight 1800, Timpel, Brazil). An EIT belt was placed around the patient's thorax in the transversal plane corresponding to the 4^{th} to 5^{th} intercostal parasternal space. The belt was placed daily (Pulmovista) or once in three 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. PEEP was increased stepwise until PEEP was 10 cmH_2O above baseline PEEP with a minimum PEEP of 24 cmH_2O ($PEEP_{high}$), corresponding to the maximum PEEP advised by the PEEP-FiO_2 table. The PEEP trial was limited to a lower PEEP level in case of hypotension

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(mean arterial blood pressure <60 mmHg) or desaturation (SpO_2 <88%). $PEEP_{high}$ was maintained for at least one minute. From $PEEP_{high}$, PEEP was reduced in 2 cmH_2O steps of 30 seconds until EIT showed evident collapse. PEEP was reduced an additional 2 cmH_2O in order to confirm a further increase in collapse. The EIT devices provided percentages of relative alveolar overdistention and collapse at every PEEP step. Lastly, 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 CT scan similar to the LIVE study.(7)

Statistical analysis

Data were presented as median and inter-quartile range (IQR). Only $PEEP_{set}$ as determined by the first PEEP trial of each patient was used for analyses. The absolute distance in cmH_2O between $PEEP_{set}$ and closest PEEP level that could have been set based on the lower PEEP-FiO_2 table or 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 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 (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 cmH_2O). All patients had high concentrations of C-reactive protein (CRP) and required vasopressors during the first week following ICU admission. In addition, 14 (93%) patients had or progressed to diffuse ARDS on chest x-ray or lung CT scan.

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$PEEP_{set}$ in COVID-19 related ARDS

We conducted a total of 63 PEEP trials of which 52 were performed in supine position. Median amount of PEEP trials per patient was 3 (IQR 2-4.5). $PEEP_{set}$ based on EIT was 21 cmH_2O (IQR 16-22 cmH_2O). Driving pressure was below 13 cmH_2O in all patients (**Table 1**). In one PEEP trial (1.6%) we did not reach a $PEEP_{high}$ of 10 cmH_2O above baseline PEEP because of hemodynamic instability (mean arterial blood pressure <60 mmHg). No pneumothoraxes were observed. At 28-days, four patients died (26.7%), three patients were weaning from mechanical ventilation (20.0%), and 8 patients were discharged from the ICU (53.3%).

$PEEP_{set}$ was 2 cmH_2O (IQR 0-5 cmH_2O) above PEEP set by the higher PEEP-FiO_2 table and 10 cmH_2O (IQR 7-14 cmH_2O) above PEEP set by the lower PEEP-FiO_2 table (p-value for the absolute difference 0.01) (**Figure 2A**). There was no correlation between $PEEP_{set}$ and FiO_2 (ρ = 0.11, p-value 0.69). However, we did find a significant correlation between $PEEP_{set}$ and BMI (ρ = 0.76, p-value 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 to the higher PEEP-FiO_2 table than the lower PEEP-FiO_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 amount of non-aerated lung tissue on lung CT scan.(8) Especially in patients with the L-type, low PEEP was advised, as higher PEEP would only result in alveolar overdistention without the benefit of alveolar recruitment. In 12 patients with COVID-19 related ARDS, Pan et al.(9) used the recruitment-to-inflation ratio and found that lung recruitability was

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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 non-aerated lung tissue as a result of edema. Gattinoni et al.(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 non-aerated 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 interleukin-6, tumor necrosis factor receptor and use of vasopressors. Given the very high CRP 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 patients with diffuse ARDS 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 COVID-19 patients were likely to respond to higher PEEP.

We realize that availability of EIT is limited in ICUs worldwide. In clinical practice, the PEEP-FiO_2 table is often used, as 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 to the higher PEEP-FiO_2 table in 15 patients with COVID-19 related ARDS. However, the patients in our study had a high BMI, resulting in lower transpulmonary pressure and increased PEEP requirement. Higher PEEP should be

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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 Section

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Conflict of Interest Disclosure: Philip van der Zee, Peter Somhorst and Henrik Endeman declare no conflict of interest. Diederik Gommers received speakers fee and travel expenses from Dräger, GE Healthcare (medical advisory board 2009-2012), Maquet, and Novalung (medical advisory board 2015-2018).

Data sharing statement: all data is available from the corresponding author upon reasonable request

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Legends

Figure 1 $PEEP_{set}$ based on electrical impedance tomography

Figure 1a. 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 cmH_2O the dorsal areas of the lung are mainly ventilated, while the ventral parts are not ventilated due to overdistention. At a total PEEP of 9 cmH_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 due to alveolar collapse. At a total PEEP between 15-21 cmH_2O ventilation is mainly distributed to the center.

Figure 1b. 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 cmH_2O PEEP there is relative alveolar overdistention but no relative collapse, whereas at 9 cmH_2O PEEP there is relative alveolar collapse but no relative overdistention. Total PEEP was set at the PEEP level above the intersection of the curves representing relative alveolar overdistention and collapse, in this case 21 cmH_2O.(6) Images: Pulmovista 500, Dräger, Germany.

Figure 2a. $PEEP_{set}$ versus higher and lower PEEP-FiO_2 table

The solid and dashed lines represent the PEEP-FiO_2 combination to be used according to the lower and higher PEEP-FiO_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

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the first PEEP trial of each patient is presented. The crosses indicate subjects that died within 28-days following ICU admission. There was no correlation between $PEEP_{set}$ and FiO_2 (ρ = 0.11, p-value 0.69).

Figure 2b. $PEEP_{set}$ versus body mass index

The correlation between BMI and $PEEP_{set}$ after the first PEEP trial for each patient. Spearman's rank correlation coefficient ρ = 0.76 with p-value 0.001. Similar markers in figure 2a and 2b represent the same patient.

Figure 2c. Change in PEEP as compared to the first PEEP trial

The change in $PEEP_{set}$ as compared to the first PEEP trial, represented by the median (orange line), interquartile range (box) and minimum/maximum values (whiskers). $PEEP_{set}$ did not change significantly over time. The number between parentheses represents the amount of patients measured at that day.

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Table 1. Patient characteristics

Gender (M/F)	Age (year)	BMI (kg/m^2)	APACHE IV Score	PaO_2/FiO_2 ratio (mmHg)*	Baseline PEEP (cmH_2O)†	Duration of MV (days) ‡	Prone positioning §	DP (cmH_2O) **	P_L (cmH_2O)‖		Compliance (mL/cmH_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

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

† Baseline PEEP level at moment of PaO_2/FiO_2 ratio measurement. Baseline PEEP was set at the discretion of the attending clinician.

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

§ Received at least one session of prone positioning.

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** Highest measured value (in cmH_2O) in the first seven days of admission, driving pressure was calculated as the difference between plateau pressure and total PEEP.

‖ Lowest measured end-expiratory value and highest measured end-inspiratory value (in cmH_2O) in the first seven 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 three days of admission.

‡‡ Unavailable due to loss of data.

§§ Not available due to unsuccessful attempt to place esophageal balloon catheter.

Abbreviations: ARDS acute respiratory distress syndrome, APACHE acute physiology and chronic health evaluation, BMI body mass index, CW chest wall, CRP C-reactive protein, DP Driving pressure, Exp expiratory, F female, FiO_2 fraction of inspired oxygen, ICU intensive care unit, Insp inspiratory, n.a. not available, M male, MV mechanical ventilation, PEEP positive end-expiratory pressure, P_L transpulmonary pressure, RS respiratory system.

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Figure 1A

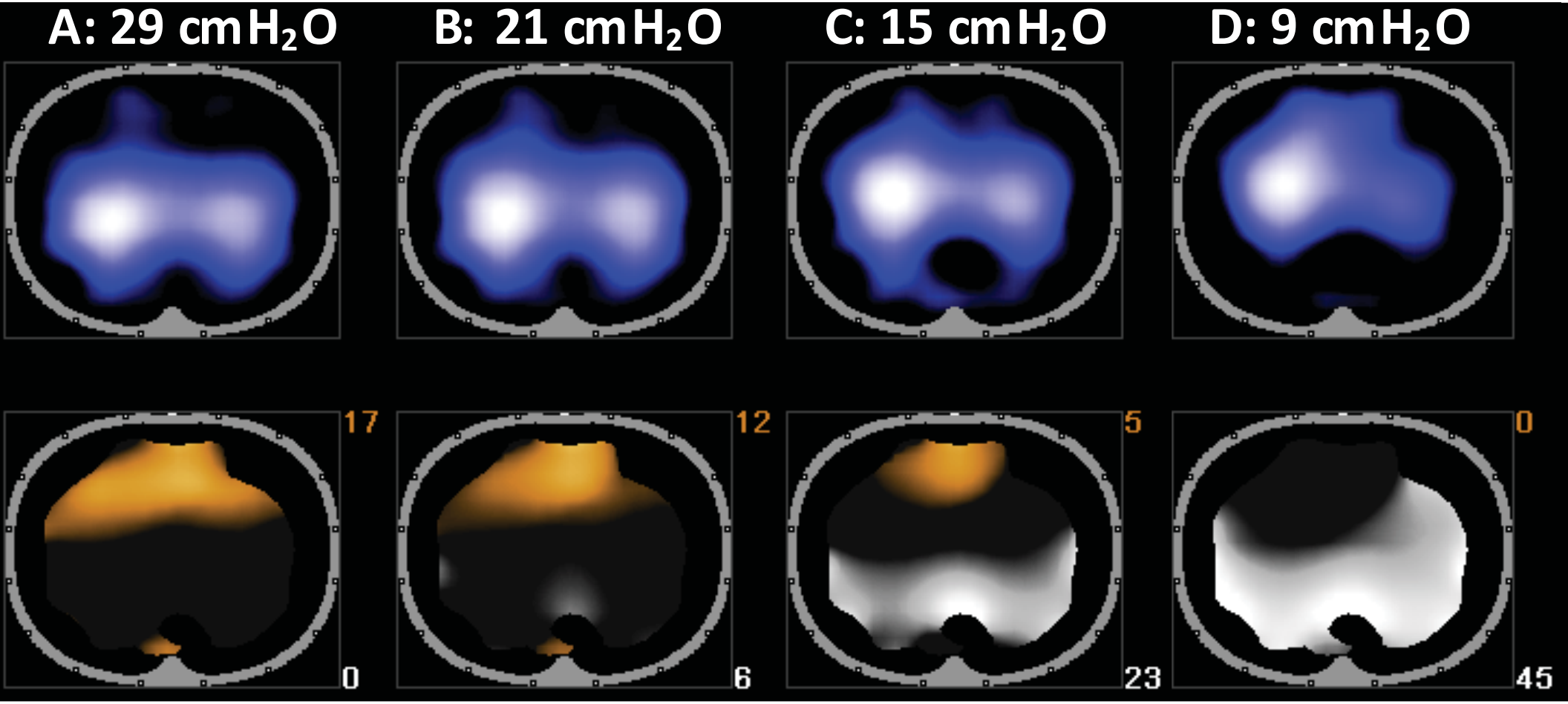

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Figure 1B

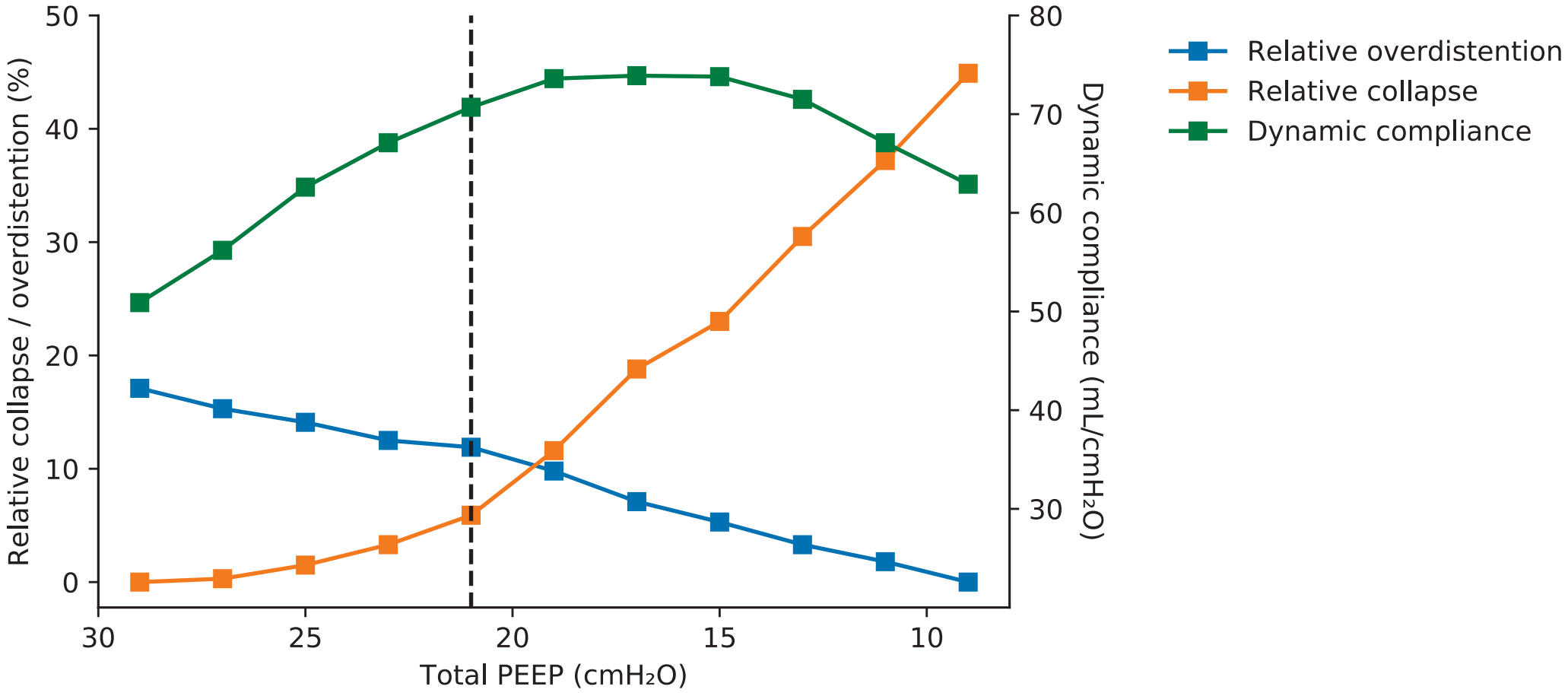

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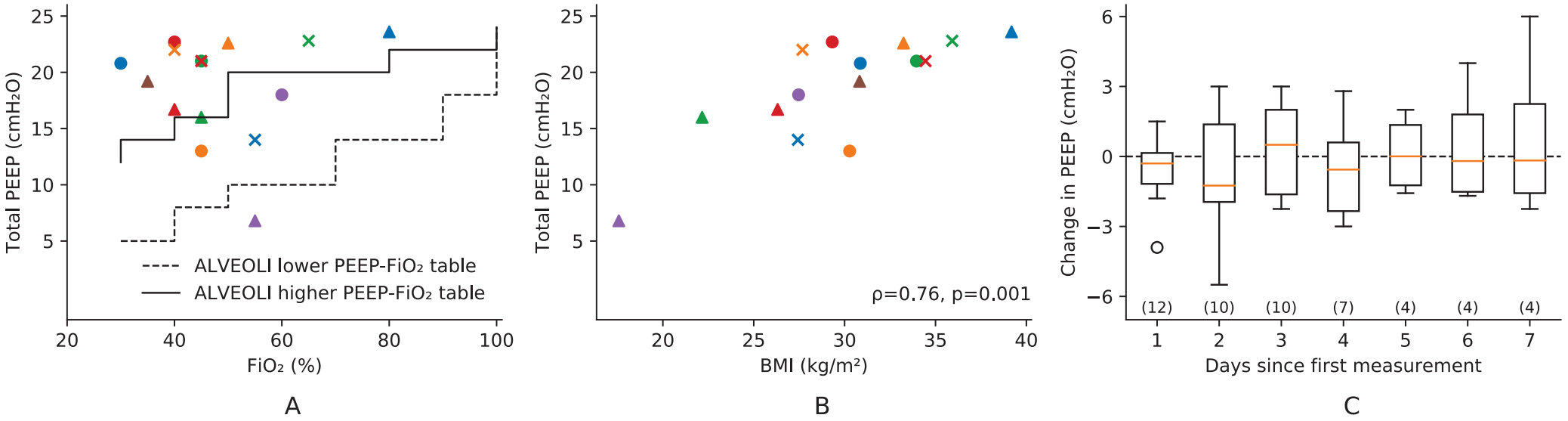
Figure 2



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