The Recruitment-to-Inflation Ratio is Correlated with EIT-Derived Collapse and Overdistention in COVID-19 ARDS

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Conflicts of Interest

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Running title

Recruitment-to-inflation ratio correlates with collapse and overdistention in CARDS

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What This Study Adds to the Field

In patients with acute respiratory distress syndrome (ARDS) secondary to coronavirus disease (COVID)-19, positive end-expiratory pressure (PEEP) selection should balance the beneficial and injurious effects of PEEP based on the potential for lung recruitment. We observed that the recruitment-to-inflation ratio (RIR) maneuver, a simple bedside method recently shown to differentiate patients based on their potential for lung recruitment, is linearly correlated with the risk of collapse and overdistension estimated with electrical impedance tomography and may help titrate PEEP in ARDS patients.

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INTRODUCTION

In patients with acute respiratory distress syndrome (ARDS), the potential for lung recruitment and the response to positive end-expiratory pressure (PEEP) are variable and PEEP selection should balance the beneficial and injurious effects of PEEP based on the potential for lung recruitment (1). This holds true also for ARDS secondary to coronavirus disease-19 (CARDS) (2-3).

Electrical impedance tomography (EIT) allows monitoring lung ventilation distribution by measuring thoracic impedance variation to small electrical currents applied through electrodes aligned on a belt closed around the patient's chest (4). EIT allows identifying the optimal PEEP corresponding to the best compromise between compliance losses due to collapse and overdistension (5), and has been proposed for determining optimal PEEP also in CARDS patients (6-7).

Determining recruitment-to-inflation ratio (RIR) requires a relatively simple two-step maneuver for bedside assessment of lung recruitment potential. First, the presence of airway closure is assessed and the airway opening pressure (AOP) identified through a slow inflation, and second, a single-breath 10-cmH_2O release of PEEP is performed (8). RIR is the ratio between the compliance of the recruited lung volume and respiratory system compliance after PEEP release. RIR values ≥ 0.5 characterize high-recruiters (8).

This prospective observational study aims assessing the correspondence between RIR and the compliance losses secondary to either collapse or overdistension, as estimated by EIT, at varying PEEP levels in CARDS patients.

METHODS

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The study, approved by the local Institutional Ethical Committee (protocol 4853AO20), was conducted in accordance with the principles of the Helsinki Declaration. Informed consent was obtained according to national regulation.

We enrolled all consecutive sedated and paralyzed patients with EIT-based optimal PEEP ≥ 14 cmH_2O, to allow 10-cmH_2O release for RIR assessment for all PEEP values. Mechanical ventilation was applied in volume-targeted controlled mode with tidal volume of 6 mL/kg of ideal body weight. PEEP titration by EIT (Pulmovista 500, Draeger, Lubeck, Germany) was performed through a 2-cmH_2O-step decremental trial from 20 to 8 cmH_2O (4). The curves representing the cumulative percentage of compliance loss due to either collapse or overdistension were obtained and optimal PEEP was considered as the level corresponding to the intersection between these two curves (5). RIR was then measured as proposed by Chen et al. (8), immediately after the EIT-guided PEEP titration procedure. RIR was determined releasing PEEP by 10 cmH_2O from five PEEP levels, i.e., EIT-based optimal PEEP, and 2 and 4 cmH_2O above and below optimal PEEP.

Data are presented as numbers (percentages) and median (first and third quartile) for categorical and continuous variables, respectively. Since the EIT software did not provide values of compliance losses for uneven values of PEEP, the trajectories of compliance loss were reconstructed on the basis of the known values at each PEEP level. A simplified approach borrowed from movement analysis and based on linear functions was adopted to derive the trajectories, independently for the two values of compliance loss (9). A linear model with robust variance estimation and 95% confidence intervals (CIs) to account for correlation within repeated observations on the same subject was carried out to assess the predictive ability of RIR on the value of compliance loss consequent to either overdistension or collapse. The intraclass correlation coefficient (ICC) is reported and the model prediction plots are obtained

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with 95% confidence bounds. All analyses were performed with R 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) with rms packages.

RESULTS

We included 36 consecutive CARDS patients (Table) admitted between December 1, 2020 and April 1, 2021. At enrollment, days from symptom onset and from intubation were 9 (4-11) and 1 (1-2), respectively. One-hundred and eighty RIR maneuvers were performed. Four (11%) patients had complete airway closure with AOP ranging from 5 to 12 cmH_2O. EIT-based optimal PEEP was 16 (14-18) cmH_2O. At EIT-based optimal PEEP, RIR was 0.48 (0.37-0.57), ranging from 0.17 to 0.77, while the loss of compliance was 6 (3-8) % and 4 (3-7) %, secondary to collapse and overdistension, respectively. Seventeen (47%) patients were high-recruiters. As depicted in the Figure, RIR was significantly directly associated with loss of compliance due to collapse (ICC 0.82, slope 0.060, 95% CI 0.020-0.100, p=0.004) and inversely correlated with loss of compliance due to overdistension (ICC 0.80, slope -0.040, 95% CI -0.080--0.007, p=0.019).

DISCUSSION

The assessment of the patient's potential for lung recruitment is necessary to identify patients benefiting from higher PEEP levels. The RIR maneuver is a relatively simple bedside method for this purpose. The lower the RIR, the greater the volume inflating the already aerated lung and, thus, the greater the risk of overdistension, and vice versa (8). We found RIR to be linearly correlated with the risk of collapse and overdistension estimated with EIT.

In CARDS patients, Grieco et al. reported a median RIR value higher than 0.48 (3), while Pan et al. found an average RIR value of 0.21 in 10 out of 12 patients (10). Differences

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in disease severity and timing of assessment, superinfections, and exposure to prone positioning may all contribute to explain this variability.

These results are clinically relevant. First, a simple bedside maneuver performed at the ventilator may give similar information as a technique requiring specific equipment still not widely available. Moreover, the linear correlation between RIR and EIT-based variables suggest that the higher the RIR, the greater the risk of alveolar collapse and the lower the risk of alveolar overdistention, and vice versa. Further studies are needed to understand whether or not an “optimal” RIR level can be defined for each patient and specific RIR ranges exist that correspond to ranges of percentage of collapse and overdistension.

Our study has some limitations. First, because we explored the association between RIR and EIT variables over a predefined range of PEEP surrounding the optimal PEEP, we cannot rule out a non-linear relationship when assessing a broader range of PEEP levels. Second, these findings do not necessarily apply to patients with ARDS of other etiologies. Third, our findings are limited to patients with optimal PEEP ≥ 14 cmH_2O.

In conclusion, we observed in CARDS patients that RIR and the loss of compliance secondary to either collapse or overdistension estimated by EIT are strictly correlated.

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REFERENCES

1. Sahetya SK, Goligher EC, Brower RG. Fifty years of research in ARDS. Setting positive end-expiratory pressure in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017;195:1429–1438.

2. Haudebourg A-F, Perier F, Tuffet S, de Prost N, Razazi K, Mekontso Dessap A, *et al*. Respiratory mechanics of COVID-19–versus non–COVID-19–associated acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020;202:287–290.

3. Grieco DL, Bongiovanni F, Chen L, Menga LS, Cutuli SL, Pintaudi G, *et al*. Respiratory physiology of COVID-19-induced respiratory failure compared to ARDS of other etiologies. *Crit Care* 2020;24:529.

4. Sella N, Pettenuzzo T, Zarantonello F, Andreatta G, De Cassai A, Schiavolin C, *et al*. Electrical impedance tomography: A compass for the safe route to optimal PEEP. *Respir Med* 2021;187:106555.

5. Costa ELV, Borges JB, Melo A, Suarez-Sipmann F, Toufen C, Bohm SH, *et al*. Bedside estimation of recruitable alveolar collapse and hyperdistension by electrical impedance tomography. *Intensive Care Med* 2009;35:1132–1137.

6. Sella N, Zarantonello F, Andreatta G, Gagliardi V, Boscolo A, Navalesi P. Positive end-expiratory pressure titration in COVID-19 acute respiratory failure: electrical impedance tomography vs. PEEP/FiO2 tables. *Crit Care* 2020;24:540.

7. van der Zee P, Somhorst P, Endeman H, Gommers D. Electrical impedance tomography for positive end-expiratory pressure titration in COVID-19–related acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020;202:280–284.

AJRCCM Articles in Press. Published July 23, 2022 as 10.1164/rccm.202203-0555LE

8. Chen L, Del Sorbo L, Grieco DL, Junhasavasdikul D, Rittayamai N, Soliman I, *et al*. 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* 2020;201:178–187.

9. Cappello A, La Palombara PF, Leardini A. Optimization and smoothing techniques in movement analysis. *Int J Biomed Comput* 1996;41:137–151.

10. Pan C, Chen L, Lu C, *et al*. Lung Recruitability in COVID-19–associated acute respiratory distress syndrome: a single-center observational study. *Am J Respir Crit Care Med* 2020;201:1294–1297.

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FIGURE LEGEND

Association between recruitment-to-inflation ratio (RIR) and proportion of lung compliance loss due to alveolar overdistension (red line) and collapse (blue line), as estimated by electrical impedance tomography. Dashed lines around continuous lines represent 95% confidence intervals. The RIR value associated with the best compromise for the concomitant compliance losses was about 0.45.

At a lower RIR, the potential of recruitment is reduced, with an increased risk of volume distribution to the already aerated lung. Contrariwise, at a higher RIR, the potential of recruitment is greater, with a decreased risk of lung of overdistension. For example, in our patient series, the proportions of overdistension and collapse were 15% and 0%, respectively, at RIR 0.37, while 0% and 10%, respectively, at RIR 0.47.

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TABLE

Table. Patient characteristics (n = 36)	
Anthropometric characteristics	
Age (years)	66 (52-72)
Female (n, %)	8 (22)
Weight (kg)	85 (80-110)
Body mass index (kg/m^2)	29 (26-34)
Ideal body weight (kg)	66 (63-71)
Ventilator settings at ICU admission	
Tidal volume (mL)	400 (370-420)
Respiratory rate (breaths/minute)	20 (18-23)
Positive end-expiratory pressure (cmH_2O)	12 (10-14)
Fraction of inspired oxygen (%)	50 (40-60)
Driving pressure (cmH_2O)	9 (8-10)
Static compliance of the respiratory system (mL/cmH_2O)	44 (38-53)
PaO_2/FiO_2 (mmHg)	189 (127-216)
$PaCO_2$ (mmHg)	42 (39-49)
Outcomes	
Pronation during ICU stay (n, %)	36 (100)
V-V ECMO during ICU stay (days)	4 (11)
Duration of invasive mechanical ventilation (days)	8 (5–14)
ICU length of stay (days)	13 (10-19)
ICU mortality (n, %)	3 (8)

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Data are reported as median (first quartile-third quartile) or number (percentages), as appropriate.

Abbreviations: PaO_2/FiO_2, arterial partial pressure of oxygen to inspired oxygen fraction ratio; $PaCO_2$, arterial partial pressure of carbon dioxide, ICU, intensive care unit; V-V ECMO, veno-venous extracorporeal membrane oxygenation.

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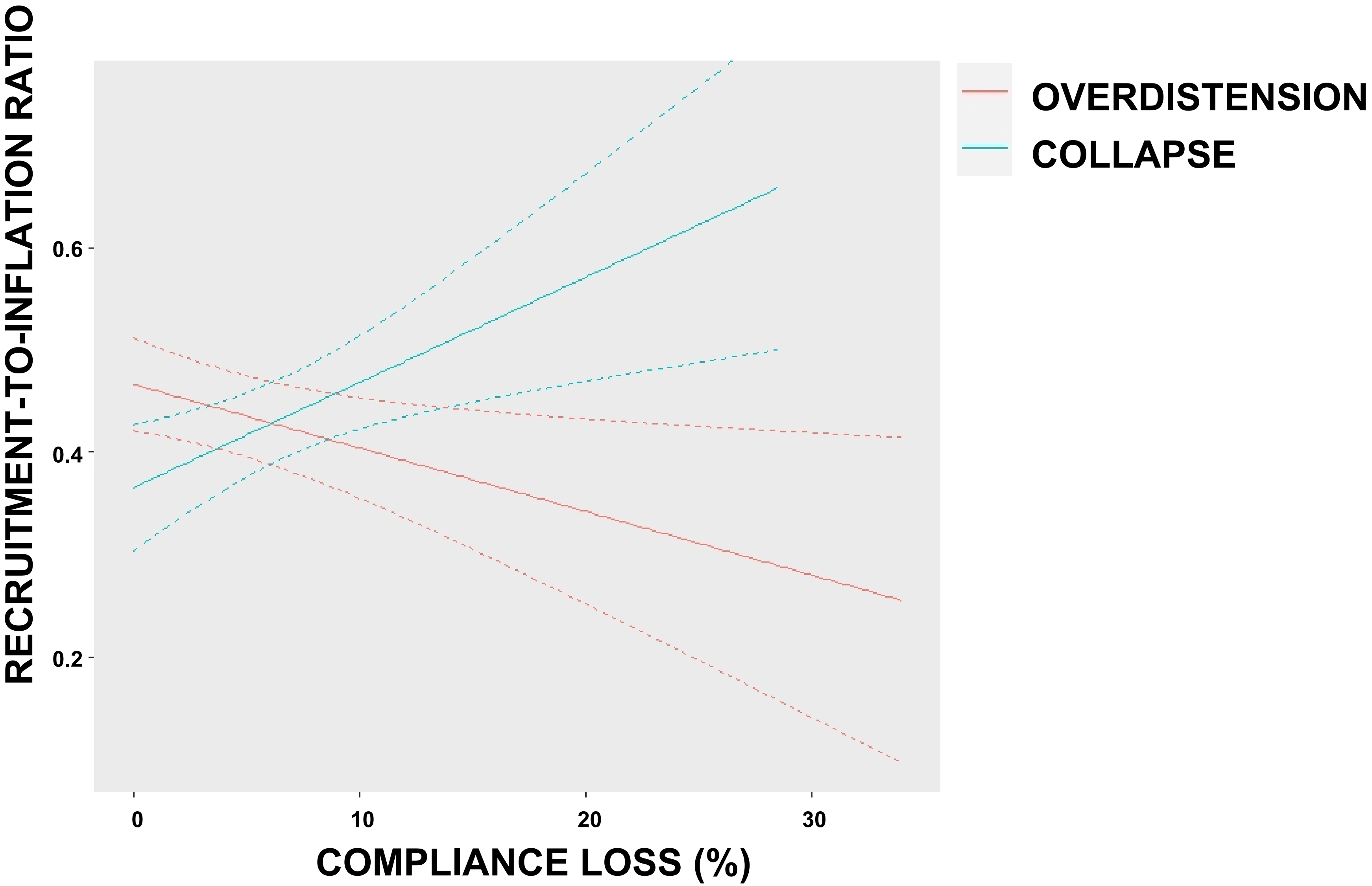

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