



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Lung Recruitability and Positive End-Expiratory Pressure Setting in ARDS Caused by COVID-19

Domenico Luca Grieco, MD
Gennaro De Pascale, MD
Massimo Antonelli, MD
Rome, Italy



In ARDS, mechanical ventilation represents the milestone treatment to restore adequate gas exchange but may itself aggravate lung damage by ventilator-induced lung injury because incorrect ventilator settings are applied. Established strategies to prevent ventilator-induced lung injury include limiting tidal volume, plateau and driving pressure, and the extensive use of prone position, which are all interventions capable of improving survival.¹ Differently, the role of positive end-expiratory pressure (PEEP) is debated: although the use of low PEEP (5 to 8 cm H₂O) in mild-to-moderate cases (PaO₂/F_{IO}₂, > 200 mm Hg) seems wise, there is no conclusive evidence to support the setting of higher vs lower PEEP in patients with moderate-to-severe disease (PaO₂/F_{IO}₂, ≤ 200 mm Hg).

Five different randomized studies that compared higher vs lower PEEP, with high PEEP set according to respiratory system mechanics,² to oxygenation

FOR RELATED ARTICLE, SEE PAGE 979

AFFILIATIONS: From the Department of Anesthesiology and Intensive Care Medicine, Catholic University of The Sacred Heart, and the Department of Anesthesia, Emergency and Intensive care medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS.

FINANCIAL/NONFINANCIAL DISCLOSURES: The authors have reported to *CHEST* the following: D. L. G. has received payments for travel expenses and/or personal fees by Getinge, Intersurgical and Gilead. M. A. has received payments for Board participation from Maquet, Air Liquide and Chiesi. D. L. G. and M. A. disclose a research grant by General Electric Healthcare. None declared (G. D. P.)

CORRESPONDENCE TO: Domenico L. Grieco, MD; email: dlgrieco@outlook.it

Copyright © 2022 American College of Chest Physicians. Published by Elsevier Inc. All rights reserved.

DOI: <https://doi.org/10.1016/j.chest.2021.12.651>

impairment,^{3,4} to maximize respiratory system compliance,⁵ or to achieve different degrees of positive end-expiratory transpulmonary pressure⁶ failed to detect a significant clinical benefit.

Physiologically, PEEP always generates some sort of hyperinflation in the aerated compartment (ie, the baby lung), although it may reduce risk of ventilator-induced lung injury solely when significant alveolar recruitment occurs because of reopening of collapsed tissue, finally increasing the size of the aerated lung available for tidal ventilation. Indeed, the potential for lung recruitment as response to PEEP has wide interindividual variability.⁷ Mechanistically, in early moderate-to-severe ARDS, PEEP setting should aim to a balance between its capability to recruit new alveoli and the unavoidable overinflation produced in already open tissue.^{8,9} High PEEP is beneficial only in patients who have greater potential for lung recruitment, in whom PEEP increases the size of the aerated lung available for tidal ventilation, yielding reduced dynamic strain (ratio of tidal volume to functional residual capacity¹⁰). Conversely, in patients who are not or are poorly recruitable, PEEP only enhances lung injury by increasing static stress and strain in the baby lung.

Patients with COVID-19-induced acute respiratory failure are treated with relatively high PEEP (14 cm H₂O on average),¹¹ which may depend on the positive oxygenation response to PEEP that commonly is observed in these patients, which may happen to be a falsely reassuring clinical finding, however.^{12,13} Improved oxygenation does not necessarily imply alveolar recruitment and less injurious ventilation but may reflect a PEEP-induced reduction in cardiac output and a change in the distribution of alveolar perfusion and/or hypoxic vasoconstriction. On the other hand, PEEP-induced significant recruitment may be accompanied by worsen or unchanged oxygenation when intracardiac shunt is increased in the presence of patent foramen ovale.^{14–17}

The effect of PEEP in patients with COVID-19 ARDS and whether the extent of recruitability is similar to or different from ARDS of other causes remain debated topics.^{12,18–20}

In this issue of *CHEST*, Protti et al²¹ reported a nicely performed physiologic study to assess the potential for lung recruitment and its relationship with PEEP-induced

changes in respiratory mechanics in 40 patients with moderate-to-severe ARDS caused by COVID-19 soon after intubation. The study was performed rigorously, and the data were analyzed thoroughly. Potential for lung recruitment was assessed by CT scan. Similar to ARDS of other causes, results showed great heterogeneity in potential for lung recruitment, fostering the idea that PEEP should be individualized based on the individual response also in patients with COVID-19. A second relevant finding was that changes in respiratory mechanics (compliance and driving pressure) that are induced by PEEP do not yield any information about the potential for lung recruitment and may mislead clinicians; importantly, maximization of compliance (and reduction of driving pressure) is a popular PEEP-setting strategy.⁵ In the study, presence of significant recruitment was not accompanied systematically by increases in compliance, which is consistent with what previously has been reported both in COVID-19 and in ARDS of other causes^{12,13} and may be explained by baby lung hyperinflation and the possible occurrence of tidal recruitment at low PEEP. Compliance and driving pressure are global measures and do not account for the regional behavior of lung tissue.²² Tidal recruitment is the cyclic opening and closing of alveolar units during tidal ventilation; tidal recruitment makes static respiratory system compliance very high at low PEEP, which explains the reason that increases in PEEP may generate worsening compliance also in case of significant recruitment.

The authors demonstrated that potential for lung recruitment cannot be predicted by PEEP-induced changes in PaCO_2 .²¹ With constant minute ventilation, changes in PaCO_2 reflect dead space modifications. With alveolar recruitment, the overdistension by tidal-volume should be mitigated, and this should yield reduction in ventilation-perfusion mismatch with facilitated CO_2 clearance.^{23,24} Differently, in case of poorly recruitable lungs, alveolar dead space may increase because of compression of pulmonary vessels,²⁵ and airway dead space augments because of gas compression in the respiratory circuit and airways; these mechanisms should hamper CO_2 clearance.²⁶ However, CO_2 dynamics are complex and affected strongly by the hemodynamic equilibrium and the amount of CO_2 production, possibly obscuring any PEEP-induced direct effect that is guided by these mechanisms.

We think the authors should be commended for their nicely performed study in such a complex clinical scenario; these results have important clinical implications.²¹

First, the interindividual heterogeneity in the potential for lung recruitment warrants the development of strategies for individualizing PEEP setting at the bedside.²⁷ CT scan is the most accurate tool for evaluating recruitment but requires expertise, fundings, time, and transport of the patient outside the ICU, which may not be available for all patients, especially in the context of a pandemic. Novel approaches that are based on electrical impedance tomography or simplified maneuvers on the ventilator to estimate the extent of recruitment at the bedside have been proposed with promising results, warranting further investigations to determine whether PEEP-settings strategies based on these monitoring tools may improve clinical outcome significantly.^{13,28,29}

Second, commonly applied parameters deemed reliable to assess the effect of PEEP, such as oxygenation, PaCO_2 , respiratory system compliance, and driving pressure, often mislead clinicians. They do not reflect (solely) the occurrence of alveolar recruitment and suffer from the interference of several complex and interdependent physiologic mechanisms whose effects cannot be discriminated with conventional bedside monitoring tools.

Studies such as the one performed by Protti et al²¹ represent a further step ahead in the understanding of the complex physiology that rules the interaction between the individual patient and ventilator. These results represent a further call for the identification of strategies to individualize PEEP settings also in ARDS caused by COVID-19.

References

1. Laffey JG, Bellani G, Pham T, et al. Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study. *Intensive Care Med.* 2016;42(12):1865-1876.
2. Mercat A, Richard JM, Vielle B, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA.* 2008;299(6):646-655.
3. Meade MO, Cook DJ, Guyatt GH, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA.* 2008;299(6):637-645.
4. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med.* 2004;351(4):327-336.
5. Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators, Cavalcanti AB, Suzumura EA, et al. 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.* 2017;318(14):1335-1345.
6. Beitler JR, Sarge T, Banner-Goodspeed VM, et al. Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal

- pressure-guided strategy vs an empirical high PEEP-Fio2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA*. 2017;321(9):846-857.
7. Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med*. 2006;354(17):1775-1786.
 8. Chiumello D, Carlesso E, Cadringer P, et al. Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2008;178(4):346-355.
 9. Protti A, Andreis DT, Monti M, et al. Lung stress and strain during mechanical ventilation: any difference between statics and dynamics? *Crit Care Med*. 2013;41(4):1046-1055. C.
 10. Grieco DL, Russo A, Romanò B, et al. Lung volumes, respiratory mechanics and dynamic strain during general anaesthesia. *Br J Anaesth*. 2018;121(5):1156-1165.
 11. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA*. 2020;24(1):122.
 12. Grieco DL, Bongiovanni F, Chen L, et al. Respiratory physiology of COVID-19-induced respiratory failure compared to ARDS of other etiologies. *Crit Care*. 2020;24(1):529.
 13. Chen L, Sorbo L Del, Grieco DL, 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(2):178-187.
 14. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2020;201(10):1299-1300.
 15. Dessap A, Charron C, Devaquet J, et al. Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome. *Intensive Care Med*. 2009;35(11):1850-1858.
 16. Haudebourg A-F, Perier F, Tuffet S, et al. Respiratory mechanics of COVID-19- versus non-COVID-19-associated acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2020;202(2):287-290.
 17. Dell'Anna AM, Carelli S, Cicetti M, et al. Hemodynamic response to positive end-expiratory pressure and prone position in COVID-19 ARDS. *Respir Physiol Neurobiol*. 2022;298:103844.
 18. Mauri T, Spinelli E, Scotti E, et al. Potential for lung recruitment and ventilation-perfusion mismatch in patients with the acute respiratory distress syndrome from coronavirus disease 2019. *Crit Care Med*. 2020;48(8):1129-1134.
 19. Beloncle FM, Pavlovsky B, Desprez C, et al. Recruitability and effect of PEEP in SARS-Cov-2-associated acute respiratory distress syndrome. *Ann Intensive Care*. 2020;10(1):55.
 20. Chiumello D, Busana M, Coppola S, et al. Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: a matched cohort study. *Intensive Care Med*. 2020;46(12):2187-2196.
 21. Protti A, Santini A, Pennati F, et al. Lung response to a higher positive end-expiratory pressure in mechanically ventilated patients with COVID-19. *Chest*. 2022;161(4):979-988.
 22. Grieco DL, Chen L, Dres M, Brochard L. Should we use driving pressure to set tidal volume? *Curr Opin Crit Care*. 2017;23(1):38-44.
 23. Eronia N, Mauri T, Maffezzini E, et al. Bedside selection of positive end-expiratory pressure by electrical impedance tomography in hypoxemic patients: a feasibility study. *Ann Intensive Care*. 2017;7(1):76.
 24. Bellani G, Guerra L, Musch G, et al. Lung regional metabolic activity and gas volume changes induced by tidal ventilation in patients with acute lung injury. *Am J Respir Crit Care Med*. 2011;183(9):1193-1199.
 25. Pintado M-C, Pablo R de, Trascasa M, et al. Individualized PEEP setting in subjects with ARDS: a randomized controlled pilot study. *Respir Care*. 2013;58(9):1416-1423.
 26. Chen L, Sorbo L Del, Grieco DL, et al. Airway closure in acute respiratory distress syndrome: an underestimated and misinterpreted phenomenon. *Am J Respir Crit Care Med*. 2018;197(1):132-136.
 27. Spinelli E, Grieco DL, Mauri T. A personalized approach to the acute respiratory distress syndrome: recent advances and future challenges. *J Thorac Dis*. 2019;11(12):5619-5625.
 28. Frerichs I, Amato MBP, Kaam AH van, et al. Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus statement of the TRanslational EIT developmeNt stuDy group. *Thorax*. 2017;72(1):83-93.
 29. Spinelli E, Mauri T, Fogagnolo A, et al. Electrical impedance tomography in perioperative medicine: careful respiratory monitoring for tailored interventions. *BMC Anesthesiol*. 2019;19(1):140.