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Guy Brusselle, M.D., Ph.D.
Department of Respiratory Medicine
Ghent University Hospital
Ghent, Belgium
and
Departments of Epidemiology and Respiratory Medicine
Erasmus Medical Center Rotterdam
Rotterdam, The Netherlands

Sebastian Riemann, M.D.
Department of Respiratory Medicine
Ghent University Hospital
Ghent, Belgium

ORCID IDs: 0000-0001-7021-8505 (G.B.); 0000-0003-1184-7234 (S.R.).

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Electrical Impedance Tomography: The Electrocardiogram for the Lungs?

Even patients with so-called mild acute respiratory distress syndrome (ARDS) have high 30-day mortality rates (1), and this has incited large-scale international trials to explore means of improving clinical outcome, such as increasing positive end-expiratory pressure (PEEP) (2). Meta-analyses of randomized clinical trials suggest that higher constant PEEP reduces mortality with estimates for the risk ratio of 0.77 to 0.91 (3, 4) and better results without recruitment maneuvers (4). Our hopes are that, by individualizing PEEP, clinical outcomes can be improved further, but we have yet to find the "ECG for the lungs" to facilitate such optimization.

In this issue of the *Journal* (pp. 25–38), Jonkman and colleagues (5) present data from patients with coronavirus disease (COVID-19) from the observational RECRUIT (Lung RecruitmEnt assessed by eleCtRical Impedance Tomography) trial. Intubated patients with moderate to severe ARDS ($Pa_{O_2}/Fi_{O_2} < 200$ mm Hg) were recruited from ICUs in North America and South America, as well as Europe, within 1 week of ARDS diagnosis. With these inclusion criteria, the authors ensured that the patients' prognosis was predominantly determined by ARDS. Decremental PEEP titration was performed to determine optimal PEEP on the basis of a balance between collapse and overdistension according to electrical impedance tomography (EIT). EIT may outperform other PEEP optimization strategies, such as minimal driving pressure (or compliance) because it provides regional functional information on changes in aeration (6).

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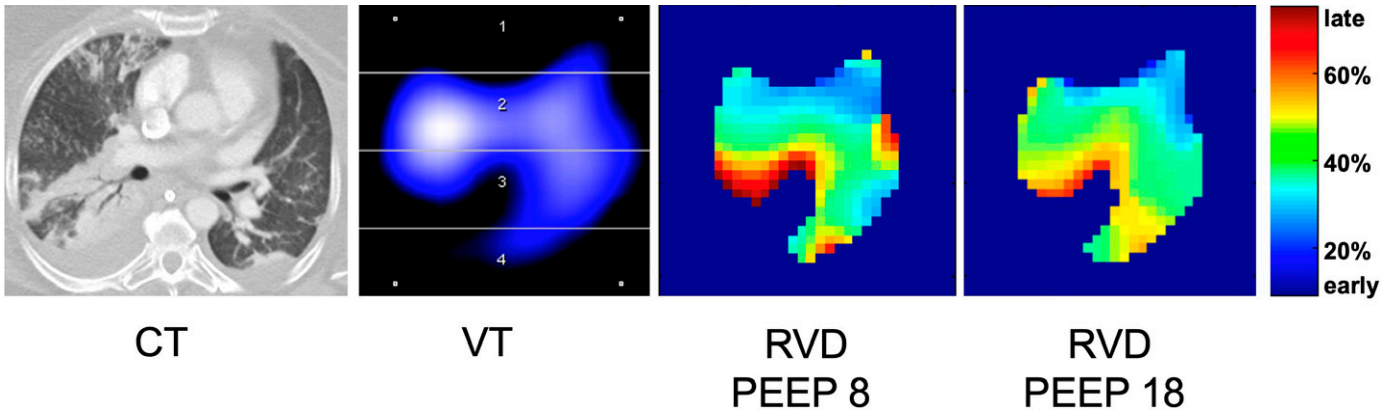

Figure 1. Effects of PEEP on RVD. CT = computed tomography; PEEP 8 = positive end-expiratory pressure of 8 cm H_2O; PEEP 18 = positive end-expiratory pressure of 18 cm H_2O; RVD = regioinal ventilation delay; VT = tidal ventilation image.

The RECRUIT trial was a physiological trial without clinical outcomes initially designed to study ARDS patients, but because of the high prevalence of COVID-19–associated ARDS (CARDS), this editorial presents an unplanned subgroup analysis midway in the study to discuss results from this interesting and potentially idiosyncratic patient cohort.

Following a fairly complex ventilation protocol including a PEEP step with various respiratory mechanical and blood gas measurements, decremental PEEP titration started at 24 cm H_2O with a driving pressure of 15 cm H_2O above PEEP, and EIT tracings were recorded at each step. As suggested by Costa and colleagues on the basis of a proof-of-principle paper that examined two patients (7), collapse and hyperinflation curves were plotted by PEEP level, and the optimum was defined as the crossing point of the two. The protocol foresaw testing the patients' tolerance for high pressure after safety issues observed in the Acute Respiratory Distress Syndrome Trial (2), and all but 4 of 108 patients tolerated the highest maximal pressure of 39 cm H_2O.

Although a compromise between collapse and overdistention seems natural, the particular optimization can be questioned, and the conceptual foundations may require sharpening. The terms *overdistension*, *hyperinflation*, *overinflation*, and *overventilation* all encompass fundamentally different concepts such as mechanical strain and stress of collagen fibers, flattening of a pressure-volume curve, physiological dead space because of compression of perfusion in capillaries on an alveolar level, gray scales in a thoracic computed tomography scan, biotrauma to lung cells with a mechanically induced boost in inflammation, and so forth. After choosing which concept is most relevant, one must a means of measuring and minimizing it. The definition of relative overdistention used in the RECRUIT trial led to values greater than 15% in some patients at a PEEP of 6 cm H_2O (*see* Figure E3 in 5), whereas they would have been 0% by construction had the measurements from step 1 (*see* Figure 1 in 5) not been counted. This and other properties demonstrate a certain arbitrariness inherent to the crossing-point method. Moreover, by optimizing a surrogate parameter such as any EIT measure, one does not necessarily arrive at the optimum for the intended parameter, whichever it may be. In addition, validation of imaging methods for overdistention is complicated by the lack of a gold standard.

It is arguable that one should exploit the high temporal resolution inherent to EIT, typically 50 Hz. Hundreds of measurements per breath are thus available, although the method in the RECRUIT trial uses only two. On the other hand, this information is used to define regional ventilation delay (RVD) (8), where early filling may indicate overdistention toward the end of each breath, and delayed filling was shown to correspond to tidal recruitment (9). Hence, an alternative EIT-optimization strategy is minimizing this inhomogeneity in delay by finding the PEEP with the lowest RVD index. In Figure 1, the computed tomography slice shows a lung from a patient with viral pneumonia and bilateral infiltrates. The tidal volume image shows the sum of impedance changes over one breath cycle and visualizes nonventilated regions in the dependent right lung. The two RVD maps visualize the time differences in regional ventilation at the pixel level during a low-flow maneuver (8). At a PEEP of 8 cm H_2O, there is tidal recruitment mainly in the middle part of the right lung, denoted by red and yellow squares, whereas the blue colored pixels denote very early filling and may indicate regions prone to overdistention. The RVD map at the PEEP of 18 cm H_2O is more homogeneous, indicating a better balance of avoiding tidal recruitment and overdistention.

Beyond issues regarding the best measure, there is also the question as to whether optimization on the timescales of minutes can adequately capture the aforementioned biotraumas that may result from cyclic processes over days. This leads to the question of whether regular (daily) measurements and adjustments of ventilation parameters could be beneficial to clinical outcome.

ARDS subsumes many pathophysiological etiologies, whereas CARDS is a single disease, and one might expect less heterogeneity among this population. It is, thus, surprising at first sight that recruitability varied widely in this CARDS cohort (5). However, evidence shows that, in a first phase, COVID-19 is an endothelial insult with arterial thrombosis, which includes pulmonary artery (micro)thromboses (10) and impaired oxygenation despite relatively little impaired respiratory system compliance (11), alveolar collapse (11, 12), and thus recruitment potential. In a second phase, the lung incurs inflammatory damage with consequences for recruitment more comparable with typical ARDS (13). The high range of recruitability, even in CARDS patients, highlights the need for individualizing PEEP settings, and EIT has been shown to be a

promising tool for doing so. Like ECG, EIT results are available at bedside after a brief processing time, albeit not yet entirely automated in commercially available devices. The fact that the RECRUIT trial constitutes a multicenter study using different EIT machines confirms that EIT is truly a viable option for use in clinical routine and could be used in future trials to select patients who could benefit most from PEEP individualization. The high temporal resolution of EIT noted earlier also has the potential to measure changes in lung perfusion, especially if an "electrical contrast agent" such as saline solution is used (14). Some preliminary studies with bedside computation use not only ventilation but also ventilation/perfusion ratios (6, 15–17).

The RECRUIT trial is the largest EIT trial to date, and even this COVID-19 subgroup consists of 108 patients. It provides important information on the logistic and clinical viability of EIT as well as physiological data on a CARDS cohort, all of which help pave the way toward EIT trials with patient-centered clinical outcomes. It shows that recruitability differs substantially between CARDS patients, where those on the low end do not show an improved oxygenation at any PEEP setting in contrast to others. It will be of great interest to compare with the ARDS patients once the data are available. ■

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Hermann Wrigge, M.D., Ph.D.
Department of Anesthesiology, Intensive Care, Emergency Medicine, and Pain Therapy
Bergmannstrost Hospital
Halle, Germany
and
Medical Faculty
Martin-Luther University Halle-Wittenberg
Halle, Germany

Thomas Muders, M.D.
Department of Anesthesiology and Intensive Care Medicine
University Hospital Bonn
Bonn, Germany

David Petroff, M.Sc., Ph.D.
Clinical Trial Centre
University of Leipzig
Leipzig, Germany

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