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Lung Response to a Higher Positive End-Expiratory Pressure in Mechanically Ventilated Patients With COVID-19



Alessandro Protti, MD; Alessandro Santini, MD; Francesca Pennati, PhD; Chiara Chiurazzi, MD; Massimo Cressoni, MD; Michele Ferrari, MD; Giacomo E. Iapichino, MD; Luca Carenzo, MD; Ezio Lanza, MD; Giorgio Picardo, MD; Pietro Caironi, MD; Andrea Aliverti, PhD; and Maurizio Cecconi, MD



BACKGROUND: International guidelines suggest using a higher (> 10 cm H₂O) positive end-expiratory pressure (PEEP) in patients with moderate-to-severe ARDS due to COVID-19. However, even if oxygenation generally improves with a higher PEEP, compliance, and PaCO₂ frequently do not, as if recruitment was small.

RESEARCH QUESTION: Is the potential for lung recruitment small in patients with early ARDS due to COVID-19?

STUDY DESIGN AND METHODS: Forty patients with ARDS due to COVID-19 were studied in the supine position within 3 days of endotracheal intubation. They all underwent a PEEP trial, in which oxygenation, compliance, and PaCO₂ were measured with 5, 10, and 15 cm H₂O of PEEP, and all other ventilatory settings unchanged. Twenty underwent a whole-lung static CT scan at 5 and 45 cm H₂O, and the other 20 at 5 and 15 cm H₂O of airway pressure. Recruitment and hyperinflation were defined as a decrease in the volume of the non-aerated (density above -100 HU) and an increase in the volume of the over-aerated (density below -900 HU) lung compartments, respectively.

RESULTS: From 5 to 15 cm H₂O, oxygenation improved in 36 (90%) patients but compliance only in 11 (28%) and PaCO₂ only in 14 (35%). From 5 to 45 cm H₂O, recruitment was 351 (161-462) mL and hyperinflation 465 (220-681) mL. From 5 to 15 cm H₂O, recruitment was 168 (110-202) mL and hyperinflation 121 (63-270) mL. Hyperinflation variably developed in all patients and exceeded recruitment in more than half of them.

INTERPRETATION: Patients with early ARDS due to COVID-19, ventilated in the supine position, present with a large potential for lung recruitment. Even so, their compliance and PaCO₂ do not generally improve with a higher PEEP, possibly because of hyperinflation.

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KEY WORDS: acute respiratory distress syndrome; coronavirus disease 2019; mechanical ventilation; positive end-expiratory pressure

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ABBREVIATIONS: PEEP = positive end-expiratory pressure

AFFILIATIONS: From the Department of Biomedical Sciences (A. Protti, G. Picardo, and M. Cecconi), Humanitas University, Pieve Emanuele, Milan, Italy; the Department of Anesthesia and Intensive Care Units (A. Protti, A. Santini, C. Chiurazzi, M. Ferrari, G. E. Iapichino, L. Carenzo, and M. Cecconi), Humanitas Clinical and Research Center—IRCCS, Rozzano, Milan, Italy; the Dipartimento di Elettronica, Informazione e Bioingegneria (F. Pennati and A. Aliverti), Politecnico di Milano, Milan, Italy; the Unit of Radiology (M. Cressoni), IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy; the Department of Radiology (E. Lanza), Humanitas Clinical and Research Center—IRCCS, Rozzano, Milan, Italy; the Department of

Oncology (P. Caironi), University of Turin, Turin, Italy; and the Department of Anesthesia and Critical Care (P. Caironi), Azienda Ospedaliero-Universitaria S. Luigi Gonzaga, Orbassano, Italy.

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CORRESPONDENCE TO: Alessandro Protti, MD; email: alessandro.protti@hunimed.eu

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Take-home Points

Study Question: What is the response to a higher PEEP in mechanically ventilated patients with early ARDS due to COVID-19?

Results: When PEEP is increased from 5 to 15 cmH₂O, oxygenation usually improves but compliance and the PaCO₂ do not. Lung CT shows that when the airway pressure is increased from 5 up to 45 cmH₂O, recruitment is large but hyperinflation can be even larger.

Interpretation: In patients with early ARDS due to COVID-19, a higher PEEP can induce net hyperinflation with overdistention.

ARDS is characterized by inflammatory pulmonary edema with heavy lungs, acute hypoxemia, and low compliance.¹ CT has clarified that hypoxemia depends on a large number of alveoli perfused but not aerated and low compliance on the small dimension of the ventilated lung.² A higher positive end-expiratory pressure (PEEP) can be used to reopen the non-aerated alveoli (anatomical recruitment) and relieve hypoxemia.^{3,4} As ventilation gets distributed in more units, compliance will probably increase, and PaCO₂ will probably decrease.⁴⁻⁶ However, in patients with a small non-aerated compartment, recruitment is modest or nil.

Study Design and Methods

This study was approved by our institutional review board (protocol 465/20). Informed consent was obtained according to local regulations.

Forty patients with laboratory-confirmed COVID-19 underwent a PEEP trial and a lung CT within 3 days of endotracheal intubation. Inclusion criteria were: (i) admission to our ICU with ARDS²⁴; (ii) ongoing invasive mechanical ventilation with deep sedation and paralysis; and (iii) one of the authors being available for collecting data. Exclusion criteria were: (i) lung CT already taken after intubation; (ii) patient too unstable for transfer to the radiology unit; and (iii) pulmonary air leak. We studied 10 nonconsecutive patients from March 1, 2020 to May 31, 2020, when we were frequently unavailable because of the exceptional clinical workload, and 30 consecutive patients from October 16, 2020 to December 9, 2020 (e-Fig 1). Those with a BMI > 35 (obese) underwent a slightly different protocol than the others, as reported in the next two paragraphs.

PEEP Trial

Patients were studied in the supine semirecumbent position. After a recruitment maneuver,⁴ PEEP was set at 15, 10, and 5 cm H₂O. If the patient was obese, PEEP was set at 20, 15, and 10 cm H₂O. Other settings were kept constant. Gas exchange and respiratory system mechanics were assessed after 20 minutes at each PEEP level.

With a higher PEEP, oxygenation can still improve via other mechanisms, including a decrease in the cardiac output,^{6,7} but compliance and PaCO₂ probably will not, because of alveolar overdistention.⁴⁻⁶ As a general rule, the more severe the hypoxemia, the larger the alveolar collapse, the greater the probability of a positive effect of a higher PEEP on lung morphology (ie, larger recruitment), lung function (ie, better gas exchange and mechanics),⁴ and possibly survival.^{8,9}

In line with this general model and recommendations for treating ARDS of other origins,¹⁰ international guidelines suggest using a higher PEEP (> 10 cm H₂O) for moderate-to-severe hypoxemia due to COVID-19.¹¹ However, many patients with this novel disease present with less than expected alveolar collapse,^{12,13} so their potential for recruitment may be smaller than in other ARDS. Accordingly, compliance or PaCO₂ frequently worsen with a higher PEEP.¹³⁻²⁰ These and other data²¹⁻²³ suggest that in COVID-19, hypoxemia is caused not only by alveolar collapse and that the primary response to a higher PEEP is not always lung recruitment.

This study aimed to describe the response to a higher PEEP in patients with early ARDS due to COVID-19. We hypothesized that this is generally negative because the potential for lung recruitment is low.

Lung CT

Patients were studied in the supine horizontal position. After a recruitment maneuver,⁴ a lung CT was taken at 45 and 5 cm H₂O (the first 20 patients) or 15 and 5 cm H₂O (the other 20 patients) of airway pressure. If the patient was obese, CTs were taken at 45 and 10 or 20 and 10 cm H₂O. The total (tissue and gas) volume, the tissue weight, and the gas volume of the whole lung and its non-aerated (density above -100 HU, poorly aerated (from -100 to -500 HU), normally aerated (from -500 to -900 HU), and over-aerated (below -900 HU) compartments were measured as in Gattinoni et al.^{2,4} The expected pre-morbid lung weight was estimated from the subjects' height.²⁵ Recruitment and hyperinflation induced by any increase in airway pressure were computed as the absolute difference in *total volume* of the non-aerated or over-aerated compartment between 5 cm H₂O (or 10 cm H₂O in obese patients) and the higher airway pressure.^{4,26,27} We used the hyperinflation-to-recruitment ratio to weigh the risks and benefits of higher airway pressure.

To be consistent with other studies on ARDS unrelated to COVID-19,^{4,28} we also computed the recruited lung tissue as the difference in the non-aerated *tissue weight* between 5 cm H₂O (or 10 cm H₂O in obese patients) and the higher airway pressure and expressed it as a percentage of the lung weight with 5 cm H₂O (or 10 cm H₂O in obese patients). The tissue remaining non-aerated at 45 cm H₂O of airway pressure was considered consolidated.

The same methods were applied to 10 equally spaced vertical levels forming each CT slice from the sternum to the vertebra. The pressure (super)imposed on each level was obtained as in Gattinoni et al² and Pelosi et al.²⁹ In healthy subjects lying supine, the (maximal) superimposed pressure on the most dorsal level is 2.6 ± 0.5 cm H₂O.²⁵

Aiming to describe the response to a higher PEEP, we present all the results as if airway pressure had been increased throughout the study. Moreover, because we included only four obese patients, results of their PEEP trial are reported as obtained with 5, 10, and 15 (rather than 10, 15, and 20) cm H₂O of airway pressure, as for the other patients. Similarly, results of their lung CTs are reported as obtained with 5 and 45 (rather than 10 and 45), or 5 and 15 (rather than 10 and 20), cm H₂O.

Results

We studied 40 patients with COVID-19 on invasive mechanical ventilation. Their characteristics at ICU admission are reported in [e-Tables 1 and 2](#). Thirty-three (82.5%) were males and seven (17.5%) females, with a mean age of 66 (59-72) years. Three (8%) had a history of COPD, and four (10%) were obese. They were all transferred to the ICU for endotracheal intubation after 2 (1-5) days in the hospital. By that time, 36 (90%) had received some form of noninvasive ventilation. Initial C-reactive protein was 14 (8-17) mg/dL. Fifteen (38%) died in the ICU.

The study was performed 1 (0-1) day after ICU admission. The lung function and morphology of all 40 patients are described in [Table 1](#) and [e-Tables 3 and 4](#). With 5 cm H₂O of PEEP, hypoxemia was mild ($P_{aO_2}:F_{iO_2} > 200$ mm Hg) in five (13%), moderate ($P_{aO_2}:F_{iO_2}$ 101-200 mm Hg) in 19 (47%), and severe ($P_{aO_2}:F_{iO_2} \leq 100$ mm Hg) in 16 (40%). The total lung volume was 2,368 (2,148-2,624) mL: 21% (14%-32%) in the non-aerated, 30% (25%-36%) in the poorly aerated, 44% (31%-52%) in the normally aerated, and 1.8% (0.3%-5.9%) in the over-aerated compartment. The lung tissue weight was 1,318 (1,114-1,633) g, 266 (143-570) g higher than expected. The lung gas volume was 999 (756-1,309) mL. The superimposed pressure increased along the sterno-vertebral axis, up to 11 (10-13) cm H₂O. Accordingly, the non-aerated compartment was dorsal, and the over-aerated compartment was ventral ([e-Fig 2](#)).

Functional Response to a Higher PEEP

The individual changes in gas exchange and respiratory system mechanics with 5, 10, and 15 cm H₂O of PEEP are shown in [Figure 1](#). The $P_{aO_2}:F_{iO_2}$ progressively increased while the compliance initially increased but then decreased. The P_{aCO_2} did not change. The mean

Please refer to [e-Appendix 1](#) for other details on methods.

Statistical Analysis

Data are presented as the median (Q1-Q3) or proportion. They were analyzed with the Mann-Whitney rank-sum test, Wilcoxon signed rank-sum test, Fisher exact test, Spearman rank-order correlation, and Friedman's repeated-measures analysis of variance on ranks. Post hoc comparisons were run with the Wilcoxon signed rank-sum test corrected with Bonferroni's method.

These analyses were done with Stata Statistical Software release 16 (Stata Corp. LLC). A two-tailed $P < .05$ was considered significant.

arterial pressure slightly decreased, and the arteriovenous oxygen content difference increased ([e-Table 5](#)).

Overall, as PEEP was increased from 5 to 15 cm H₂O, oxygenation improved in 36 (90%) patients, but compliance in only 11 (28%) and P_{aCO_2} in only 14 (35%).

Morphological Response to a Higher PEEP

The quantitative analysis of lung CTs is shown in [Tables 2 and 3](#) and in [Figures 2 and 3](#), and [e-Figures 2-4](#).

From 5 to 45 cm H₂O of airway pressure, the total lung volume increased by 2,131 (1,516-2,327) mL. The non-aerated compartment decreased by 351 (161-462) (range, 79-771) mL, and the over-aerated increased by 465 (220-681) (range, 5-1,197) mL. On average, the over-aerated compartment increased by 1.7 (0.5-3.8) mL for a 1-mL decrease of the non-aerated compartment. Hyperinflation exceeded recruitment in 12 (60%) patients. The recruited tissue was 24% (14%-35%) (range, 8%-45%), and the consolidated tissue 16% (9%-23%) of the lung weight with 5 cm H₂O of PEEP.

From 5 to 15 cm H₂O of airway pressure, changes were similar but smaller. The total lung volume increased by 861 (751-1,077) mL. The non-aerated compartment decreased by 168 (110-202) (range, 50-585) mL, and the over-aerated increased by 121 (63-270) (range, 8-524) mL. The over-aerated compartment increased by 1.1 (0.3-1.7) mL for a 1-mL decrease of the non-aerated compartment. Hyperinflation exceeded recruitment in 11 (55%) patients. The recruited tissue was 11% (9%-14%) (range, 5%-30%).

With a higher airway pressure, recruitment occurred dorsally and hyperinflation ventrally ([e-Fig 3](#)).

The hyperinflation-to-recruitment ratio was associated with (i) the maximal superimposed pressure

TABLE 1] Characteristics of 40 Patients With COVID-19, the Day of the Study, and With 5 cm H₂O of PEEP

Variable	Data
No.	40
Ventilatory setting	
Tidal volume, mL	420 (385-445)
Tidal volume, mL/kg of PBW	6.1 (5.9-6.7)
Respiratory rate, breaths/min	20 (18-22)
F _{IO₂} , %	60 (55-95)
Minute ventilation, L/min	8.3 (7.3-9.9)
Respiratory system mechanics	
Plateau airway pressure, cm H ₂ O	15 (14-16)
Driving airway pressure, cm H ₂ O	9 (8-10)
Compliance, mL/cm H ₂ O	45 (42-51)
Gas exchange	
Arterial pH	7.39 (7.34-7.43)
P _{aCO₂} , mm Hg	47 (40-51)
P _{aO₂} , mm Hg	78 (66-90)
P _{aO₂} /F _{IO₂} , mm Hg	112 (84-154)
Lung tissue and gas distribution	
Total lung	
Tissue, g	1,318 (1,114-1,633)
Gas, mL	999 (756-1,309)
Non-aerated	
Tissue, g	526 (384-743)
Gas, mL	5 (0-10)
Poorly aerated	
Tissue, g	516 (406-601)
Gas, mL	216 (167-244)
Normally aerated	
Tissue, g	286 (193-382)
Gas, mL	713 (507-959)
Over-aerated	
Tissue, g	3 (1-7)
Gas, mL	40 (8-129)

All data refer to the time of the study. Respiratory system mechanics and gas exchange were measured with 5 cm H₂O PEEP. Other ventilator settings were at the discretion of the attending physicians. Lung CTs were taken in static conditions during an end-expiratory pause with 5 cm H₂O of PEEP. PBW = predicted body weight; F_{IO₂} = inspiratory fraction of oxygen; P_{aO₂} = arterial tension of oxygen. The driving airway pressure was the difference between the plateau airway pressure and total PEEP measured with a 5-second end-inspiratory and end-expiratory pause. The compliance was the ratio of the tidal volume to the driving airway pressure. Data are reported as median (Q1-Q3). If the non-aerated compartment had a density > 0 HU (ie, higher than the density of water), the gas volume (in mL) was considered zero.

(rho -0.862 and $P < .001$ in patients studied at 5 and 45 cm H₂O; rho -0.838 and $P < .001$ in those studied at 5 and 15 cm H₂O); (ii) the gas volume in the whole lung (rho 0.725 and $P < .001$; rho 0.787 and $P < .001$); (iii) the gas volume in the over-aerated compartment (rho 0.784 and $P < .001$; rho 0.785 and $P < .001$); and (iv) to some extent, compliance (rho 0.417 and $P = .068$; rho 0.444 and $P = .050$) (e-Table 6), all measured with 5 cm H₂O of PEEP. It was not associated with P_{aO₂}:F_{IO₂} with 5 cm H₂O of PEEP (rho 0.216 and $P = .361$; rho 0.390 and $P = .090$). It was associated with the circulating C-reactive protein measured at ICU admission (rho -0.714 and $P < .001$; rho -0.741 and $P < .001$). To summarize, with a higher airway pressure, hyperinflation tended to exceed recruitment in patients with lower superimposed pressure, larger aeration and over-aeration with 5 cm H₂O of PEEP, somewhat higher compliance with 5 cm H₂O of PEEP, and less inflammation.

Discussion

The main findings of this study can be summarized as follows. In patients with early ARDS caused by COVID-19, ventilated in the supine position, the response to a higher PEEP was variable. Arterial oxygenation usually improved, but compliance and P_{aCO₂} frequently did not even if lung recruitment was large. This disagreement between changes in lung physiology and anatomy can be at least partly explained by the simultaneous occurrence of hyperinflation and overdistention.

The functional response to a higher PEEP suggested a *small* potential for recruitment. The arterial oxygenation quite constantly improved, but the compliance and the P_{aCO₂} did not. An isolated increase in arterial oxygenation does not necessarily signal large recruitment. Other mechanisms can play a role.^{6,7} With a higher PEEP, the mean arterial pressure decreased, and the arteriovenous oxygen content difference increased as if the cardiac output had decreased. Arterial oxygenation thus may have increased because the nonaerated compartment became less perfused, independently of recruitment (see also e-Fig 5).⁷ The decrease in compliance with a PEEP > 10 cm H₂O also suggests little recruitment with net overdistention.⁴⁻⁶ Other authors have hypothesized the same based on a very similar response to the PEEP trial in patients with early COVID-19.¹³ However, those authors did not study the

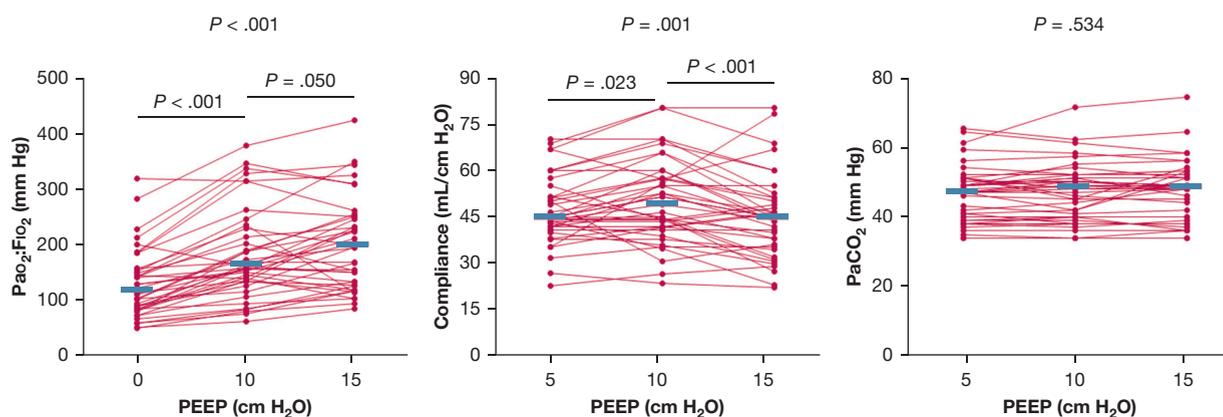


Figure 1 – The functional response to a higher PEEP. Gas exchange and respiratory system compliance were measured with 5, 10, and 15 cm H₂O of positive end-expiratory pressure (PEEP) while other ventilatory settings were kept constant (the so-called “PEEP trial”). Herein we show individual data recorded with the three different levels of PEEP and the group median values (red bars). PaO₂ = arterial tension of oxygen. FiO₂ = inspiratory fraction of oxygen. The compliance was the ratio of tidal volume to driving airway pressure, the difference between plateau airway pressure and total PEEP. P-values refer to the overall Friedman’s test (above), and the posthoc Wilcoxon signed rank-sum test, corrected with Bonferroni’s method (below).

morphological response to a higher PEEP, so that they could not verify their hypothesis as we did.

Discovering with lung CT that patients with early COVID-19 have a very large potential for recruitment came as a surprise. In most^{14,18,30} but not all³¹ other studies on COVID-19, the potential for lung recruitment was small. Herein it was 24% (14%-35%), probably

larger than reported in other pulmonary ARDS (16% [9%-25%])²⁸ (see also e-Fig 6). The reasons why our findings differ from previous ones may include our use of CT, the performance of a recruitment maneuver at the beginning of the study, and enrollment of patients soon after their ICU admission, before any later decrease in lung recruitability.^{14,32,33} In our study population, the

TABLE 2] Lung Tissue and Gas Distribution With 5 and 45 cm H₂O of Airway Pressure

Variable	Quantitative Analysis of Lung CT		P
Airway pressure, cm H ₂ O	5	45	...
No.	20	20	...
Total lung			
Tissue, g	1,336 (1,112-1,586)	1,439 (1,157-1,575)	.062
Gas, mL	950 (577-1,230)	2,905 (2,410-3,345)	< .001
Non-aerated			
Tissue, g	555 (404-742)	197 (115-307)	< .001
Gas, mL	3 (0-10)	0 (0-2)	.008
Poorly aerated			
Tissue, g	502 (364-601)	378 (313-498)	.011
Gas, mL	192 (160-256)	199 (164-274)	.852
Normally aerated			
Tissue, g	255 (156-382)	777 (598-882)	< .001
Gas, mL	658 (356-922)	2,288 (1,474-2,484)	< .001
Over-aerated			
Tissue, g	3 (0-7)	31 (18-45)	< .001
Gas, mL	46 (6-131)	476 (217-766)	< .001

Twenty patients underwent a lung CT at 5 and 45 cm H₂O of airway pressure. Herein we compare the distribution of tissue and gas in their whole lungs and in their four compartments at these two airway pressures. Data are reported as median (Q1-Q3). P value refers to the Wilcoxon signed rank-sum test. If the nonaerated compartment had a density > 0 HU (ie, higher than the density of water), the gas volume was considered zero.

TABLE 3] Lung Tissue and Gas Distribution With 5 and 15 cm H₂O of Airway Pressure

Variable	Quantitative Analysis of Lung CT		P
	5	15	
Airway pressure, cm H ₂ O	5	15	...
No.	20	20	...
Total lung			
Tissue, g	1,301 (1,157-1,658)	1,331 (1,172-1,696)	.003
Gas, mL	999 (913-1,393)	1,943 (1,683-2,322)	< .001
Non-aerated			
Tissue, g	475 (311-754)	301 (140-444)	< .001
Gas, mL	5 (0-10)	2 (0-6)	.002
Poorly aerated			
Tissue, g	517 (438-596)	479 (345-601)	.794
Gas, mL	219 (190-233)	220 (174-293)	.014
Normally aerated			
Tissue, g	305 (255-388)	517 (471-598)	< .001
Gas, mL	722 (642-989)	1,414 (1,225-1,749)	< .001
Over-aerated			
Tissue, g	1 (1-7)	10 (6-26)	< .001
Gas, mL	16 (8-102)	130 (70-324)	< .001

Twenty patients underwent a lung CT at 5 and 15 cm H₂O of airway pressure. Herein we compare the distribution of tissue and gas in their whole lungs and in their four compartments at these two airway pressures. Data are reported as median (Q1-Q3). *P*-value refers to the Wilcoxon signed rank-sum test. If the nonaerated compartment had a density > 0 HU (ie, higher than the density of water), the gas volume was considered zero.

alveolar collapse was almost fully reversible (see also [e-Fig 7](#)), and the residual consolidated tissue only 16% (9%-22%) of the lung weight (in other pulmonary ARDS it is 28% [17%-38%]).²⁸

This disagreement between the functional and morphological response to a higher PEEP can be at least partly explained by simultaneous alveolar overdistention.^{26,27} The net effect of PEEP depends on two opposite phenomena: non-aerated units regaining aeration vs already aerated units receiving more gas, up to the point of becoming over-stretched.^{4,34,35} As PEEP was increased from 5 to 10 cm H₂O, the predominant response seemed to be dorsal recruitment, with less non-aerated tissue, better arterial oxygenation, and better compliance. When PEEP was increased to 15 cm H₂O, overdistention of the nondependent lung regions possibly prevailed over any additional dorsal recruitment, with ventral overdistention at the CT and a sharp decline in compliance. Three aspects of our findings should be noted. First, CT is not ideal for measuring overdistention, for the following reasons: hyperinflation can occur without overdistention, as in emphysema³⁶; overdistention may develop without hyperinflation, at the interface between non-aerated and aerated units³⁷; with ARDS, the decrease in CT density due to excessive inflation can be masked by the

increased tissue mass.² With all these limitations, the decrease in compliance of the whole respiratory system ([e-Table 5](#)) and of the ventral lung levels ([e-Fig 2](#)) suggest that overdistention developed in most patients. Second, end-expiratory lung CT underestimates end-inspiratory hyperinflation. Third, all of these changes occurred with seemingly protective ventilation. In all patients but one, including those with the largest PEEP-induced hyperinflation, driving and plateau airway pressures did not exceed 15 and 30 cm H₂O, not even with 15 cm H₂O of PEEP.³⁸

Other factors may have contributed to the poor functional response to a higher PEEP in the face of large anatomical recruitment. On one side, the modest improvement in gas exchange could have been due to an abnormal distribution of pulmonary blood flow.²¹⁻²³ Arterial oxygenation will not increase much if the recruited alveoli are not well perfused. Conversely, compliance measured during tidal ventilation may not have increased with a higher PEEP because of cyclic recruitment (which increases compliance per se) with a lower PEEP.^{39,40} The relationship between changes in lung aeration and compliance is complex; recruitment should not be estimated only from the latter.^{41,42}

The superimposed pressure can be defined as the hydrostatic pressure acting on each lung level. With

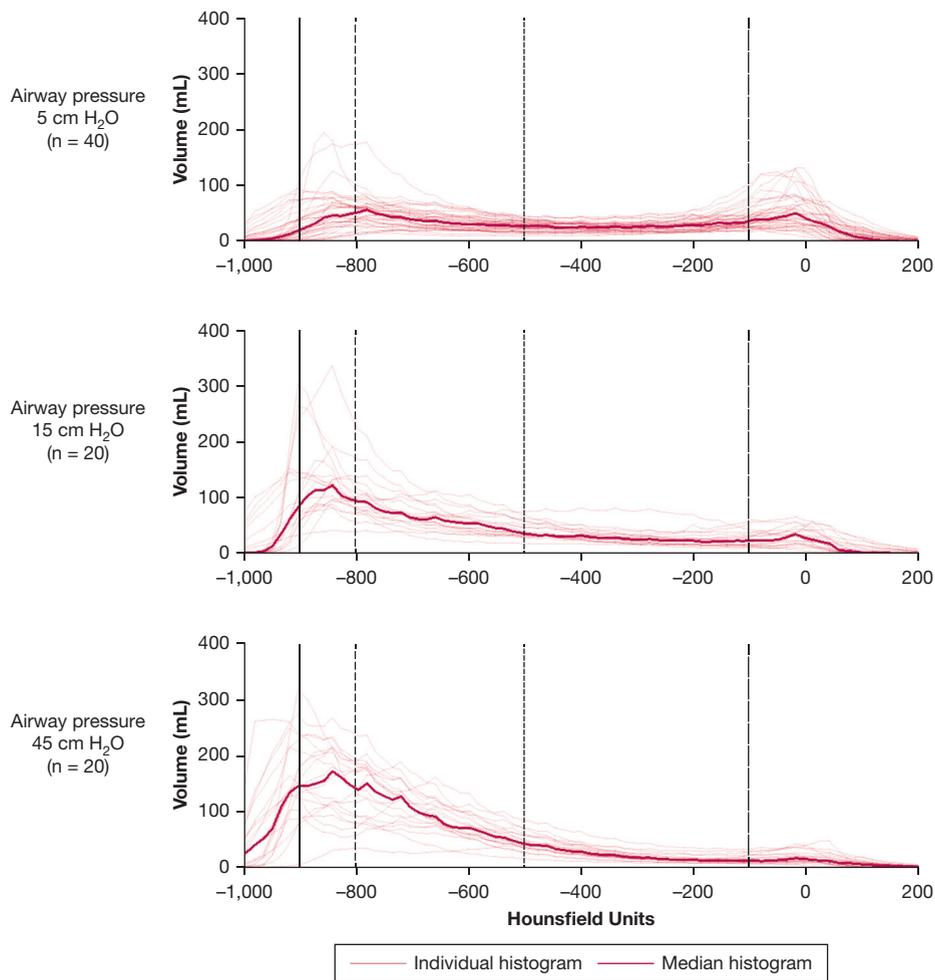


Figure 2 – Lung volume distribution of CT densities at 5, 15, or 45 cm H₂O of airway pressure. Forty patients with COVID-19 underwent a lung CT at 5 cm H₂O of airway pressure. Twenty of them had a second CT taken at 15 cm H₂O, and the other 20 at 45 cm H₂O of airway pressure. Herein we show the individual and median distributions of lung volume (tissue and gas) as a function of the physical densities measured in Hounsfield units (HU). With a higher pressure, volumes with density above –100 HU (non-aerated) decreased, as for alveolar recruitment, whereas those with density from –500 to –900 (normally aerated) increased, as for better aeration. Volumes with a density below –900 HU (over-aerated) simultaneously increased, as for hyperinflation. Volumes with a density from –800 to –900 HU, which can become over-aerated after tidal inflation,²⁶ increased as well. The over-aerated compartment in some patients at 5 or 15 cm H₂O was larger than in others at 45 cm H₂O of airway pressure (see also e-Fig 4).

ARDS, it increases and contributes to the alveolar collapse.^{2,29,43} PEEP restores aeration by counteracting the superimposed pressure.⁴³⁻⁴⁵ Considering that in early ARDS due to COVID-19 the lung weight gain is modest (approximately 250 g), the airway pressure needed to recruit the lung (the opening pressure) and keep it open (PEEP) may be quite low. If so, a PEEP > 10 cm H₂O will induce significant overdistention.⁴⁶

Net hyperinflation was associated with C-reactive protein and compliance. With less inflammation, there will be less pulmonary edema, lower superimposed pressure, less alveolar collapse, larger lung gas volume, and higher compliance.⁵ Changes in pulmonary perfusion will play a major role in the pathogenesis of hypoxemia.²¹⁻²³ Possibly, a lower PEEP will be

appropriate. By contrast, with more inflammation and lower compliance, the superimposed pressure should be higher and the balance between hyperinflation and recruitment more favorable. A higher PEEP will be more indicated.

Some of the limitations of this study deserve a comment. First, the sample size was based on feasibility limitations caused by the ongoing pandemic. Some subgroup analyses were probably underpowered. Second, during the first wave of the pandemic, we could not enroll all consecutive eligible patients, which may have been a source of bias. Third, we did not include a control group to compare patients with COVID-19 with those with other ARDS, especially for the frequency and severity of overdistention. It may be worth noting that in our study,

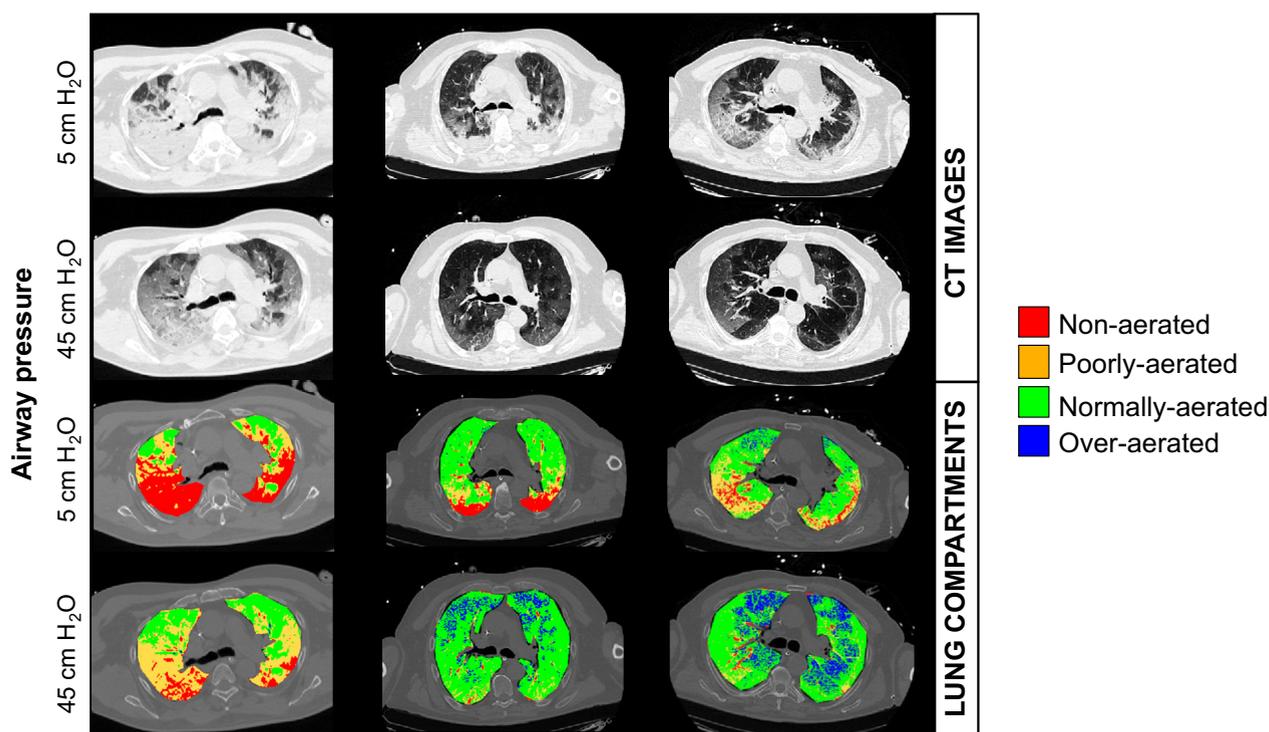


Figure 3 – Color-coded analysis of lung CT data. Representative CT images taken at the level of carina at 5 and 45 cm H₂O of airway pressure from three patients with COVID-19 and very different degrees of recruitment and hyperinflation. Upper panels: original lung CT images, with aeration shown on a continuous grayscale. Lower panels: using an automated encoding system, we attributed a specific color to the non-aerated, poorly aerated, normally aerated, and over-aerated compartments. Left panels: recruitment 457 mL and hyperinflation 5 mL. With 5 cm H₂O of PEEP, maximal superimposed pressure was 13.4 cm H₂O; compliance 27 mL/cm H₂O; Pao₂:Fio₂ 90 mm Hg. C-reactive protein at ICU admission was 20 mg/dL. Central panels: recruitment 347 mL and hyperinflation 661 mL. Maximal superimposed pressure 11.5 cm H₂O; compliance 44 mL/cm H₂O; Pao₂:Fio₂ 104 mm Hg. C-reactive protein 10 mg/dL. Right panels: recruitment 160 mL and hyperinflation 993 mL. Maximal superimposed pressure 9.4 cm H₂O; compliance 60 mL/cm H₂O; Pao₂:Fio₂ 80 mm Hg. C-reactive protein 1 mg/dL. None of these patients had a history of COPD or was obese.

increasing PEEP from 5 to 15 cm H₂O enlarged the over-aerated compartment in all patients, including 19 with no history of COPD (on average by 118 [53-253] mL). By contrast, in a previous study on 32 patients with ARDS of other origins, increasing PEEP from 0 to 15 cm H₂O did the same in only 14 (44%), and only in eight (31%) of those with no history of COPD (on average by 25 [19-28] mL).²⁷ Fourth, lung CTs were not taken at 10 cm H₂O of PEEP. Our model, with predominant recruitment below that threshold and hyperinflation above it, has to be validated. Fifth, the lung phenotype in COVID-19 changes over time,⁴⁷ so that our findings may not be valid for later stages of the disease.^{14,32,33}

Clinical Implications

International guidelines suggest using a higher PEEP to relieve moderate-to-severe hypoxemia caused by COVID-19.¹¹ Accordingly, among 3,988 patients admitted to an ICU in our region (Lombardy, Italy), half were ventilated with a PEEP > 12 cm H₂O, and one fourth with a PEEP > 15 cm H₂O.⁴⁸ In retrospect, PEEP on day 1 of ICU admission was an independent risk

factor of death: for any 1-cm H₂O increase, mortality increased by 4%.⁴⁸

We did not study the impact of a higher or lower PEEP on clinically relevant outcomes, such as survival or duration of mechanical ventilation. Therefore, our findings do not provide any evidence on how to set the ventilation in patients with COVID-19. Even so, they suggest that the response to a higher PEEP can be hardly predictable; and that some patients might benefit from a lower PEEP, even if their ARDS is moderate or severe. Considering changes in gas exchange, respiratory system mechanics, and lung aeration (measured with the CT or other technique) as a whole may help the clinicians to set PEEP according to the characteristics of every single patient.

In conclusion, in this group of patients with early COVID-19, ventilated in the supine position, the response to a higher PEEP was variable and usually less favorable than expected for the severity of hypoxemia and the potential for lung recruitment. Signs of hyperinflation and overdistention were common.

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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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