Assessment of Lung Reaeration at 2 Levels of Positive End-expiratory Pressure in Patients With Early and Late COVID-19-related Acute Respiratory Distress Syndrome

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Purpose: Patients with novel coronavirus disease (COVID-19) frequently develop acute respiratory distress syndrome (ARDS) and need invasive ventilation. The potential to reaerate consolidated lung tissue in COVID-19-related ARDS is heavily debated. This study assessed the potential to reaerate lung consolidations in patients with COVID-19-related ARDS under invasive ventilation.

Materials and Methods: This was a retrospective analysis of patients with COVID-19-related ARDS who underwent chest computed tomography (CT) at low positive end-expiratory pressure (PEEP) and after a recruitment maneuver at high PEEP of 20 cm H_2O. Lung reaeration, volume, and weight were calculated using both CT scans. CT scans were performed after intubation and start of ventilation (early CT), or after several days of intensive care unit admission (late CT).

Results: Twenty-eight patients were analyzed. The median percentages of reaerated and nonaerated lung tissue were 19% [interquartile range, IQR: 10 to 33] and 11% [IQR: 4 to 15] for patients with early and late CT scans, respectively ($P = 0.049$). End-expiratory lung volume showed a median increase of 663 mL [IQR: 483 to 865] and 574 mL [IQR: 292 to 670] after recruitment for patients with early and late CT scans, respectively ($P = 0.43$). The median decrease in lung weight attributed to nonaerated lung tissue was 229 g [IQR: 165 to 376] and 171 g [IQR: 81 to 229] after recruitment for patients with early and late CT scans, respectively ($P = 0.16$).

Conclusions: The majority of patients with COVID-19-related ARDS undergoing invasive ventilation had substantial reaeration of lung consolidations after recruitment and ventilation at high PEEP. Higher PEEP can be considered in patients with reaerated lung consolidations when accompanied by improvement in compliance and gas exchange.

Key Words: lung reaeration, COVID-19, acute respiratory distress syndrome, computed tomography, critical care

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Patients with novel coronavirus disease (COVID-19) often need invasive ventilation due to severe hypoxemia and respiratory failure.[1] Invasive positive pressure ventilation may facilitate recruitment of previously poorly aerated or nonaerated lung tissue.[2] This not only improves matching of ventilation to perfusion but also leads to a more equal distribution of the energy generated by mechanical ventilation (MV) over the lung, as more surface area will receive the energy transferred from the ventilator to the respiratory system. This may limit ventilator-induced lung injury (VILI).[3–6]

There is ongoing debate on the best way to ventilate COVID-19 patients.[7,8] In particular, it is uncertain whether consolidated lung tissue of COVID-19 patients can and should be opened by recruitment maneuvers and using higher airway pressures.[9,10] The use of recruitment maneuvers and/or higher positive end-expiratory pressures (PEEP), however, may have negative effects such as overdistention of already opened alveoli and cardiovascular compromise.[2,11] If airway pressure is increased, but no reaeration of lung tissue occurs, then use of higher airway pressures can be seen as net-harmful.

Chest computed tomography (CT) is the gold standard to assess the regional morphology of lung aeration and calculate lung weight and volume in vivo.[12,13] Lung reaeration can be quantified by comparison of lung aeration before and after a recruitment maneuver, such as sustained inflation, followed by ventilation at higher PEEP.[14] Quantitative CT analyses have shown that the lungs of some patients with non–COVID-19-related acute respiratory distress syndrome (ARDS) can be "reaerated," whereas others cannot.[15] Actually, when lungs cannot be reaerated, the use of higher airway pressures may increase the risk of overdistention shown on CT imaging as hyperinflation, and thus development of additional VILI.[16,17]

We evaluated chest CT scans performed at 2 PEEP levels of patients with severe COVID-19 pneumonia who required invasive ventilation and fulfilled the criteria for ARDS to assess the potential to reaerate lung tissue. We hypothesized that patients with COVID-19-related ARDS who required mechanical ventilation frequently have lung consolidations that can be reaerated.

MATERIALS AND METHODS

Ethics, Patients, and Setting

This study was carried out at a large university hospital. We retrospectively analyzed patients who (1) had severe confirmed COVID-19 pneumonia based on a positive PCR for SARS-COV2 or characteristic CT images in the absence of other infections and (2) underwent a CT scan at 2 levels of PEEP, which is standard in our hospital.[18] The decision to perform this type of CT scan was at the discretion of the treating physician. The institutional review board approved the study protocol and waived the need for informed consent as the CT scans were performed as part of routine practice.

Patients either received chest CT scans early after intubation and start of ventilation, for the purpose of this report called "early" CT scans, or during their stay in the intensive care unit (ICU), for the purpose of this report called "late" CT scans. During this period of the pandemic, only patients receiving invasive mechanical ventilation were admitted to the ICU; thus, the duration of ICU stay is equal to the duration of invasive mechanical ventilation at the time of the CT scan in this particular cohort.

CT and Lung Recruitment Maneuver

CT scans were performed using a high-end dual source CT (CT Somatom Force, Siemens Healthineers, Forchheim, Germany) in the emergency department dedicated to COVID-19 patients during the pandemic. Scans were acquired using the following parameters: Tube voltage: 100/Sn150 kVp, Tube current-time product: Qref mAs 200, Pitch: 1.8, Rotation time: 0.25 seconds, and Automatic Tube Current Modulation: CareDose4D. Reconstructions were performed using the bone and soft tissue filter for 1 and 3 mm slices.

In patients who underwent an early CT scan, just after intubation, the ventilation protocol was as follows: volume-controlled mode, with PEEP 10 cm H_2O, tidal volume 6 mL/kg predicted body weight, and respiratory rate between 20 and 30/min. In patients who underwent a late CT scan, the ventilation protocol was as follows: pressure-controlled or pressure support ventilation, PEEP according to the low PEEP/FiO_2 table by the ARDSnet, and respiratory rate adjusted to have the arterial pH > 7.25. Clinicians could always deviate from this protocol based on clinical grounds. Patients were prone positioned for at least 16 h a day (evening and night-time) when PaO_2/FiO_2 was below 150 mm Hg. Continuous administration of neuromuscular blockade was discouraged.

In every patient, the first scan was performed at the PEEP that was used directly before scanning. Then, the Hamilton C2 ventilator (Hamilton Medical, Bonaduz, Switzerland) was used to deliver a sustained inflation by pushing the inspiratory hold button for 10 seconds. This way, the airway pressure is increased to 40 cm H_2O for the duration of the hold. This procedure was repeated a total of 3 times. Finally, PEEP was set at 20 cm H_2O, and a second CT scan was performed. Both scans were performed in the end-expiratory phase of the respiratory cycle.

Segmentation and Quantification of Aeration

Automated segmentation of lung tissue in CT scans was performed using an open-source artificial intelligence algorithm.[19] All segmentations were inspected and optimized with manual retouches using ITK-snap software.[20] Pleural effusions and hilar bronchi and vessels were excluded from the segmentation.

Lung aeration was categorized based on CT numbers (HU): hyperinflated (from −1000 to −901 HU), normally aerated (from −900 to −501 HU), poorly aerated (from −500 to −101 HU), and nonaerated (from −100 to 100 HU), to allow for comparison with previous ARDS literature.[15] Lung volume was calculated by multiplication of the number of lung voxels and the size of one voxel in milliliters and thus indicates the total volume of the lung irrespective of aeration of the tissue. Lung tissue is assumed to be a composition of air (−1000 HU) and lung parenchyma with similar density and attenuation characteristics to water (0 HU).[21] Therefore, lung weight could be calculated using the tissue fraction of the lung derived from CT numbers (equation 1):

$$\text{Lung weight} = \left(1 - \frac{\text{mean CT number}}{-1000}\right) \times \text{lung volume}, \quad (1)$$

with lung weight in grams, mean CT number of all lung voxels in HU, and lung volume in milliliters.

End-expiratory lung volume was calculated with the gas fraction of the lung using the following formula (equation 2):

$$\text{End-expiratory lung volume} = \left(\frac{\text{mean CT number}}{-1000}\right) \times \text{lung volume}, \quad (2)$$

with end-expiratory lung volume in milliliters, mean CT number of all lung voxels in HU, and lung volume in milliliters.

Definitions

Lung weight of nonaerated lung tissue was estimated as the volume of nonaerated tissue in milliliters as this closely corresponds to weight in grams. Lung reaeration was defined as the difference in nonaerated lung tissue weight between low PEEP and high PEEP, expressed in percentage of total lung weight at low PEEP (equation 3)[15]:

$$\text{Reaeration} = \frac{\text{lung weight}_{\text{nonaerated, PEEP Low}} - \text{lung weight}_{\text{nonaerated, PEEP High}}}{\text{lung weight}_{\text{total, PEEP Low}}} \times 100\%, \quad (3)$$

with reaeration in percentage and lung weights in grams.

Primary Endpoint and Secondary Endpoints

The primary endpoint of this study was the percentage of reaerated nonaerated lung tissue after recruitment maneuvers and ventilation at high PEEP. The secondary endpoints were (1) change in end-expiratory lung volume, total lung volume, and weight of nonaerated lung tissue at high PEEP and (2) change in hyperinflated lung volume at high PEEP. All endpoints were stratified for scans performed at the start of intubation and ventilation or later in the course of ICU admission.

Statistical Analysis

Data were analyzed in MATLAB version R2019a (The MathWorks Inc., Natick, MA) and R[22] through the R-studio interface (Version 1.2.5001). The distribution of continuous variables was assessed, and normally distributed variables were shown as mean with SD and compared using a *T* test, whereas non-normally distributed variables were shown as median with inter-quartile range (IQR) and compared using a Mann-Whitney *U* test. Categorical variables were shown as numbers and percentages and compared using a χ^2 test. The association between lung reaeration and prerecruitment variables was assessed by linear regression analysis. Specifics of this analysis
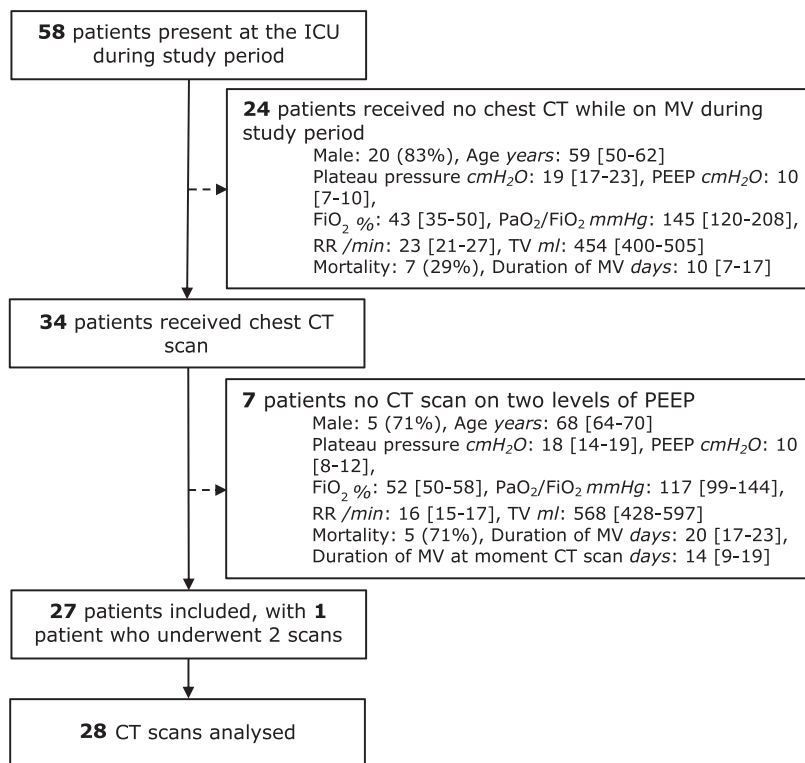
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┌─────────────────────────────────┐
│ 58 patients present at the ICU  │
│    during study period          │
└─────────────────────────────────┘
          │
          │      ┌──────────────────────────────────────────────────────┐
          │      │ 24 patients received no chest CT while on MV during   │
          ┆----->│ study period                                          │
          │      │    Male: 20 (83%), Age years: 59 [50-62]             │
          │      │    Plateau pressure cmH₂O: 19 [17-23], PEEP cmH₂O: 10 │
          │      │    [7-10],                                            │
          │      │    FiO₂ %: 43 [35-50], PaO₂/FiO₂ mmHg: 145 [120-208], │
          │      │    RR /min: 23 [21-27], TV ml: 454 [400-505]          │
          │      │    Mortality: 7 (29%), Duration of MV days: 10 [7-17] │
          │      └──────────────────────────────────────────────────────┘
          ▼
┌─────────────────────────────────┐
│ 34 patients received chest CT   │
│    scan                         │
└─────────────────────────────────┘
          │
          │      ┌──────────────────────────────────────────────────────┐
          │      │ 7 patients no CT scan on two levels of PEEP           │
          ┆----->│    Male: 5 (71%), Age years: 68 [64-70]              │
          │      │    Plateau pressure cmH₂O: 18 [14-19], PEEP cmH₂O: 10 │
          │      │    [8-12],                                            │
          │      │    FiO₂ %: 52 [50-58], PaO₂/FiO₂ mmHg: 117 [99-144],  │
          │      │    RR /min: 16 [15-17], TV ml: 568 [428-597]          │
          │      │    Mortality: 5 (71%), Duration of MV days: 20 [17-23]│
          │      │    Duration of MV at moment CT scan days: 14 [9-19]   │
          │      └──────────────────────────────────────────────────────┘
          ▼
┌─────────────────────────────────┐
│ 27 patients included, with 1    │
│ patient who underwent 2 scans   │
└─────────────────────────────────┘
          │
          ▼
┌─────────────────────────────────┐
│ 28 CT scans analysed            │
└─────────────────────────────────┘
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FIGURE 1. Flow chart for patient inclusion.

and the definition of the assessed prerecruitment variables can be found in the Supplemental Digital Content 1 (http://links.lww.com/JTI/A191).

RESULTS

Patients

Fourteen patients underwent an early chest CT scan after intubation and start of invasive ventilation, and 14 patients underwent a late chest CT scan after several days of ICU stay and invasive ventilation. The flowchart for patient inclusion is presented in Figure 1. The median duration of ICU stay and duration of mechanical ventilation in the "late CT group" was 12.5 days [IQR: 10.0 to 14.8 d]. The median age of the cohort was 62 years [IQR: 57 to 66 y]. All patients fulfilled the Berlin criteria for ARDS. Other patient characteristics are shown in Table 1. CT measures from both CT scans and corresponding PEEP levels are presented in Table 2.

Lung Reaeration

The median percentages of reaerated nonaerated lung tissues were 14% [IQR: 8% to 21%] in all patients, 19% [IQR: 10% to 33%] in patients with an early chest CT scan, and 11% [IQR: 4% to 15%] in patients with a late chest CT scan ($P = 0.049$ between early and late; Fig. 2). Lung reaeration was not different between patients with a positive PCR for SARS-COV2 and patients who were diagnosed with COVID-19 based on characteristic CT images in the absence of other infections (reaeration: 14% [IQR: 7% to 19%] vs. 15% [IQR: 9% to 26%], respectively, $P = 0.55$). Lung reaeration was dependent on the duration of mechanical ventilation and the weight of nonaerated lung tissue, but not on lung morphology, weight, or volume nor by severity of hypoxemia or compliance of the respiratory

system. Additional data on the association between lung reaeration and prerecruitment variables are presented in the Supplemental Digital Content 1 (Figure E1 and Table E1, http://links.lww.com/JTI/A191).

The median change in total lung volume after recruitment (lung volume irrespective of aeration of the tissue) was +666 mL [IQR: +492 to +789 mL] in all patients, +762 mL [IQR: +580 to +1036 mL] in patients with an early chest CT scan and +630 [IQR: +361 to +746 mL] in patients with a late chest CT scan ($P = 0.19$ between early and late). End-expiratory lung volume (lung volume taken by gas) showed a median change after recruitment of +587 mL [IQR: +435 to +824 mL] in all patients, +663 mL [IQR: +483 to 865 mL] in patients with an early chest CT scan, and +574 mL [IQR: +292 to 670 mL] in patients with a late CT scan ($P = 0.43$ between early and late; Fig. 3). The median change in lung weight attributed to nonaerated lung tissue after recruitment was −180 g [IQR: −294 to −137 g] in all patients, −229 g [IQR: −376 to −165 g] in patients with an early chest CT scan, and −171 g [IQR: −229 to −81 g] in patients with a late CT scan ($P = 0.16$ between early and late; Fig. 3). Representative CT slices at low and high PEEP of 2 patients with substantial reaeration of the lungs and 2 patients without reaeration of the lungs are shown in Figure 4. Per patient distribution of change in end-expiratory lung volume and lung weight (Fig. E2, E3) can be found in the Supplemental Digital Content 1 (http://links.lww.com/JTI/A191).

Hyperinflation

The lung volume of hyperinflated areas increased after recruitment with 5.8 mL [IQR: 1.1 to 16.8 mL] in all patients, with 7.2 mL [IQR: 2.6 to 15.6 mL] in patients with an early chest CT scan, and with 3.7 mL [IQR: 0.4 to

TABLE 1. Patient Characteristics

Characteristic	Early CT Scan (N = 14)	Late CT Scan (N = 14)	P
Age, mean (SD) (y)	61 (7.45)	60.36 (9.41)	0.76
Male, n (%)	6 (42.9)	10 (71.4)	0.25
Symptoms duration before ICU admission and start MV (median [IQR]) (d)	10.00 [6.00, 11.00]	11.00 [8.50, 14.00]	0.28
Length of ICU stay and MV at the time of the CT scan (median [IQR]) (d)	0.00 [0.00, 0.00]	12.50 [10.00, 14.75]	< 0.001
Positive PCR for SARS-COV2, n (%)	11 (78.6)	13 (92.9)	0.60
Prone positioning, n (%)	11 (78.6)	13 (92.9)	0.60
Comorbidities, n (%)			
COPD	0 (0.0)	1 (7.1)	0.39
Cardiovascular disease	4 (28.6)	1 (7.1)	0.17
Hypertension	7 (50.0)	7 (50.0)	1.00
Diabetes mellitus	4 (28.6)	5 (35.7)	0.92
Laboratory values*			
C-reactive protein (median [IQR]) (mmol/L)	98 [58, 169]	158 [43, 257]	0.64
Creatinine (median [IQR]) (mmol/L)	65 [57, 88]	137 [80, 181]	0.016
D-dimer (median [IQR]) (mmol/L)	3.7 [1.1, 5.7]	4.1 [2.4, 7.8]	0.34
Ventilation and oxygenation†			
PEEP (median [IQR]) (cm H_2O)	10 [10, 14]	8 [6, 10]	0.017
Driving pressure (median [IQR]) (cm H_2O)	15 [11, 17]	15 [11, 16]	0.85
Plateau pressure (median [IQR]) (cm H_2O)	27 [22, 33]	22 [18, 26]	0.098
Crs (median [IQR]) (mL/cm H_2O)	24.6 [20.2, 33.6]	28.5 [26.4, 36.3]	0.17
TV per PBW (median [IQR]) (mL/kg)	5.7 [5.2, 6.2]	5.9 [5.6, 6.8]	0.38
Respiratory rate (median [IQR]) (/min)	25 [24, 30]	26 [20, 31]	0.64
Minute volume ventilation (median [IQR]) (L/min)	9.0 [8.6, 10.7]	10.3 [9.6, 12.6]	0.12
I:E 1: (median [IQR])	2.00 [1.43, 2.00]	2.94 [2.12, 3.52]	0.012
PaO_2 (median [IQR]) (kPa)	10.4 [8.9, 11.0]	9.6 [8.8, 10.3]	0.30
FiO_2% (median [IQR])	80 [60, 100]	70 [42, 84]	0.18
PaO_2/FiO_2 (median [IQR]) (mm Hg)	95.6 [74.3, 145.3]	107.3 [75.8, 182.4]	0.70
$PaCO_2$ (median [IQR]) (kPa)	6.4 [5.9, 8.2]	8.6 [6.5, 9.5]	0.12
$etCO_2$% (median [IQR])	5.4 [4.8, 6.3]	6.5 [5.5, 7.7]	0.027
Ventilatory ratio (median [IQR])	1.9 [1.7, 3.0]	2.4 [2.2, 3.1]	0.21
Patient outcomes			
Duration of MV days (median [IQR])	8.5 [5.5, 14.5]	16.5 [13.5, 30.5]	0.017
Total duration ICU stay days (median [IQR])‡	9.5 [6, 16]	16 [13, 27]	0.063
ICU mortality, n (%)	3 (21.4)	5 (35.7)	0.56

*Laboratory values available closest to CT.
†Ventilation and oxygenation characteristics just before the CT scan.
‡Patients were discharged to the medical ward.
COPD indicates chronic obstructive pulmonary disease; C$_{rs}$, respiratory system compliance; etCO$_2$, end-tidal carbon dioxide; FiO$_2$, fraction of inspired oxygen; I:E, inspiration:expiration ratio; MV, mechanical ventilation; PaCO$_2$, partial pressure of carbon dioxide; PaO$_2$, partial pressure of oxygen; PBW, predicted body weight; TV, tidal volume.

TABLE 2. CT Measurements at High and Low PEEP Stratified for Early and Late CT Scans

Characteristic	Patients With Early CT Scan (N = 14)			Patients With Late CT Scan (N = 14)		
	Low PEEP	High PEEP	P	Low PEEP	High PEEP	P
PEEP level (median [IQR]) (cm H_2O)	10 [10, 14]	20 [20, 20]	< 0.001	8 [6, 10]	20 [20, 20]	< 0.001
Lung weight (median [IQR]) (g)	1343 [938, 1495]	1468 [1022, 1608]	0.38	1656 [1444, 1713]	1675 [1453, 1798]	0.67
Lung weight nonaerated lung tissue (median [IQR]) (g)	542 [247, 677]	206 [62, 349]	0.01	396 [326, 571]	253 [146, 373]	0.03
Lung volume (median [IQR]) (mL)	2293 [1740, 2522]	2856 [2645, 3386]	0.01	2726 [2490, 3295]	3497 [2855, 3776]	0.07
End-expiratory lung volume (median [IQR]) (mL)	882 [772, 1149]	1583 [1328, 1905]	0.01	1115 [849, 1285]	1688 [1163, 2179]	0.03
Proportion of nonaerated lung tissue (median [IQR]) (%)	23 [12, 32]	5 [2, 13]	0.01	15 [12, 22]	8 [5, 12]	0.003
Proportion of poorly aerated lung tissue (median [IQR]) (%)	28 [24, 34]	29 [18, 37]	0.95	42 [25, 49]	34 [24, 44]	0.43
Proportion of normally aerated lung tissue (median [IQR]) (%)	47 [37, 57]	62 [48, 77]	0.04	40 [30, 53]	57 [46, 67]	0.06
Proportion of hyperinflated lung tissue (median [IQR]) (%)	0 [0, 1]	1 [0, 1]	0.21	0 [0, 0]	0 [0, 1]	0.11

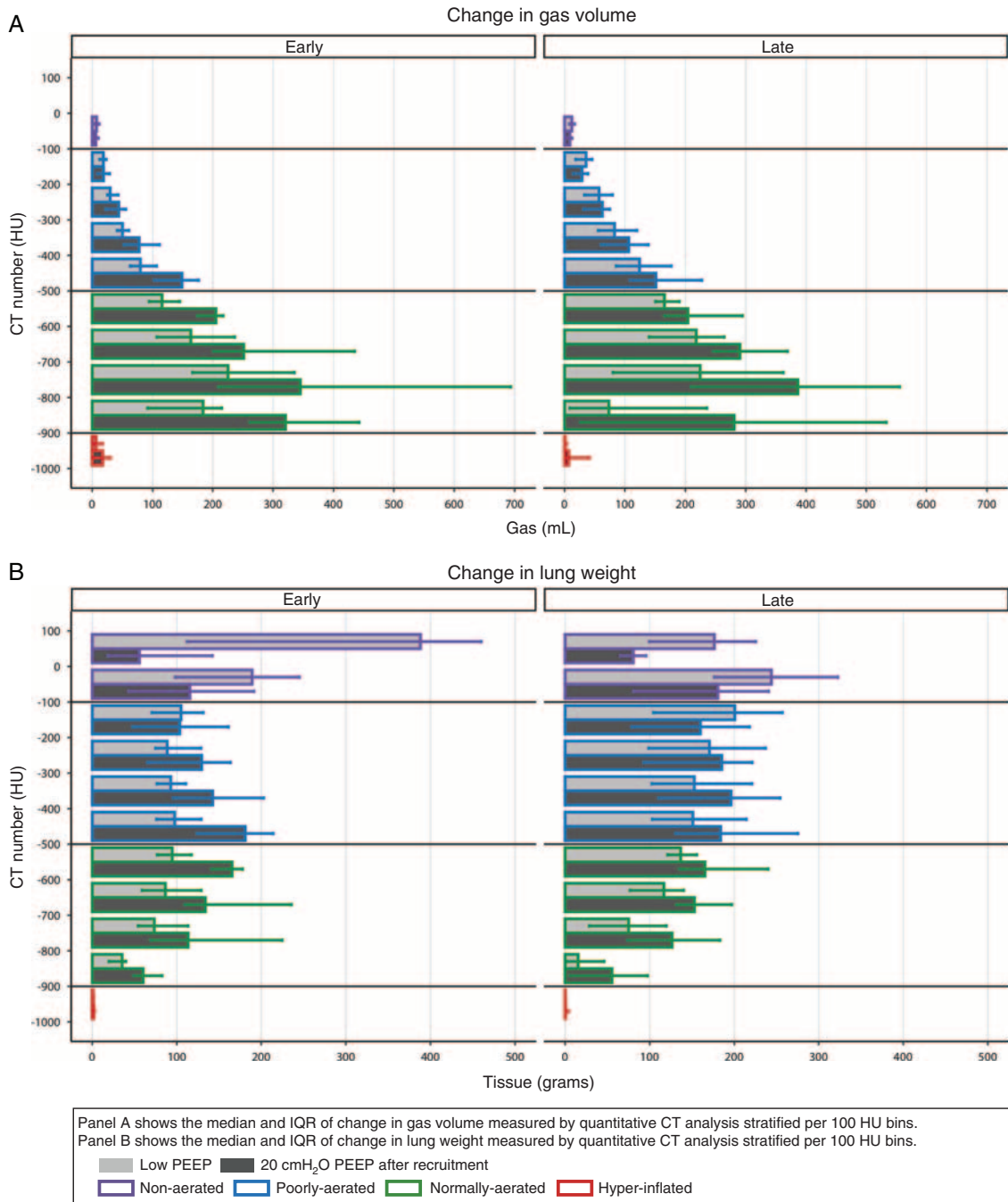CT indicates computed tomography; PEEP, Positive end-expiratory pressure; IQR, interquartile range.

FIGURE 2. Distribution of change in gas volume and weight stratified for early/late timing of the scan. full color online

17.5 mL] in patients with a late CT scan ($P = 0.40$ between early and late). In one patient, an increase in hyperinflated volume of 570 mL was observed after recruitment (Fig. 2). The increase in hyperinflated lung volume was not correlated with the amount of reaeration of nonaerated lung tissue (Spearman $\rho = 0.27$, $P = 0.17$).

DISCUSSION

The main finding of our study was that the majority of critically ill patients with COVID-19-related ARDS

undergoing invasive ventilation showed substantial reaeration of lung consolidations after recruitment and ventilation at high PEEP. The amount of reaerated lung was higher in patients with an early CT scan at the start of intubation and ventilation than in patients with a late CT scan who were already invasively ventilated for several days.

In this study, the median percentage of reaerated lung tissue was 14%. This is markedly higher and more variable between patients compared with a previous CT study in COVID-19-related ARDS.[23] A possible explanation for these contrasting findings is the absence of a recruitment maneuver and the lower
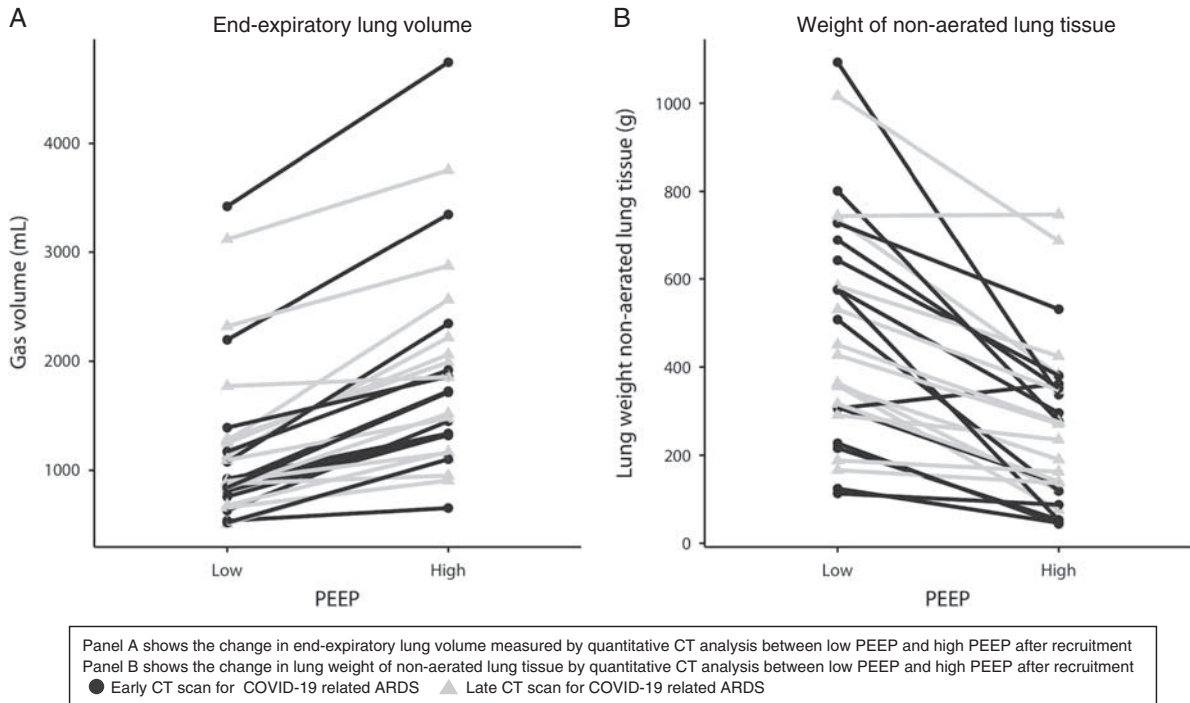
A End-expiratory lung volume

B Weight of non-aerated lung tissue

Panel A shows the change in end-expiratory lung volume measured by quantitative CT analysis between low PEEP and high PEEP after recruitment
Panel B shows the change in lung weight of non-aerated lung tissue by quantitative CT analysis between low PEEP and high PEEP after recruitment
● Early CT scan for COVID-19 related ARDS   ▲ Late CT scan for COVID-19 related ARDS

FIGURE 3. Change in end-expiratory lung volume and weight of nonaerated lung tissue after recruitment.

Hyperinflated lung
-1000 to -901 HU

Normally aerated lung
-900 to -501 HU

Poorly aerated lung
-500 to -101 HU

Non-aerated lung
-100 to 100 HU

Low PEEP   High PEEP

Re-aerated lung

Non re-aerated lung

Top panel: CT scans of two patients with re-aerated lungs. On the left the CT image at low PEEP and on the right the same slice at high PEEP. **Bottom panel:** CT scans of two patients with non re-aerated lungs. On the left the CT image at low PEEP and on the right same slice at high PEEP.

FIGURE 4. Overview of CT scans of reaerated and nonreaerated lungs.

PEEP levels used in the previous study. The presence of a recruitment maneuver is the main difference between the previous and present study, suggesting that it might be an essential step to achieve reaeration in COVID-19-related ARDS patients. The percentage of reaerated lung tissue was in fact comparable to a previous study in non–COVID-19-related ARDS,[15] although the present study used significantly lower levels of airway pressure after recruitment and thus might result in an underestimation of reaeration potential. Also in line with previous studies in non–COVID-19-related ARDS, there was considerable variation in lung reaeration that was partly explained by the nonaerated lung tissue weight.[24] Duration of mechanical ventilation was also associated with lung reaeration, with a less reaeration potential later in the course of COVID-19-related ARDS. This has not been noticed in studies carried out in patients with non–COVID-19-related ARDS.[15] A limited volume of hyperinflated lung tissue was observed; however, we did not perform an inspiratory CT scan and therefore cannot exclude further hyperinflation during inspiration. We rarely observed > 50 mL over distended lung volume at 20 cm H_2O PEEP, whereas others have reported > 100 mL median over distended lung volume at 15 cm H_2O PEEP in non–COVID-19-related ARDS.[24] Moreover, the amount of hyperinflated lung in the present study was markedly lower compared with a previous study in COVID-19-related ARDS as well, even though both studies performed CT during the end of expiration.[23] However, in the assessment of hyperinflation, comparison between studies is hampered by the influence of CT reconstruction parameters.[25]

Using high enough airway pressures, lung reaeration can nearly always be realized. However, high airway pressures are associated with significant risks.[11,26] Therefore, routine or preventive recruitment maneuvers should not be used and, when used, should be tailored to the patients' respiratory and hemodynamic condition. Our finding that lungs of patients with COVID-19-related ARDS can be opened by moving from 10 to 20 cm H_2O PEEP seems promising for the use of higher PEEP to maintain lung-protective mechanical ventilation. In clinical practice, increasing airway pressures must always be balanced against changes in hemodynamics, dead space ventilation, oxygenation, and lung mechanics and evidence-based management, informed by bedside physiology, is recommended.[27] A recent study suggests that patients with COVID-19-related ARDS show less improvement in respiratory mechanics and CO_2 clearance in response to an increase in PEEP.[28] Our study contradicts several smaller case series in COVID-19-related ARDS that showed limited recruitability.[7,29] Yet, our study and a previous study that quantified reaeration based on the recruitment-to-inflation ratio show that the lungs of patients with COVID-19-related ARDS can be reopened.[30] This may be explained by the difference in the technique for assessment of recruitment or might be the consequence of a different case-mix. Alternatively, higher transpulmonary pressures may result in reaeration, but impair gas-exchange when pulmonary angiopathy is prevalent, as has been suggested in COVID-19.[31] This does not, however, provide an explanation for the lack of improvement in compliance that has been reported.[28]

We also tested the association between the level of lung reaeration and previously described phenotypes because we recognize that ARDS is a heterogeneous syndrome with distinct subphenotypes and speculated that this would also apply to COVID-19-related ARDS.[32–34] Reaeration was not different between patients with a focal or nonfocal lung morphology. Lung morphology is a validated predictor of reaeration potential and likelihood of overdistention in non–COVID-19-related ARDS.[16] In that study, lung morphology was assessed at 0 PEEP, whereas the lungs of patients included in the current study were exposed to at least 5 cm H_2O PEEP and most frequently to 10 cm H_2O PEEP. This might bias the results toward focal morphology, as ventral consolidations are more likely to be opened up at lower PEEP levels. Furthermore, the proposed "L" and "H" phenotype classification was not associated with response to recruitment maneuvers in our study as both compliance of the respiratory system and lung weight were not associated with the potential for lung reaeration.[35] In addition, we found that patients who were just intubated were more likely to respond to recruitment maneuvers than patients who received several days of ventilation, which is inconsistent with the hypothesis that patients progress from an "L" to an "H" phenotype.[9,35] Taken together, we confirmed considerable heterogeneity in reaeration potential, consistent with the hypothesis that there is no "typical ARDS,"[33] but failed to confirm the association with particular subphenotypes that increase the likelihood of reaeration in this study.

The main strength of this study is that it provides quantitative imaging data on lung reaeration in patients with severe COVID-19 pneumonia. The validity and reliability of the results are strong, as CT scans were analyzed in a quantitative manner, which is considered the gold standard for assessing aeration of lung tissue. Our study had an adequate sample size that is comparable to non-COVID-19 studies on lung reaeration in ARDS.

Limitations of this study include the absence of data on respiratory mechanics, dead space, and shunt, as we were limited to clinically available data. Lung recruitment in non–COVID-19-related ARDS patients measured by respiratory mechanics and CT shows a very modest correlation in previous studies because respiratory mechanics determine recruitment as improvement of mechanical properties in an already inflated lung, whereas CT assesses recruitment as reaeration of a nonaerated lung.[24] The differences between tissue recruitment and physiological recruitment are referred to as the "recruitment paradox," and our data should be interpreted in this light.[36] The low PEEP CT-scan was performed at the PEEP level that was used just before the CT scans and varied between patients because the CT-scans were performed as part of clinical practice. In a proportion of patients with an early CT scan, the PEEP level at the low PEEP scan was only marginally lower than at the high PEEP scan, which could underestimate the potential for reaeration of the lungs in these patients. However, we found more rather than less reaerated lung tissue in this group, suggesting that this could not be attributed to differences in delta pressure. Furthermore, some patients were ventilated in pressure support mode, which limits the interpretation of respiratory mechanics. Selection bias could have occurred, especially in the group of patients who underwent late chest CT scans, while treating physicians only demanded a chest CT scan in patients with worsening respiratory failure. For the other patients, we have clearly described the risk of selection bias by providing an overview of all consecutive patients.

In conclusion, the majority of critically ill patients with COVID-19-related ARDS undergoing invasive ventilation showed substantial reaeration of lung consolidations after recruitment and ventilation at high PEEP. Higher PEEP can be considered in patients with reaerated lung consolidations when accompanied by improvement in compliance and gas exchange in a similar way as done in patients with ARDS due to a cause other than COVID-19.

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