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Original Article

Evolution of respiratory system compliance and potential for lung recruitment in COVID-19–induced acute respiratory distress syndrome ☆

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has been frequently complicated by severe acute respiratory distress syndrome (ARDS) with prolonged invasive ventilation. While respiratory system compliance and lung recruitability have been described within the first days after ICU admission, data about their longitudinal changes are still limited. Therefore, we conducted this study to assess the evolution of respiratory system compliance and lung recruitability in patients with COVID-19–related ARDS.

Method: We conducted a prospective single-center study in patients admitted for COVID-19–related ARDS during the first wave of the pandemic, from March 16, 2020 to April 10, 2020. Respiratory system compliance was calculated daily at clinical positive end-expiratory pressure (PEEP) during passive breathing. The potential for lung recruitment was assessed by measuring the volume derecruited between PEEP 15 cmH_2O and 5 cmH_2O, and using the calculation of the recruitment-to-inflation ratio (R/I ratio). Recruitable lung was considered when the R/I ratio was at least 0.5. The primary outcome was the evolution of respiratory mechanics over time. The secondary outcome was the evolution of lung recruitability over time.

Results: Thirty-two patients were included in this study. The respiratory mechanics were assessed 222 times (7 ± 5 times per patient). Respiratory system compliance at clinical PEEP was 29.1 mL/cmH_2O (interquartile range [IQR]: 24.1–33.9 mL/cmH_2O) and decreased significantly over time (P <0.0001). Lung recruitability was assessed in 22 out of the 32 patients (60 assessments). The median volume derecruited between PEEP 15 cmH_2O and 5 cmH_2O was 246.8 mL (IQR: 180.8–352.2 mL) and the median R/I ratio was 0.56 (IQR: 0.39–0.73). Neither changed significantly over time. The proportion of patients with recruitable lung was 50.0% (6/12) within the first 3 days after intubation, 69.2% (9/13) between day 4 and day 7, and 66.7% (8/12) after day 7 (P=0.7934).

Conclusions: In our cohort, respiratory system compliance was low and decreased over time. The potential for lung recruitment was high and persisted despite prolonged mechanical ventilation, suggesting that maintaining high PEEP levels in the later course of COVID-19 could be adequate.

Introduction

The recent coronavirus disease 2019 (COVID-19) pandemic affected millions of people and caused several thousand deaths worldwide.[1] Although most patients had good outcomes, COVID-19 has been frequently complicated by severe respiratory failure with bilateral lung infiltrates and hypoxemia requiring intubation and invasive mechanical ventilation. Once intubated, most patients met the criteria for acute respiratory distress syndrome (ARDS) according to the Berlin definition. [2] COVID-19–related ARDS is associated with particularly prolonged ICU stay [3–6] and high mortality rates. [7]

The management of patients with COVID-19–related ARDS has been debated since the onset of the pandemic. Based on the analysis of a small cohort,[8] key opinion leaders hypothesized that respiratory system compliance was relatively high and that

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lung recruitability was lower than non-COVID ARDS in the early course of the disease.[9] Hence, they suggested setting the ventilator differently than in non-COVID ARDS, including large tidal volume and low positive end-expiratory pressure (PEEP) in the early phase of the disease.[9], [10]

However, many subsequent large-scale studies showed that respiratory system compliance in COVID-19–related ARDS was slightly higher than in non-COVID ARDS, and that this difference was not clinically meaningful.[11–16] Similarly, lung recruitability was not lower in COVID-19–related ARDS than in non-COVID-19–ARDS, and some studies even found higher lung recruitability in COVID-19–related ARDS.[17] Therefore, the management of ARDS should probably not differ from that of non-COVID ARDS.[18]

However, respiratory system compliance and lung recruitability in patients with COVID-19–related ARDS have mainly been described within the first days of intensive care unit (ICU) admission,[3], [19], [20] and data about the longitudinal changes of respiratory mechanics are scarce.[21] As these patients have a longer duration of mechanical ventilation than those with other viral ARDS,[22] knowledge of the evolution of respiratory system compliance and lung recruitability over time may be crucial with respect to individualizing ventilation.

Therefore, we conducted a prospective study to assess the evolution of respiratory system compliance and lung recruitability in patients with COVID-19–related ARDS.

Methods

Study

This prospective, single-center, observational study was conducted in the medical ICU at the University Hospital of Poitiers, France. Data collection was approved by the hospital's local ethics committee (CHU86-RECH-R2020–11–02), and informed consent was waived given the observational nature of the study.

Patients

From March 16, 2020 to April 10, 2020, all patients admitted to our ICU for COVID-19–related ARDS infection according to the Berlin definition [2] were included. Patients not intubated or intubated for reasons other than COVID-19 infection, those with hemodynamic instability defined based on norepinephrine dose requirement ≥1 μg/kg/min, those with partial pressure of oxygen(PaO_2)/fraction of inspired oxygen(FiO_2) <80 mmHg at the time of measurements, those with severe chronic obstructive lung disease, and those with raised intracranial pressure were excluded.

Management of patients

In our unit, the management of COVID-19–related ARDS did not differ from the usual management of non-COVID ARDS that included the use of low tidal volume ventilation of 6 mL/kg of predicted body weight (PBW), high PEEP targeting plateau pressure of 28–30 cmH_2O when PaO_2/FiO_2 was ≤200 mmHg,[23] neuromuscular blockers when PaO_2/FiO_2 was <150 mmHg,[24] and 16-h sessions of prone positioning when PaO_2/FiO_2 remained <150 mmHg despite neuromuscular blockers.[25] Extracorporeal membrane oxygenation was initiated when PaO_2/FiO_2 was ≤80 mmHg for >6 h, <50 mmHg for >3 h, or pH was <7.25 with $PaCO_2$ >60 mmHg.[26] Patients were extubated after a 1-h successful spontaneous breathing trial with low-level of pressure support when awake with PaO_2/FiO_2 ≥150 mmHg with PEEP ≤8 cmH_2O and FiO_2 ≤40%.

Data collection

Baseline characteristics such as age, sex, body mass index, and severity scores[27], [28] were collected at ICU admission. Time from the first symptoms to ICU admission; first-line noninvasive ventilation strategies; time from ICU admission to intubation; respiratory mechanics; results from the first arterial blood gas analysis after intubation; prone positioning; extracorporeal membrane oxygenation; and outcomes such as duration of mechanical ventilation, duration of extracorporeal membrane oxygenation, length of ICU stay, and in-ICU mortality were collected.

Clinical plateau pressure, PEEP, tidal volume, respiratory rate, and the corresponding arterial blood gas analyses were collected daily during passive ventilation in supine position from electronic charts (Metavision Software, MDsoft, Wakefield, MA, USA). Passive ventilation was defined as measured respiratory rate equal to the set respiratory rate with stable plateau pressure and expired tidal volume >3 min on the electronic charts. Values were validated individually by attending nurses during their rounds.

Assessment of lung recruitability

On a daily basis, potential for lung recruitment was assessed by calculation of the recruitment-to-inflation ratio (R/I ratio) during a single-breath PEEP reduction maneuver as previously described.[29] Measurements were performed in supine semi-recumbent position, with the head of the bed elevated at 30°, in volume-controlled mode with tidal volume of 6 mL/kg of PBW, and a constant inspiratory flow of 60 L/min. For patients with spontaneous breathing efforts before or during the assessment, the maneuver was aborted. First, PEEP was set at 15 cmH_2O for 10 min, and respiratory rate was decreased to 10 breaths/min to eliminate intrinsic PEEP. Expired tidal volume at PEEP 15 cmH_2O was collected. PEEP was then decreased to 5 cmH_2O over one breath. The first expired tidal volume after PEEP reduction and plateau pressure at PEEP 5 cmH_2O was collected. Low-flow (5 L/min) inflation pressure-time curve from PEEP 5 cmH_2O was performed to detect airway closure. Airway opening pressure (AOP) was defined by the airway pressure corresponding to the inflection point on pressure-time curve, whenever present. Clinical ventilator settings were then resumed. Of note, clinical ventilator settings were not adjusted according to the R/I ratio as the benefits of R/I ratio-adjusted management have yet to be proven. Doses of sedatives and neuromuscular blockers at the time of R/I ratio assessment were collected.

Calculations

Airway closure was considered in all calculations given that it significantly influences respiratory mechanics.[30] Respiratory system compliance at clinical PEEP was calculated as follows:

tidal volume/(clinical plateau pressure – the highest value between clinical total PEEP or AOP). PEEP reduction was calculated as PEEP 15 cmH_2O minus the highest value between PEEP 5 cmH_2O and AOP. Volume derecruited between PEEP 15 cmH_2O and 5 cmH_2O or AOP was computed as the first expired tidal volume after PEEP reduction minus set tidal volume minus predicted volume (calculated as compliance at PEEP 5 cmH_2O × PEEP reduction). Compliance of the derecruited lung was calculated as volume derecruited/PEEP reduction. R/I ratio was calculated as compliance of the recruited lung/compliance at PEEP 5 cmH_2O. An R/I ratio of ≥0.5 was indicative of a recruitable lung.[29]

Outcomes

The primary outcome was the relationship between respiratory mechanics and time in patients with COVID-19–related ARDS. The secondary outcome was the relationship between lung recruitability and time in patients with COVID-19–related ARDS.

Statistical analysis

Continuous variables were described as mean ± standard deviation or median (interquartile range [IQR]: 25th–75th percentiles) according to their distribution. Categorical variables were described as number (percentage). To test the relationship among compliance, volume recruited, and R/I ratio over time, linear mixed-effect regression models were performed considering random effect for patients and fixed effect for time since intubation. Additionally, time was arbitrarily categorized into three time intervals according to the day of intubation: within the first 3 days, between day 4 and day 7, and after day 7. Values of compliance, volume recruited, and R/I ratio at each time interval were compared using Kruskal–Wallis test for continuous variables and Fisher's exact test for categorical variables. No imputation for missing data was carried out. Two-tailed *P*-value <0.05 was considered to indicate statistical significance. Statistical analyses were performed using R software (https://www.r-project.org).

Results

Population

Among the 38 patients admitted for COVID-19 infection during the study period, 32 (84.2%) required invasive mechanical ventilation, and all of them met the Berlin definition for ARDS [Figure 1]. Ventilators used for patients' management were EVITA XL ventilator (Draeger, Lübeck, Germany) in 20 out of 32 patients (62.5%), Carescape R860 ventilator (General Electrics Healthcare, Chicago, IL, USA) in 11 patients (34.4%), and Servo I ventilator (Getinge, Göteborg, Sweden) in one patient (3.1%). Characteristics of patients included are displayed in Table 1. Median (IQR) time from first symptoms to ICU admission was 10.0 (6.0–12.0) days, and from ICU admission to intubation was 1.0 (1.0–2.0) days. Median PaO_2/FiO_2 after intubation was 125.0 (88.0–188.0) mmHg. Prone positioning was required in 75.0% cases (24/32), and extracorporeal membrane oxygenation in 12.5% cases (4/32 patients). Duration of mechanical ventilation was 18.0 (11.0–25.3) days and in-ICU mortality was 18.8% (6/32).

Table 1
Baseline characteristics and outcomes (*n* = 32).

Variables	Data
Baseline characteristics	
Age (years)	65.0 (55.8–70.0)
Sex (female)	5 (15.6)
Body mass index (kg/m^2)	29.5 (26.1–32.8)
Comorbidities	
Diabetes	8 (25.0)
Hypertension	15 (46.9)
Immunosuppression	1 (3.1)
Underlying chronic cardiac disease	3 (9.4)
Underlying chronic lung disease	5 (15.6)
Simplified Acute Physiology Score 2	39.5 (32.8–42.3)
Sequential Organ Failure Assessment score	4.0 (3.0–4.0)
Management before intubation	
Time from first symptoms to ICU admission (days)	10.0 (6.0–12.0)
Time from ICU admission to intubation (days)	1.0 (1.0–2.0)
High-flow nasal oxygen	14 (43.8)
Time of therapy (days)	0.0 (0.0–1.0)
Non-invasive ventilation	2 (6.2)
Time of therapy (days)	0.0 (0.0–0.0)
Management after intubation	
Tidal volume (mL/kg)	6.0 (5.9–6.2)
Respiratory rate (breaths/min)	28.0 (25.5–30.0)
PEEP (cmH_2O)	12.0 (8.0–13.5)
Plateau pressure (cmH_2O)	26.0 (23.0–27.0)
Respiratory system compliance (mL/cmH_2O)	29.3 (23.9–35.0)
PaO_2/FiO_2 after intubation (mmHg)	125.0 (88.0–188.0)
$PaCO_2$ after intubation (mmHg)	46.5 (41.0–49.5)
Ventilatory ratio	2.1 (1.7–2.2)
Prone positioning	24 (75.0)
Number of sessions	3.0 (1.8–4.0)
Extracorporeal membrane oxygenation	4 (12.5)
Outcomes	
Duration of mechanical ventilation (days)	18.0 (11.0–25.3)
Duration of extracorporeal membrane oxygenation (days)	13.5 (7.0–20.3)
Length of ICU stay (days)	21.5 (16.0–29.0)
In-ICU mortality	6 (18.8)

Data are expressed as median (IQR) or *n* (%).
ICU: Intensive care unit; IQR: Interquartile range; $PaCO_2$: Partial pressure of carbon dioxide in artery; PaO_2/FiO_2: partial pressure of oxygen/fraction of inspired oxygen; PEEP: Positive end-expiratory pressure.

Evolution of respiratory mechanics over time

Respiratory mechanics were assessed 222 times (7 ± 5 times per patient) during the ICU stay. The median (IQR) tidal volume was 6.0 (5.9–6.2) mL/kg of PBW, PEEP was 12.0 (10.0–14.0) cmH_2O, plateau pressure was 25.0 (23.0–28.0) cmH_2O, and respiratory system compliance at clinical PEEP was 29.1 (24.1–

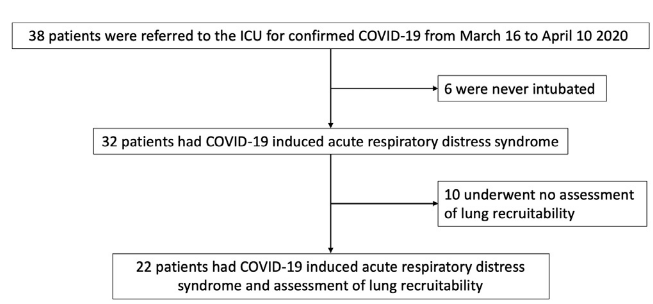

Figure 1. Flowchart of patients included in the study.
COVID-19: Coronavirus disease 2019.

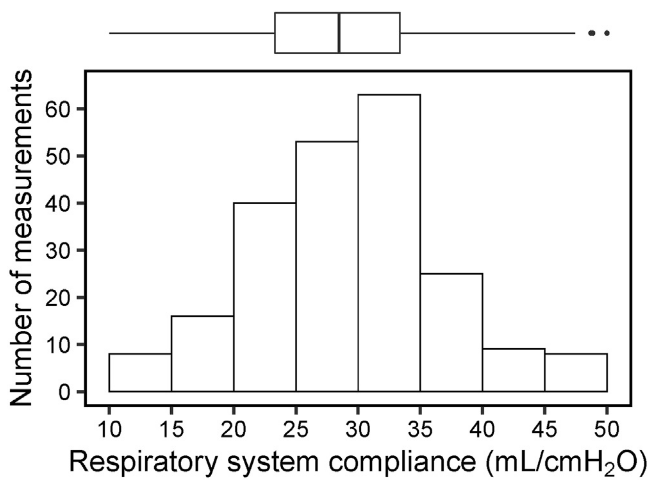

Figure 2. Distribution of respiratory system compliance at clinical PEEP in the 32 patients included (222 measurements, 7 ± 5 measures per patient). Boxplot shows the 25th, 50th, and 75th percentiles (box); 10th and 90th percentiles (whiskers); and outlying points (circles).
PEEP: Positive end-expiratory pressure.

33.9) mL/cmH_2O. Distribution of respiratory system compliance at clinical PEEP is displayed in Figure 2. Compliance at clinical PEEP decreased significantly over time (*P* <0.0001): from median 34.4 mL/cmH_2O (IQR: 29.2–37.2 mL/cmH_2O) within the first 3 days after intubation to 30.8 mL/cmH_2O (IQR: 27.4–34.4 mL/cmH_2O) between day 4 and day 7, and 27.4 mL/cmH_2O (IQR: 21.3–32.0 mL/cmH_2O) after day 7 ($P_{Kruskal\text{-}Wallis}$ <0.0001, Figure 3).

Evolution of lung recruitability over time

Lung recruitability was assessed in 22 of the 32 patients (60 assessments). Three out of 22 patients (13.6%), accounting for five assessments, had airway closure with median AOP of 5 cmH_2O, 7 cmH_2O, and 8 cmH_2O, respectively. All patients were treated with sedatives and neuromuscular blockers at the time of R/I ratio assessment. Median (IQR) doses were 10.0 (10.0–13.1) mg/h for midazolam, 150.0 (112.5–150.0) mg/h for propofol, 10.0 (10.0–15.0) μg/h for sufentanil, 40.0 (40.0–40.0) mg/h for atracurium, and 20.0 (15.0–20.0) mg/h for cisatracurium.

The volume derecruited between PEEP 15 cmH_2O and 5 cmH_2O was 246.8 (IQR: 180.8–352.2) mL [Figure 4] and did not significantly change over time: 237.5 (IQR: 187.4–372.0) mL within the first 3 days after intubation, 270.5 (IQR: 179.3–380.1) mL between day 4 and day 7, and 222.5 (IQR: 179.7–284.4) mL after day 7 ($P_{Kruskal\text{-}Wallis}$=0.4678, Figure 5). The volume derecruited exceeded 150 mL in 11 out of 13 cases (84.6%) within the first 3 days after intubation, in 21 out of 24 cases (87.5%) between day 4 and day 7, and in 19 out of 23 cases (82.6%) after day 7 (*P*=0.9007).

The median R/I ratio was 0.56 (IQR: 0.39–0.73) [Figure 6] and did not significantly change over time: 0.50 (IQR: 0.42–0.64) between day 1 and day 3, 0.61 (IQR: 0.39–0.77) between day 4 and day 7, and 0.52 (IQR: 0.39–0.75) after day 7 ($P_{\text{Kruskal-Wallis}}$=0.7601, Figure 7). The proportion of patients with recruitable lung was 50.0% (6/12) within the first 3 days after intubation, 69.2% (9/13) between day 4 and day 7, and 66.7% (8/12) after day 7 (*P*=0.7934).

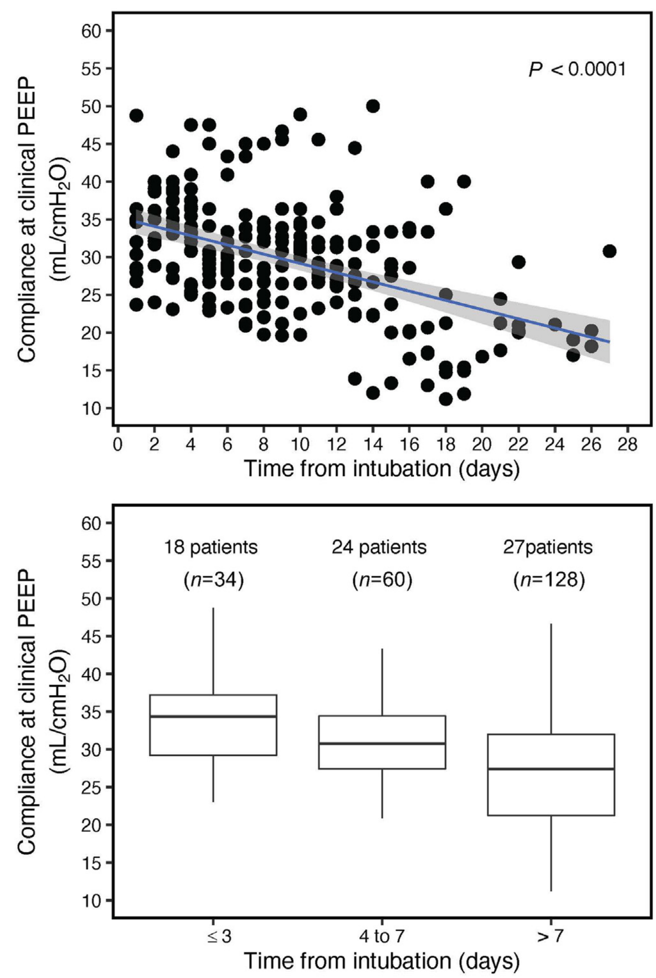

Figure 3. Evolution of respiratory system compliance at clinical PEEP over time as a continuous variable in the upper panel (*P* <0.0001), and as a discretized variable in the low panel in the 32 included patients.
PEEP: Positive end-expiratory pressure.

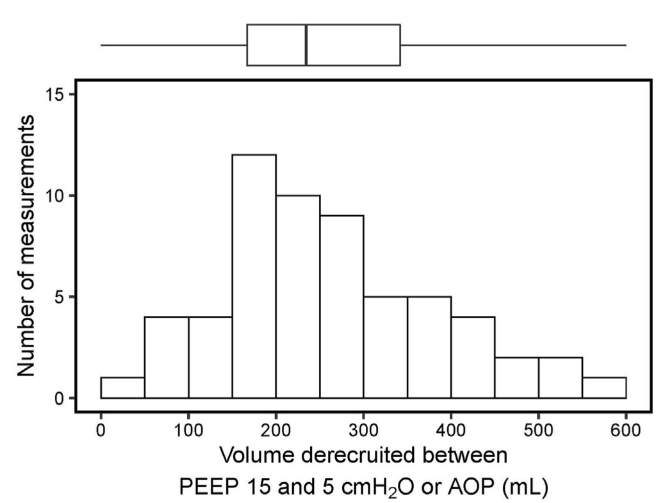

Figure 4. Distribution of volume derecruited in the 22 patients whose recruitability was assessed (60 measurements, 2 ± 2 measures per patient). Boxplot shows the 25th, 50th, and 75th percentiles (box); 10th and 90th percentiles (whiskers); and outlying points (circles).
AOP: Airway opening pressure; PEEP: Positive end-expiratory pressure.

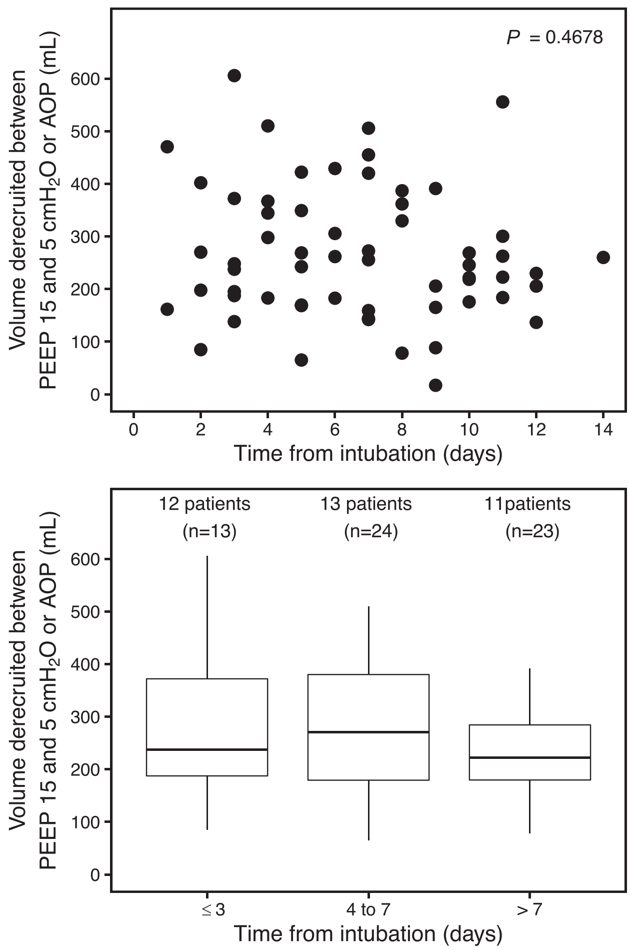

Figure 5. Evolution of volume derecruited over time as a continuous variable in the upper panel ($P > 0.9999$), and as a discretized variable in the low panel in the 22 included patients. AOP: Airway opening pressure; PEEP: Positive end-expiratory pressure.

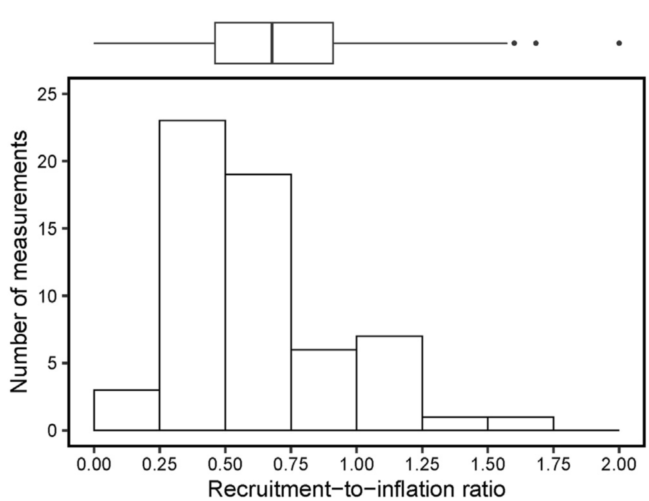

Figure 6. Distribution of recruitment-to-inflation ratio in the 22 patients whose recruitability was assessed (60 measurements, 2 ± 2 measures per patient). Box-plot shows the 25th, 50th, and 75th percentiles (box); 10th and 90th percentiles (whiskers); and outlying points (circles).

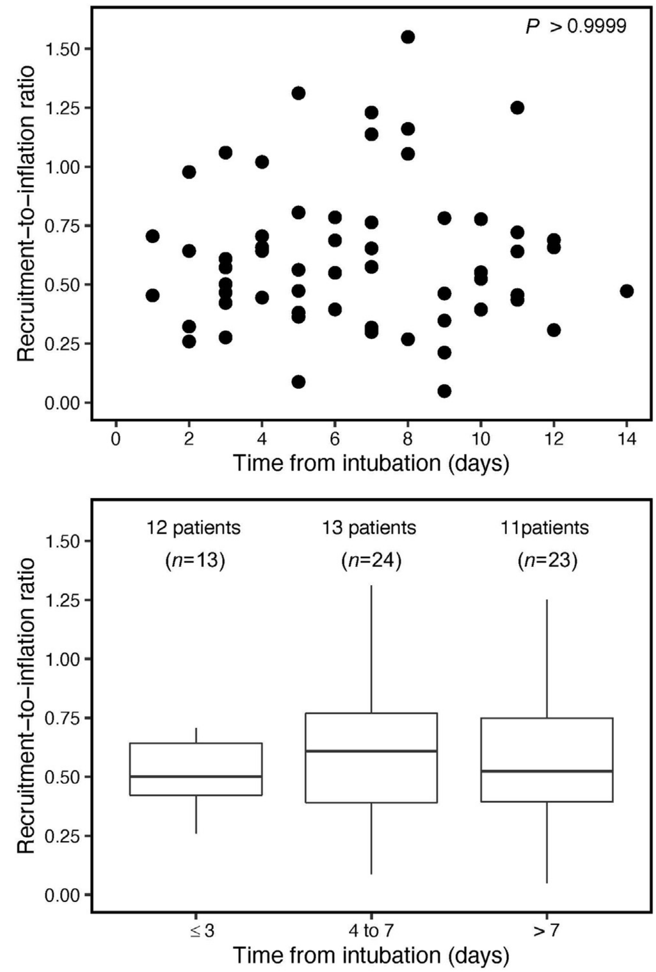

Figure 7. Evolution of recruitment-to-inflation ratio as a continuous variable in the upper panel ($P > 0.9999$), and as a discretized variable in the low panel in the 22 included patients.

Discussion

Our main findings were that respiratory system compliance was low, even within the first days after intubation, and significantly decreased over time. Despite this, most patients had recruitable lungs that persisted over a prolonged duration of mechanical ventilation.

Since the first reports, respiratory system compliance of COVID-19–related ARDS has been a hugely debated topic, with values ranging from very low in some cohorts[19] to almost normal in others.[8] Of note, these cohorts were single-centered and had very small sample sizes (12 and 16 patients, respectively). We hypothesize that these differences in respiratory system compliance can be explained by different first-line managements of patients with COVID-19. Indeed, strong breathing efforts have been reported in patients with COVID-19,[31] and the prolonged use of non-invasive ventilation in this setting may have worsened lung injury, thereby reducing respiratory system compliance.[32] Interestingly in our study, respiratory system compliance was in between the two above-mentioned extremes, and was in keeping with large multicenter observational cohorts,[7], [13] reinforcing the external validity of our results.

In our cohort, respiratory system compliance decreased over time. Data regarding the evolution of mechanical properties of the respiratory system are scarce in patients with COVID-19–related ARDS. In a cohort study comparing 112 patients with COVID-19–related ARDS matched to 198 patients with non-COVID-19 ARDS, respiratory system compliance was higher in the COVID-19 group than in the non-COVID group at day 1 after intubation, but not at day 3 or day 7.[33] In this study, 10% measurements were performed in pressure-support mode at day 1 and 28% at day 7.[33] Although the calculation of respiratory system compliance is feasible in the pressure-support mode,[34] this technique overestimates respiratory system compliance as compared to conventional calculation in controlled ventilation.[35] Therefore, respiratory system compliance reported in the COVID-19 group could have been overestimated at day 7.[33] By contrast, our reported respiratory system compliance was assessed exclusively in patients ventilated in volume-controlled mode, ruling out this potential bias. Additionally, we assessed respiratory mechanics only in patients who were ventilated passively. Therefore, patients for whom respiratory system compliance improved and who were weaned from sedatives or were switched to pressure-support mode were not assessed. As a consequence, decreased respiratory system compliance was relevant only for patients requiring deep sedation and/or neuromuscular blockers in the late course of the disease. Therefore, we can conclude that respiratory system compliance decreased over time in COVID-19 patients requiring prolonged passive ventilation. Decreased respiratory system compliance over time is in line with that reported in non-COVID ARDS patients who require prolonged mechanical ventilation,[36] and could be explained by the evolution of histological lung lesions over time. Diffuse alveolar damage is the classical histological feature of non-COVID ARDS,[37] and has also been observed in patients with COVID-19–related ARDS.[38], [39] Diffuse alveolar damage occurs preferentially after 3 days of evolution in non-COVID ARDS and can evolve to fibrosis from the second week of evolution, possibly leading to major loss of lung compliance.[36], [40], [41]

Lung recruitability was high in most patients in the first days after ICU admission. These results do not support the initial hypothesis raised by Gattinoni et al.,[9] whereby lung recruitability was low in the early course of COVID-19–related ARDS. However, this finding is in line with others who reported high lung recruitability in most patients within the first days after ICU admission.[20], [21], [42] Unlike decreased respiratory system compliance, we found that lung recruitability remained high over time in most patients. Data about the evolution of lung recruitability over time during COVID-19 are scarce. In a single-center study including 25 patients with COVID-19–related ARDS, lung recruitability was high at day 1 in 64% cases, and in 73% of the 15 patients whose lung recruitability was assessed at day 5.[21] Although the threshold defining high lung recruitability (R/I ratio ≥0.5) is debatable, our results suggest that PEEP could be kept high in patients with COVID-19 who were passively ventilated for a prolonged period and with a high potential for lung recruitment, despite decreased respiratory system compliance. Lung recruitability can be assessed using chest computed tomography,[43] electrical impedance tomography,[44] multiple low-flow inflation pressure-volume curves,[45] or the R/I ratio.[29] The volume derecruited during a single-breath maneuver between PEEP 15 cmH_2O and 5 cmH_2O is equivalent to the volume recruited using the multiple low-flow inflation pressure-volume curves method. With this technique, lungs are considered recruitable when the volume recruited exceeds the arbitrary cut-off of 150 mL.[46], [47] However, this threshold has some limitations. First, it does not consider the actual reduction of end-expiratory alveolar pressure. Indeed, when PEEP is decreased by 10 cmH_2O (from 15 cmH_2O to 5 cmH_2O), the alveolar pressure decreases by 10 cmH_2O only when the airways are open.[48] In patients with airway closure, the airways no longer communicate with the alveoli when airway pressure is below the AOP, and the AOP is considered the nearest measurable alveolar pressure.[29] As a consequence, when PEEP is decreased from 15 cmH_2O to 5 cmH_2O in patients with airway closure, the reduction of end-expiratory alveolar pressure could be estimated by the difference between 15 cmH_2O and the alveolar pressure at low PEEP, i.e., AOP, which is >5 cmH_2O. Therefore, the actual reduction of end-expiratory alveolar pressure is <10 cmH_2O, which may lead to smaller derecruited volume. Second, this threshold does not consider the size of the lung at low PEEP. Indeed, the clinical significance of the volume recruited may be different for a patient with a "large baby lung" (i.e., high respiratory system compliance at PEEP 5 cmH_2O) than for a patient with a "small baby lung" (i.e., low respiratory system compliance at PEEP 5 cmH_2O).[49] By contrast, for calculation of the R/I ratio, the volume derecruited during PEEP reduction is adjusted to the reduction of the end-expiratory alveolar pressure, taking airway closure into consideration, thereby allowing compliance of the derecruited lung to be calculated. Moreover, the compliance of the derecruited lung is normalized to the compliance of the "baby lung."[29] Therefore, this index accounts for interindividual variability in respiratory mechanics.

Our study has some limitations. First, the sample size was small and the study was single-centered. However, the characteristics of the included patients and the reported values of respiratory system compliance were similar to those previously reported.[7], [13] Second, we only reported respiratory system compliance and lung recruitability in the supine position. It is quite likely that prone positioning, which was performed in most of our patients, influenced respiratory system compliance and lung recruitability. Third, patients were included during the first wave of the pandemic, and none of them received corticosteroids in the early course of the disease. Whether the early use of dexamethasone influences respiratory mechanics is still unknown. Fourth, lung recruitability was assessed using the R/I ratio. Although adjustment of ventilator settings according to the R/I ratio seems relevant from a pathophysiological standpoint, its impact on outcomes remains to be tested (NCT03963622).

Conclusions

According to our cohort of COVID-19–related ARDS, respiratory system compliance was low and decreased over time. The potential for lung recruitment was high and persisted after prolonged mechanical ventilation, despite the reduction of respiratory system compliance. These findings suggest that maintaining high PEEP levels could be adequate in selected patients, even in the late course of COVID-19.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA 2020;324(8):782–93. doi:10.1001/jama.2020.12839.

[2] Definition Task Force ARDS, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012;307(23):2526–33. doi:10.1001/jama.2012.5669.

[3] Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. COVID-19 in critically Ill patients in the Seattle region – case series. N Engl J Med 2020;382(21):2012–22. doi:10.1056/NEJMoa2004500.

[4] Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, et al. Characteristics and outcomes of 21 critically Ill patients with COVID-19 in Washington State. JAMA 2020;323(16):1612–14. doi:10.1001/jama.2020.4326.

[5] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8(5):475–81. doi:10.1016/S2213-2600(20)30079-5.

[6] Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli 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;323(16):1574–81. doi:10.1001/jama.2020.5394.

[7] COVID-ICU Group on behalf of the REVA Network and the COVID-ICU InvestigatorsClinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med 2021;47(1):60–73. doi:10.1007/s00134-020-06294-x.

[8] 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):1299–300. doi:10.1164/rccm.202003-0817LE.

[9] Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes. Intensive Care Med 2020;46(6):1099–102. doi:10.1007/s00134-020-06033-2.

[10] Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. JAMA 2020;323(22):2329–30. doi:10.1001/jama.2020.6825.

[11] Brault C, Zerbib Y, Kontar L, Fouquet U, Carpentier M, Metzelard M, et al. COVID-19- versus non-COVID-19-related acute respiratory distress syndrome: differences and similarities. Am J Respir Crit Care Med 2020;202(9):1301–4. doi:10.1164/rccm.202005-2025LE.

[12] 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(1):529. doi:10.1186/s13054-020-03253-2.

[13] Grasselli G, Tonetti T, Protti A, Langer T, Girardis M, Bellani G, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med 2020;8(12):1201–8. doi:10.1016/S2213-2600(20)30370-2.

[14] Chiumello D, Camporota L, Gattinoni L, Marini JJ. Complexity and unanswered questions in the pathophysiology of COVID-19 ARDS. Intensive Care Med 2021;47(4):495–6. doi:10.1007/s00134-021-06353-x.

[15] Panwar R, Madotto F, Laffey JG, van Haren F. Compliance phenotypes in early acute respiratory distress syndrome before the COVID-19 Pandemic. Am J Respir Crit Care Med 2020;202(9):1244–52. doi:10.1164/rccm.202005-2046OC.

[16] Ziehr DR, Alladina J, Petri CR, Maley JH, Moskowitz A, Medoff BD, et al. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. Am J Respir Crit Care Med 2020;201(12):1560–4. doi:10.1164/rccm.202004-1163LE.

[17] Haudebourg AF, 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(2):287–90. doi:10.1164/rccm.202004-1226LE.

[18] Goligher EC, Ranieri VM, Slutsky AS. Is severe COVID-19 pneumonia a typical or atypical form of ARDS? And does it matter. Intensive Care Med 2021;47(1):83–5. doi:10.1007/s00134-020-06320-y.

[19] Pan C, Chen L, Lu C, Zhang W, Xia JA, Sklar MC, 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(10):1294–7. doi:10.1164/rccm.202003-0527LE.

[20] Mauri T, Spinelli E, Scotti E, Colussi G, Basile MC, Crotti S, 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):1129–34. doi:10.1097/CCM.0000000000004386.

[21] Beloncle FM, Pavlovsky B, Desprez C, Fage N, Olivier PY, Asfar P, et al. Recruitability and effect of PEEP in SARS-Cov-2-associated acute respiratory distress syndrome. Ann Intensive Care 2020;10(1):55. doi:10.1186/s13613-020-00675-7.

[22] Cobb NL, Sathe NA, Duan KI, Seitz KP, Thau MR, Sung CC, et al. Comparison of clinical features and outcomes in critically ill patients hospitalized with COVID-19 versus influenza. Ann Am Thorac Soc 2021;18(4):632–40. doi:10.1513/AnnalsATS.202007-805OC.

[23] Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA 2010;303(9):865–73. doi:10.1001/jama.2010.218.

[24] Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363(12):1107–16. doi:10.1056/NEJMoa1005372.

[25] Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368(23):2159–68. doi:10.1056/NEJMoa1214103.

[26] Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378(21):1965–75. doi:10.1056/NEJMoa1800385.

[27] Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. JAMA 1993;270(24):2957–63. doi:10.1001/jama.270.24.2957.

[28] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on sepsis-related problems of the European society of intensive care medicine. Intensive Care Med 1996;22(7):707–10. doi:10.1007/BF01709751.

[29] 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(2):178–87. doi:10.1164/rccm.201902-0334OC.

[30] Coudroy R, Vimpere D, Aissaoui N, Younan R, Bailleul C, Couteau-Chardon A, et al. Prevalence of complete airway closure according to body mass index in acute respiratory distress syndrome. Anesthesiology 2020;133(4):867–78. doi:10.1097/ALN.0000000000003444.

[31] Esnault P, Cardinale M, Hraiech S, Goutorbe P, Baumstrack K, Prud'homme E, et al. High respiratory drive and excessive respiratory efforts predict relapse of respiratory failure in critically ill patients with COVID-19. Am J Respir Crit Care Med 2020;202(8):1173–8. doi:10.1164/rccm.202005-1582LE.

[32] Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. Am J Respir Crit Care Med 2017;195(4):438–42. doi:10.1164/rccm.201605-1081CP.

[33] Beloncle F, Studer A, Seegers V, Richard JC, Desprez C, Fage N, et al. Longitudinal changes in compliance, oxygenation and ventilatory ratio in COVID-19 versus non-COVID-19 pulmonary acute respiratory distress syndrome. Crit Care 2021;25(1):248. doi:10.1186/s13054-021-03665-8.

[34] Bellani G, Grassi A, Sosio S, Foti G. Plateau and driving pressure in the presence of spontaneous breathing. Intensive Care Med 2019;45(1):97–8. doi:10.1007/s00134-018-5311-9.

[35] Bianchi I, Grassi A, Pham T, Telias I, Teggia Droghi M, Vieira F, et al. Reliability of plateau pressure during patient-triggered assisted ventilation. Analysis of a multicentre database. J Crit Care 2022;68:96–103. doi:10.1016/j.jcrc.2021.12.002.

[36] Matamis D, Lemaire F, Harf A, Brun-Buisson C, Ansquer JC, Atlan G. Total respiratory pressure-volume curves in the adult respiratory distress syndrome. Chest 1984;86(1):58–66. doi:10.1378/chest.86.1.58.

[37] Ashbaugh DG, Bigelow DB, Petty TL, Levine BE, Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. The lancet, Saturday 12 August 1967. Crit Care Resusc 2005;7(1):60–1.

[38] Schaller T, Hirschbühl K, Burkhardt K, Braun G, Trepel M, Märkl B, et al. Postmortem examination of patients with COVID-19. JAMA 2020;323(24):2518–20. doi:10.1001/jama.2020.8907.

[39] Satturwar S, Fowkes M, Farver C, Wilson AM, Eccher A, Girolami I, et al. Postmortem findings associated with SARS-CoV-2: systematic review and meta-analysis. Am J Surg Pathol 2021;45(5):587–603. doi:10.1097/PAS.0000000000001650.

[40] Thille AW, Esteban A, Fernández-Segoviano P, Rodriguez JM, Aramburu JA, Vargas-Errázuriz P, et al. Chronology of histological lesions in acute respiratory distress syndrome with diffuse alveolar damage: a prospective cohort study of clinical autopsies. Lancet Respir Med 2013;1(5):395–401. doi:10.1016/S2213-2600(13)70053-5.

[41] Thille AW, Esteban A, Fernández-Segoviano P, Rodriguez JM, Aramburu JA, Peñuelas O, et al. Comparison of the Berlin definition for acute respiratory distress syndrome with autopsy. Am J Respir Crit Care Med 2013;187(7):761–7. doi:10.1164/rccm.201211-1981OC.

[42] Zerbib Y, Lambour A, Maizel J, Kontar L, De Cagny B, Soupison T, et al. Respiratory effects of lung recruitment maneuvers depend on the recruitment-to-inflation ratio in patients with COVID-19-related acute respiratory distress syndrome. Crit Care 2022;26(1):12. doi:10.1186/s13054-021-03876-z.

[43] Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 2006;354(17):1775–86. doi:10.1056/NEJMoa052052.

[44] Frerichs I, Amato MB, van Kaam AH, Tingay DG, Zhao Z, Grychtol B, 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. doi:10.1136/thoraxjnl-2016-208357.

[45] Lu Q, Constantin JM, Nieszkowska A, Elman M, Vieira S, Rouby JJ. Measurement of alveolar derecruitment in patients with acute lung injury: computerized tomography versus pressure-volume curve. Crit Care 2006;10(3):R95. doi:10.1186/cc4956.

[46] Grasso S, Fanelli V, Cafarelli A, Anaclerio R, Amabile M, Ancona G, et al. Effects of high versus low positive end-expiratory pressures in acute respiratory distress syndrome. Am J Respir Crit Care Med 2005;171(9):1002–8. doi:10.1164/rccm.200407-940OC.

[47] Turbil E, Terzi N, Cour M, Argaud L, Einav S, Guérin C. Positive end-expiratory pressure-induced recruited lung volume measured by volume-pressure curves in acute respiratory distress syndrome: a physiologic systematic review and meta-analysis. Intensive Care Med 2020;46(12):2212–25. doi:10.1007/s00134-020-06226-9.

[48] Loring SH, Topulos GP, Hubmayr RD. Transpulmonary pressure: the importance of precise definitions and limiting assumptions. Am J Respir Crit Care Med 2016;194(12):1452–7. doi:10.1164/rccm.201512-2448CP.

[49] Gattinoni L, Pesenti A. The concept of "baby lung. Intensive Care Med 2005;31(6):776–84. doi:10.1007/s00134-005-2627-z.