Respiratory Mechanics in a Cohort of Critically Ill Subjects With COVID-19 Infection

August Longino, Toni Riveros, Erik Risa, Chris Hebert, Joshua Krieger, Steven Coppess, Flynn McGuire, Pavan K Bhatraju, James Town, and Nicholas J Johnson

BACKGROUND: Patients with coronavirus disease 2019 (COVID-19) often develop acute hypoxemic respiratory failure and receive invasive mechanical ventilation. Much remains unknown about their respiratory mechanics, including the trajectories of pulmonary compliance and P_{aO_2}/F_{IO_2}, the prognostic value of these parameters, and the effects of prone positioning. We described respiratory mechanics among subjects with COVID-19 who were intubated during the first month of hospitalization. METHODS: We included patients with COVID-19 who were mechanically ventilated between February and May 2020. Daily values of pulmonary compliance, P_{aO_2}, F_{IO_2}, and the use of prone positioning were abstracted from electronic medical records. The trends were analyzed separately over days 1–10 and days 1–35 of intubation, stratified by prone positioning use, survival, and initial P_{aO_2}/F_{IO_2}. RESULTS: Among 49 subjects on mechanical ventilation day 1, the mean compliance was 41 mL/cm H_2O, decreasing to 25 mL/cm H_2O by day 14, the median duration of mechanical ventilation. In contrast, the P_{aO_2}/F_{IO_2} on day 1 was similar to day 14. The overall mean compliance was greater among the non-survivors versus the survivors (27 mL/cm H_2O vs 24 mL/cm H_2O; *P* = .005), whereas P_{aO_2}/F_{IO_2} was higher among the survivors versus the non-survivors over days 1–10 (159 mm Hg vs 138 mm Hg; *P* = .002) and days 1–35 (175 mm Hg vs 153 mm Hg; *P* < .001). The subjects who underwent early prone positioning had lower compliance during days 1–10 (27 mL/cm H_2O vs 33 mL/cm H_2O; *P* < .001) and lower P_{aO_2}/F_{IO_2} values over days 1–10 (139.9 mm Hg vs 167.4 mm Hg; *P* < .001) versus those who did not undergo prone positioning. After day 21 of hospitalization, the average compliance of the subjects who had early prone positioning surpassed that of the subjects who did not have prone positioning. CONCLUSIONS: Respiratory mechanics of the subjects with COVID-19 who were on mechanical ventilation were characterized by persistently low respiratory system compliance and P_{aO_2}/F_{IO_2}, similar to ARDS due to other etiologies. The P_{aO_2}/F_{IO_2} was more tightly associated with mortality than with compliance. *Key words: COVID-19; SARS-CoV-2; pneumonia; viral; hypoxemic respiratory failure; mechanical ventilation; prone positioning; pulmonary compliance;* P_{aO_2}/F_{IO_2}/ *ratio; oxygenation.* [Respir Care 2021;66(10):1601–1609. © 2021 Daedalus Enterprises]

Introduction

Pulmonary infection by the severe acute respiratory syndrome coronavirus 2 and the resulting disease known as coronavirus disease 2019 (COVID-19) has been characterized by a variable and often severe clinical course. The proportion of patients who required admission to the ICU ranges between 9% and 32%.[1,2] Hypoxemic respiratory failure and ARDS are common, and ICU mortality has been estimated to be between 17% and 62%. [3,4] As such, a more-complete understanding of the pulmonary pathophysiology, including longitudinal characterization of respiratory mechanics and clinical outcomes of patients with COVID-19 will help guide the approach to respiratory support in this population.

The pulmonary effects of COVID-19 have prompted investigations into new approaches to oxygenation and ventilation,[5-7] and the use of techniques, for example, prone positioning in patients with COVID-19 who were not intubated.[8,9] It has also highlighted the need to better understand the impact of this disease on lung physiology as a whole and its evolution over the disease course. Although changes to pulmonary compliance and P_{aO_2}/F_{IO_2} have been described during early COVID infection,[3,6] the trajectory of pulmonary mechanics over longer periods has not been thoroughly explored. Similarly, although prone positioning has demonstrated a mortality benefit in selected subjects with moderate-to-severe ARDS,[10,11] the use of prone positioning in patients with COVID-19 continues to evolve. The current study characterized a multicenter cohort of subjects with COVID-19 and in the ICU to help address these gaps in knowledge.

The Puget Sound region of Washington State was the site of the earliest COVID-19 outbreak in the United States.[12,13] This early exposure allowed for collection and analysis of information on respiratory mechanics and interventions over 4 months. Here we report subject demographics and clinical outcomes as well as changes in respiratory mechanics and gas exchange parameters throughout the entire mechanical ventilation epoch, including P_{aO_2}/F_{IO_2} and lung compliance. This study will add to the growing body of literature that describes COVID-19 pulmonary physiology and the use of interventions, for example, prone positioning.

QUICK LOOK

Current knowledge

Patients with COVID-19 are at risk for ARDS and may receive mechanical ventilation. Respiratory mechanics (eg, compliance) and the effect of interventions (eg, prone positioning) over the course of the illness are unclear.

What this paper contributes to our knowledge

In a retrospective study of subjects with ARDS secondary to COVID-19 infection who were admitted to medical ICUs the subjects had a persistently low respiratory-system compliance and P_{aO_2}/F_{IO_2}. No distinct pulmonary mechanical phenotypes were observed in this population. This is similar to patient populations with ARDS due to other etiologies.

Methods

Setting, Population, and Data Collection

This report examined subject data from 2 hospitals in Seattle, including a quaternary academic medical center and an urban safety-net hospital and level-1 trauma center, which together serve an urban area of ~3.98 million people and providing specialty care to a 5-state region (ie, Washington, Wyoming, Alaska, Montana, and Idaho). Both centers are referral hospitals for patients with severe acute respiratory failure and extracorporeal membrane oxygenation. We included patients admitted to the ICU between February 24 and May 6, 2020, with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 infection. A confirmed case of COVID-19 was defined by a positive result on a reverse-transcriptasehx2013;polymerase-chain-reaction assay of a specimen collected by nasopharyngeal swab or tracheal aspirate. Only laboratory-confirmed cases were included.

Subject data were collected by starting at the ICU admission and ending at either discharge from the ICU, death of the subject, or the time of censoring on June 1, 2020. Patient management, including timing of intubation, was conducted according to the discretion of the treating team, although clinical guidelines did exist.[14] Decisions about prone positioning were guided by the PROSEVA trial protocol.[11] Briefly, patients underwent prone positioning if they were receiving mechanical ventilation for moderate-to-severe ARDS for < 36 h, defined as a P_{aO_2}/F_{IO_2} of <150 mm Hg, with an F_{IO_2} of ≥0.6, a PEEP of ≥5 cm H_2O, and a tidal volume of ≤6 mL/kg of predicted body weight. Patients underwent prone positioning for cycles of 16–20 h, followed by supination for ≤ 4 h until one of the following stopping criteria were met: (1) oxygenation improvement defined as P_{aO_2}/F_{IO_2} 150 mm Hg with PEEP ≤ 10 cm H_2O and F_{IO_2} ≤ 0.6 at least 4 h after the end of the last prone session; P_{aO_2}/F_{IO_2} deterioration by > 20% relative to supine before 2 consecutive prone sessions or complications that occurred during a prone session and that led to its immediate interruption, or any other life-threatening reason for which the clinician decided to stop.[11] For subjects with multiple ICU admissions during the study period, only the first admission was included. The project was approved by the University of Washington Human Subjects Division.

Data were obtained through manual and automated abstraction from the electronic health record. Manually abstracted data elements were entered into a research form in Research Electronic Data Capture software.[15] Data on the subject demographics, comorbidities, laboratory results,

Dr Longino is affiliated with the Division of General Internal Medicine, University of Colorado, Aurora, Colorado. Drs Riveros, Hebert, Krieger, Bhatraju, Town, and Johnson are affiliated with the Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of Washington Medical Center, Seattle, Washington. Drs Risa and McGuire are affiliated with the School of Medicine, University of Washington Medical Center, Seattle, Washington. Drs Coppess and Johnson are affiliated with the Department of Emergency Medicine, University of Washington Medical Center, Seattle, Washington.

The authors have disclosed no conflicts of interest.

Supplementary material related to this paper is available at http://www.rcjournal.com.

Correspondence: August Longino MD.
E-mail: August.Longino@cuanschutz.edu.

DOI: 10.4187/respcare.09064

outcomes, and clinical interventions were automatically abstracted for all the subjects admitted to the ICU. Pulmonary variables, including F_{IO_2} and pulmonary compliance, were automatically abstracted for the subjects who received mechanical ventilation. Team members manually reviewed the electronic health record for every subject included to ensure the accuracy of data. Inter-rater reliability was determined by the kappa coefficient. Trends in static compliance and P_{aO_2}/F_{IO_2} were analyzed over days 1–10 and days 1–35 of intubation for the entire cohort, and comparisons of these pulmonary variables were made between the survivors and non-survivors, subjects who underwent prone positioning in the first week of their hospitalization and those who did not, and between subject groups who presented with $P_{aO_2}/F_{IO_2} > 300$ mm Hg, 200–300 mm Hg, 100–199 mm Hg, and <100 mm Hg.

Definitions and Calculated Variables

The subjects' initial oxygenation categorization as "non-ARDS," "mild," "moderate" or "severe" was defined by using the P_{aO_2}/F_{IO_2} cutoffs described in the Berlin Criteria.[16] Analyses used the latest-recorded static compliance value for each day. Static compliance of the respiratory system was obtained as part of routine clinical care. Daily P_{aO_2}/F_{IO_2} values were calculated by using the last recorded fraction of inspired oxygen and recorded P_{aO_2} per day.

Statistical Methods

Clinical data were analyzed by using descriptive statistics. Continuous variables are described as means ± SDs. Categorical variables are described as counts and percentages. Between-group analyses examined differences in the last daily compliance and calculated P_{aO_2}/F_{IO_2} over days 1–10 and days 1–35. Comparisons of continuous variables were made by using a 2-tailed Welch 2-sample *t* test by using a cutoff of 0.05. Analyses of continuous variables by ordinal categories were done by using analysis of variance and the Tukey honest significant differences pairwise comparisons of means with a cutoff of 0.05. Kappa coefficients were determined for the following variables: subject body mass index, ICU admission, and intubation status. Kappa statistics were all > 0.6, which demonstrated adequate inter-rater reliability. Calculations and analyses were conducted by using R version 4.0 and the tidyverse package.[17]

Results

Patient Demographics and Outcomes

Eighty-three patients were diagnosed with COVID-19, admitted to the ICU, and received mechanical ventilation. Six patients had incomplete mortality data. Pulmonary mechanics data were incomplete for 17 patients, including patients transferred from outside institutions. Other issues included unrecorded data, and limited monitoring equipment in COVID-19 isolation rooms. Complete pulmonary data were available for a total of 49 subjects (Fig. 1). Characteristics of the excluded patients were similar to the studied cohort, and are shown in Supplementary Table S1 (see the supplementary materials at http://www.rcjournal.com). The most common reason for exclusion was the absence of static compliance or P_{aO_2}/F_{IO_2} data during mechanical ventilation.

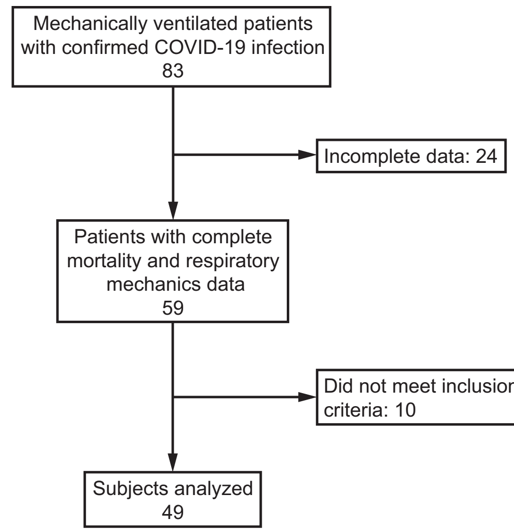

Fig. 1. Flow chart.

Demographic and clinical characteristics of the cohort are shown in Table 1. Ventilator parameters are shown in Table 2. Among the subjects with data available for analysis, a total of 45 had initial $P_{aO_2}/F_{IO_2} < 300$ mm Hg. Of these subjects, 11 (22%) met P_{aO_2}/F_{IO_2} criteria for mild ARDS, 23 (47%) for moderate ARDS, and 11 (22%) for severe ARDS. Twenty-eight percent were women and 72% were men. The mean (range) age was 59 (21–88) y. The subjects were on ventilation for a median (interquartile range) 14 (7–22) d. Overall, 27 (55%) underwent early prone positioning, 34 (63%) received neuromuscular blockade, and extracorporeal membrane oxygenation was used for 9 subjects (18%). A total of 47 subjects (96%) received immunosuppressive medications (interleukin 6 inhibitors, steroids, or other immune modulators) and seven subjects (14%) were initiated on hemodialysis (Table 3). At the end of the data collection period, a total of 22 subjects (45%) had died (Table 4).

Trends in P_{aO_2}/F_{IO_2} and Compliance

The mean ± SD compliance over days 1–35 was 25 ± 7 mL/cm H_2O. The mean ± SD static compliance among all the subjects on day 1 of hospitalization was 41 ± 11

Table 1. Clinical Characteristics of the Subjects on Admission

Characteristic	Results
Hospital site	
University of Washington (Montlake Campus)	22 (44.9)
Harborview Medical Center	27 (55.1)
Demographic information	
Age, mean ± SD y	59 ± 16
Sex	
Men	36 (72.3)
Women	13 (27.6)
Body mass index, mean ± SD kg/m^2	32.5 ± 6.4
Comorbidities	
Coronary artery disease	10 (20.4)
COPD	2 (4.1)
Hypertension	25 (51.0)
Atrial fibrillation	10 (20.4)
Diabetes mellitus	21 (42.8)
Chronic kidney disease	6 (12.2)
Initial P_{aO_2}/F_{IO_2}	
<100 mm Hg	11 (22)
100–200 mm Hg	23 (47)
201–300 mm Hg	11 (22)

Data are presented as *n* (%) unless otherwise indicated. *N* = 49.

Table 2. Ventilator Settings During Days 1–35

Variable	No. Observations*	Mean ± SD	Median (range)
F_{IO_2}	75	0.54 ± 0.20	0.50 (0.21–1.0)
Set PEEP, cm H_2O	5,109	10 ± 4	10 (0–22)
Set frequency, breaths/min	24,446	26 ± 8	26 (0–50)
Total frequency, breaths/min	4,894	26 ± 11	26 (3–60)
Inspiratory flow, L/min	3,051	65 ± 13	65 (9–120)
Hospital day of first pronation	26	3 ± 2	2 (1–6)

*The number of recorded observations for the 49 included subjects.

Table 3. Therapeutic Interventions

Intervention	Subjects, *n* (%)
High-flow nasal cannula before intubation	11 (22.4)
Mechanical ventilation	49 (100)
Prone positioning	27 (55.1)
Neuromuscular blockade	34 (63.4)
Extracorporeal membrane oxygenation	9 (18.4)
Renal replacement therapy	7 (14.3)
Steroids	12 (24.5)
Hydroxychloroquine	41 (83.7)
Azithromycin	29 (59.2)
Remdesivir (or placebo)	17 (34.7)
Tocilizumab	18 (36.7)

N = 49.

Table 4. Subject Outcomes During the Analysis Period

Outcome	Subjects
Extubated, *n* (%)	41 (83.7)
Re-intubation, *n* (%)	13 (26.5)
Hospital length of stay, mean ± SD d	22.1 ± 14.8
Deaths, *n* (%)	22 (44.9)

N = 49.

mL/cm H_2O. Notably, the values for the initial compliance measurements were normally distributed rather than demonstrating distinct phenotypes (Fig. 2). The mean ± SD static compliance on day 14, which was the median duration of ventilation, was 25 ± 12 mL/cm H_2O. The cohort's initial mean ± SD P_{aO_2}/F_{IO_2} was 171 ± 88 mm Hg (Fig. 3). The mean ± SD P_{aO_2}/F_{IO_2} on day 14 was 169.5 ± 53.8 mm Hg, and the mean ± SD P_{aO_2}/F_{IO_2} over the course of the study was 167 ± 75 mm Hg (Fig. 4).

In analyzing compliance by the admission P_{aO_2}/F_{IO_2} group (mild, moderate, severe, or non-ARDS), all groups' compliance decreased over time. The analysis of variance and Tukey honest significant differences pairwise comparisons over days 1–10 showed no significant difference between means of the different groups ($P = .34$). However, over days 1–35, a significant difference in compliance developed between the subjects who presented with P_{aO_2}/F_{IO_2} values, consistent with severe ARDS (<100 mm Hg) and those who presented with $P_{aO_2}/F_{IO_2} > 300$ mm Hg, (analysis of variance: $P = .034$; Tukey honest significant differences: severe, non-ARDS of 6.2 mm Hg; adjusted $P = .02$). The P_{aO_2}/F_{IO_2} of all the groups of subjects trended toward values consistent with moderate ARDS during the second week of hospitalization. This included those who had been hospitalized with an initial $P_{aO_2}/F_{IO_2} > 300$ mm Hg, and those hospitalized with a $P_{aO_2}/F_{IO_2} < 100$ mm Hg. After day 14, these groups diverged, and the subjects with mild ARDS and those with moderate ARDS had an improvement in P_{aO_2}/F_{IO_2}, whereas those who presented with severe ARDS and non-ARDS physiology had worsening P_{aO_2}/F_{IO_2} values between days 14 and 35 (Fig. 5).

Association of P_{aO_2}/F_{IO_2} and Compliance with In-Hospital Mortality

A small but statistically significant difference in compliance over days 1–35 was observed between the survivors and non-survivors (24 mL/cm H_2O and 27 mL/cm H_2O, respectively; P = .005), with no significant difference between these groups during days 1–10 (28.9 and 30.7; P = .15). Analysis of P_{aO_2}/F_{IO_2} by survival status over the first 10 days of hospitalization showed that the survivors had significantly higher P_{aO_2}/F_{IO_2} than did the non-survivors (159 mm Hg and 138 mm Hg, respectively; P = .002). This trend persisted over days 1–35 (175 mm Hg and 153 mm Hg; P <.001), and both groups' P_{aO_2}/F_{IO_2} values increased with time.

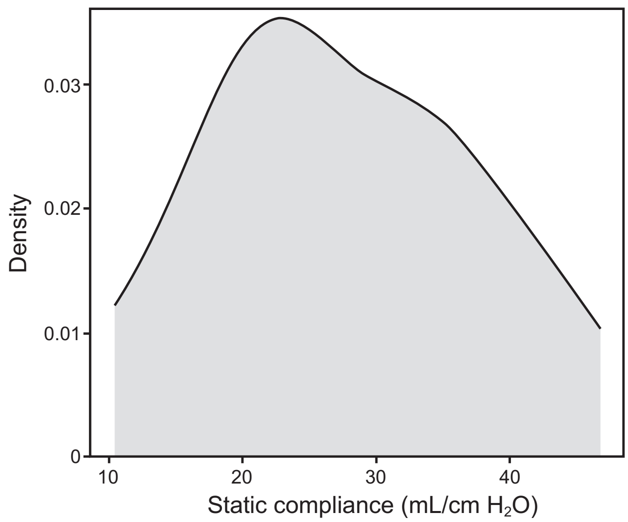

Fig. 2. Density plot of day 1 compliance among all the subjects.

Association of P_{aO_2}/F_{IO_2} and Compliance with Prone Positioning

The subjects who were placed in the prone position during the first week of hospitalization had a significantly lower compliance versus the subjects who were not in the prone position during days 1–10 (27 mL/cm H_2O vs 33 mL/cm H_2O; P < .001). Over days 1–35, this relationship remained significant. However, after day 21 of hospitalization, the average compliance of the subjects in the prone position was greater than those who had not undergone prone positioning in the first week. When analyzing P_{aO_2}/F_{IO_2} by prone positioning use during days 1–10, the subjects who underwent prone positioning during the first 7 d of their hospitalization had a significantly lower mean P_{aO_2}/F_{IO_2} than the subjects who were not in the prone position (139.9 mm Hg and 167.4 mm Hg, respectively; P < .001), which suggested that the use of prone positioning was used selectively in this cohort. However, over days 1–35, this relationship between prone positioning and P_{aO_2}/F_{IO_2} lost significance (mean, 163 mm Hg and 171 mm Hg, respectively; P = .24). Respiratory mechanics are shown in Table 5.

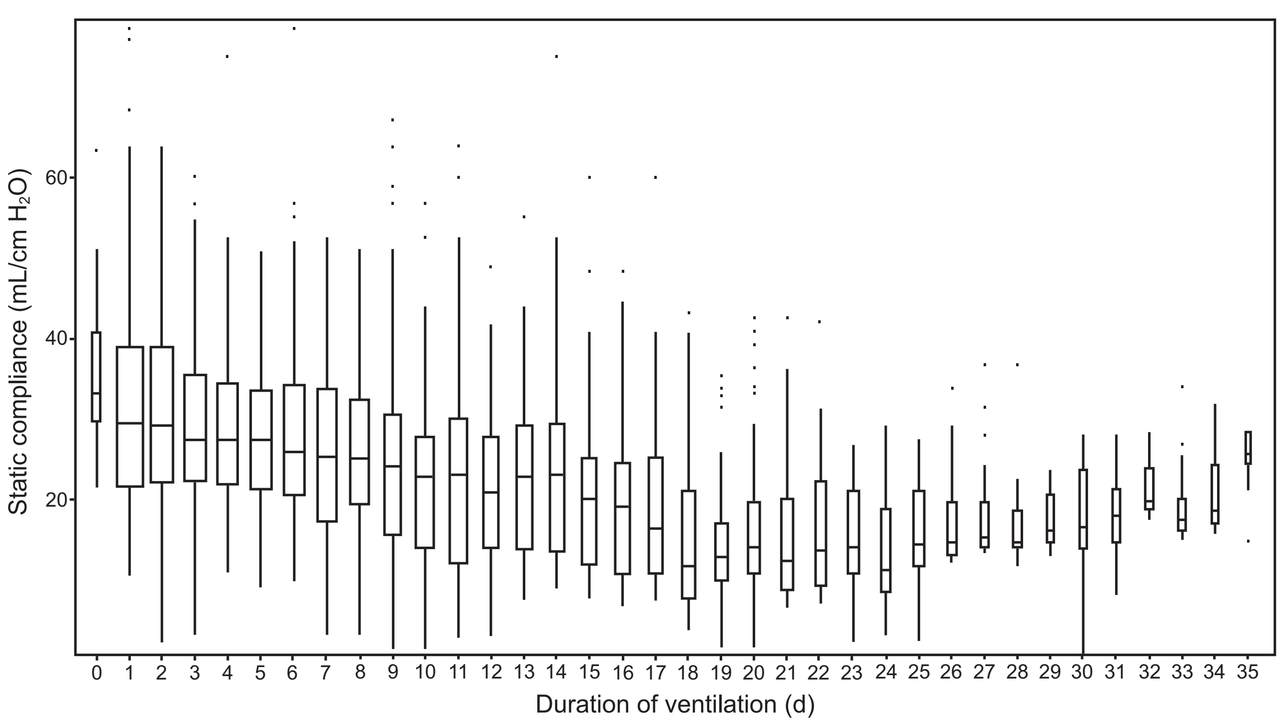

Fig. 3. Pulmonary compliance over time. Boxes show the mean and the 25th and 75th percentiles, extended lines denote 95% CI, and outlier data points falling outside the CI are denoted as dots. The box width signifies the proportion of 49 subjects who received mechanical ventilation on a given day of ventilation.

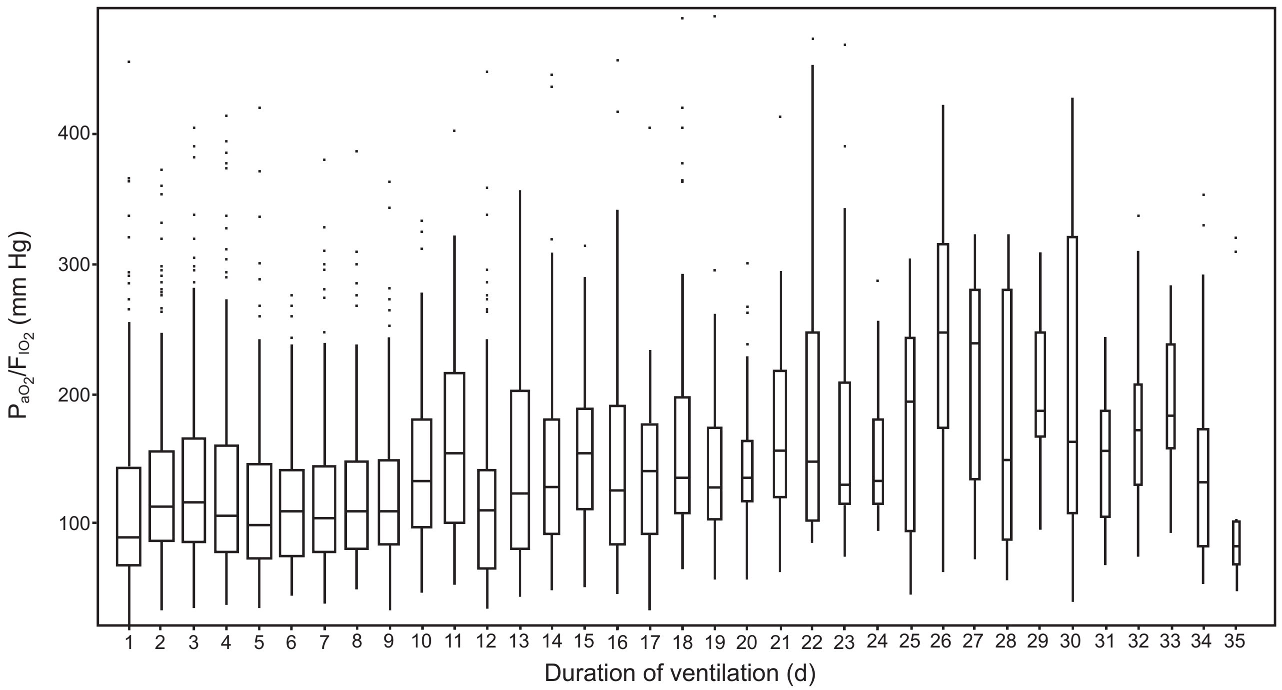

Fig. 4. The P_{aO_2}/F_{IO_2} values of all the subjects over time. Boxes show mean and the 25th and 75th percentiles, extended lines denote 95% CI, and outlier data points falling outside the CI are denoted as dots. The box width signifies the proportion of 49 subjects who received mechanical ventilation on a given day of ventilation.

Discussion

This study provided a detailed look at the changes in pulmonary mechanics and gas exchange during the first 35 days of mechanical ventilation among a cohort of subjects who were critically ill during the early stages of the COVID-19 pandemic in Washington State. The results provided insights into evolving pulmonary pathophysiology during this critical period and demonstrated similarities between COVID-19-induced respiratory illness and conventional ARDS.

COVID-19 ARDS Resembles Non-COVID ARDS

This cohort's characteristics shared similar sex, age, and comorbidities with those documented in other COVID-19 ICU studies in China,[18] Italy,[19] New York,[20] and Boston.[3] Pulmonary mechanics, including static compliance and P_{aO_2}/F_{IO_2}, were similar to other COVID-19 cohorts as well as past ARDS cohorts with lung injury from a variety of causes. The overall mean initial static compliance of 25 mL/cm H_2O was comparable with COVID-19 cohorts in New York[20] and China.[21] In comparison with non-COVID-19 coronavirus cohorts, the mean $\pm$ SD compliance was similar to a small study of subjects with ARDS and influenza pneumonia (27 $\pm$ 9 mL/cm H_2O).[22] Notably, the initial static compliance of 41 mL/cm H_2O in this cohort was identical to that observed in a multi-center prospective analysis of COVID-19 in Italy (41 mL/cm H_2O).[23] The current cohort was similar to other COVID-19 cohorts and previous COVID-19 infected cohorts but had a slightly increased initial compliance compared with cohorts with ARDS due to other etiologies, consistent with findings by Grasselli et al.[23] In the large multi-national ART study, a heterogeneous group of 1,010 subjects with ARDS from 9 countries, initial compliance values were slightly lower, with a baseline of $\sim$30 mL/cm H_2O.[24]

Initial P_{aO_2}/F_{IO_2} and changes in this ratio over time are also comparable with past ARDS cohorts with and/or without COVID-19. The mean P_{aO_2}/F_{IO_2} values during the first week were within 1 SD of first-week P_{aO_2}/F_{IO_2} values from the low-PEEP arm of the ALVEOLI trial[25] and an 83-subject study of H1N1 influenza,[26] and slightly lower than a 2018 Taiwanese cohort of subjects with influenza-ARDS.[22] The initial P_{aO_2}/F_{IO_2} of 171.4 mm Hg was similar to that observed in the large, multinational LUNG-SAFE trial, which showed a day-1 P_{aO_2}/F_{IO_2} of 161 (158–163) mm Hg.[27] It has been suggested that distinct pulmonary phenotypes of COVID-19 ARDS exist, characterized by high compliance and low P_{aO_2}/F_{IO_2}, which require different ventilation strategies.[5] In this analysis, the subjects who started at different P_{aO_2}/F_{IO_2} values experienced a similar decrease in

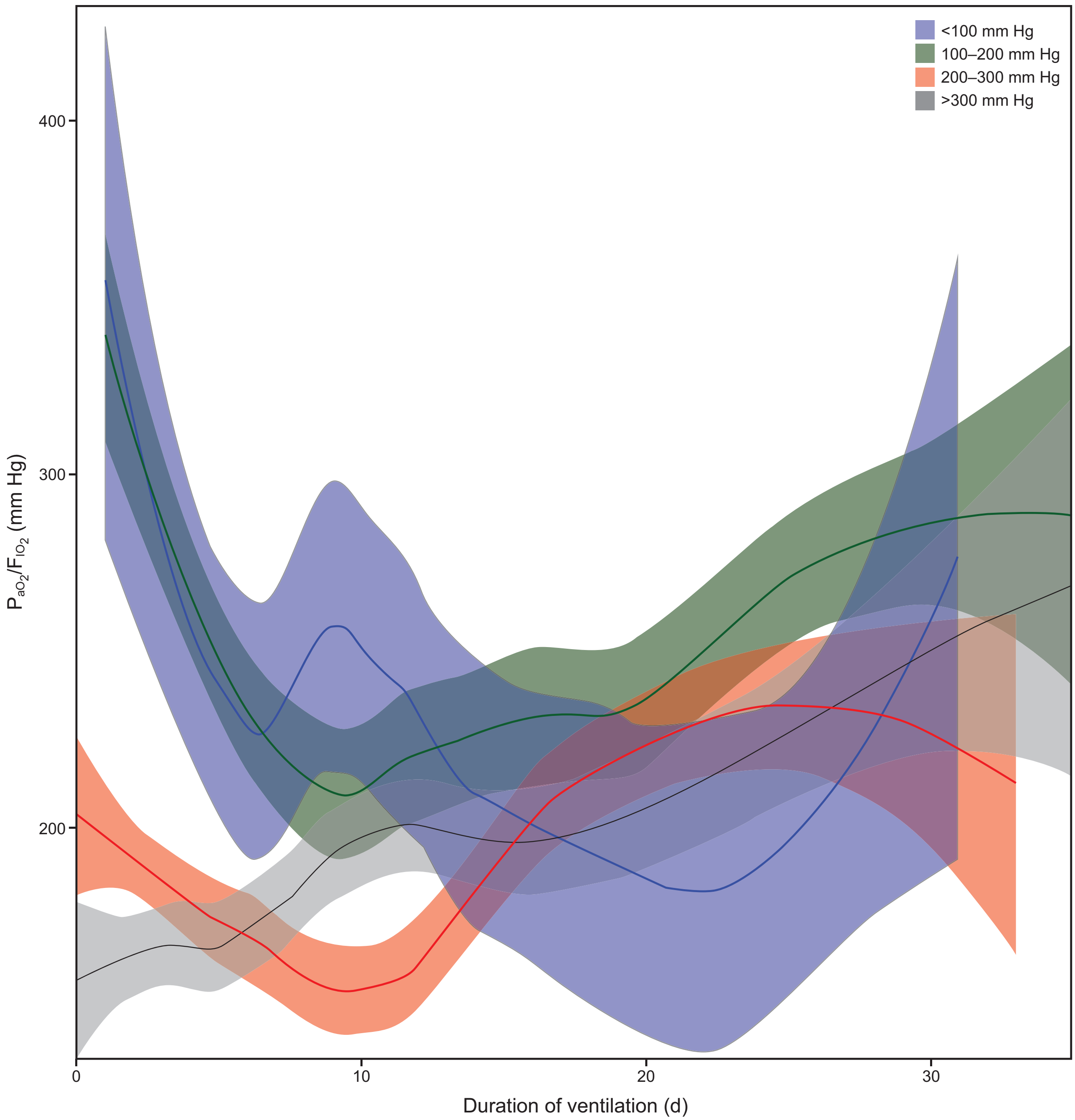

Fig. 5. The P_{aO_2}/F_{IO_2} trends over time, grouped by initial P_{aO_2}/F_{IO_2}. The values are the average daily P_{aO_2}/F_{IO_2}, represented as solid lines. Shading represents 95% CIs.

pulmonary compliance, and P_{aO_2}/F_{IO_2} values were consistent with those of moderate ARDS midway through the observation period. This argued against separate high- and low-compliance pulmonary phenotypes, and, instead, suggested the development of a persistent low-compliance, high-shunt fraction state that was previously observed in patients with viral pneumonia and other forms of ARDS.

Respiratory Mechanics and Survival

Lower compliance has been associated with higher mortality rates,[28,29] and compliance has been shown to correlate with the percentage of open, recruitable lung.[30] However, findings from this cohort showed that compliance was lower among the survivors than among the non-survivors. This suggests that compliance alone was

Table 5. Pulmonary Function Results Over Days 1–35

Parameter	Subjects, *n*	Compliance	P_{aO_2}/F_{IO_2}
Survival status			
Survivors	27	23.7 (10.7)	154 (79.9)
Non-survivors	22	29.8 (11.6)	117 (61.5)
*P**		<.001	<.001
Prone positioning			
Prone	24	28.5 (13.6)	147 (76.2)
Not prone	25	24.4 (9.57)	134 (74.4)
*P**		<.001	.006
Initial ARDS severity (P_{aO_2}/F_{IO_2})			
<100 mm Hg	7	26.5 (5.47)	70.25 (15.7)
100 – 200 mm Hg	14	33.9 (10.7)	136 (86.2)
200 – 300 mm Hg	3	36.86 (12.9)	236.3 (28.0)
>300 mm Hg	25	46.3 (5.3)	376.83 (64.1)
P†		<.001	<.001
Age group			
<44 y	9	22.5 (7.73)	144 (77.1)
45 – 64 y	20	25.1 (12.2)	142 (77.7)
64 – 74 y	12	28.4 (11.0)	133 (65.5)
>75 y	8	27.5 (11.9)	123 (56.9)
P†		<.001	<.001

Data are presented as mean (SD).
*The statistical comparison of the data between the 2 groups was performed by using Welch 2-sample *t* test.
†The statistical comparison of the data between multiple groups was performed by using the analysis of variance test.

unlikely to be a key predictor of mortality in COVID-19 ARDS and that mechanisms aside from regional alveolar collapse may contribute to hypoxemia in these subjects. Survivors had significantly higher P_{aO_2}/F_{IO_2} values than non-survivors during days 1–10 and days 1–35, which suggested that P_{aO_2}/F_{IO_2} may be a better prognostic indicator than compliance in the subjects with COVID-19 pneumonia. The correlation between P_{aO_2}/F_{IO_2} and survival suggests that hypoxemia played an important role in COVID-19 pathology or is a marker of disease severity.

Prone Positioning

The subjects who were in a prone position during the first 10 d met criteria for prone positioning as recommended by the PROSEVA trial,[11] which found a mortality benefit from early prone positioning in the subjects with $P_{aO_2}/F_{IO_2} < 150$ mm Hg. As expected, these subjects had initial values of compliance and oxygenation that were significantly lower than the subjects who did not meet criteria for prone positioning during the first 10 d of hospitalization. However, after the second week of hospitalization, the subjects who underwent prone positioning had a relative increase in P_{aO_2}/F_{IO_2} and compliance when compared with the subjects who did not receive prone positioning, which suggested that early prone positioning may have a positive effect on oxygenation and compliance in COVID-19 ARDS, as in ARDS due to other causes.[31]

Study Limitations

Our analysis had several limitations. The generalizability of these conclusions was limited by the retrospective nature of the study, the data available for analysis, and the role of survivorship bias in our sample. The sample size was also relatively small, with fewer subjects available for analysis after week 2. Approximately half of the subjects identified for the analysis had incomplete respiratory data, which could have affected the observed trends. For example, the frequency of interventions, such as extracorporeal membrane oxygenation and prone positioning, in our analysis was greater than that of COVID-19 groups in other regions, and the subjects who received more intensive therapies may have been more likely to have ongoing recording of respiratory mechanics and thus seemed overrepresented in our sample. It is unclear how the patients who were not included could have contributed to the observed trends. In addition, because the subjects in our analysis were hospitalized in the early stages of an evolving pandemic, rapidly evolving standards of treatment likely affected outcomes of the subjects treated at different time points during the analysis.

Conclusions

The subjects with COVID-19 who required mechanical ventilation had initially and persistently low compliance and severe hypoxemia, much like previous cohorts of subjects with ARDS. Analysis of our data suggested that static respiratory system compliance was less tightly associated with outcome than was P_{aO_2}/F_{IO_2}. When considering these findings, further research is needed to clarify the underlying mechanism of hypoxemia in COVID-19 ARDS to provide clinicians with more useful prognostic tools when treating subjects with COVID-19 pneumonia.

REFERENCES

1. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet 2020;395(10231):1225-1228.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506.
3. 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):1560-1564.

4. 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):475-481.
5. 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):1099-1102.
6. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med 2020;201(10):1299-1300.
7. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. JAMA 2020;323(22):2329-2330.
8. Caputo ND, Strayer RJ, Levitan R. Early self-proning in awake, non-intubated patients in the emergency department: a single ED's experience during the COVID-19 pandemic. Acad Emerg Med 2020;27 (5):375-378.
9. Ghelichkhani P, Esmaeili M. Prone position in management of COVID-19 patients; a commentary. Arch Acad Emerg Med 2020;8 (1):e48.
10. Beitler JR, Shaefi S, Montesi SB, Devlin A, Loring SH, Talmor D, Malthotra A. Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis. Intensive Care Med 2014;40(3):332-341.
11. Guérin C, Reignier J, Richard J-C, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368(23):2159-2168.
12. Buckner FS, McCulloch DJ, Atluri V, Blain M, McGuffin SA, Nalla AK, et al. Clinical features and outcomes of 105 hospitalized patients with COVID-19 in Seattle, Washington. Clin Infect Dis 2020;71 (16):2167-2173.
13. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020;382(10):929-936.
14. Johnson N, Town J. UW Medicine Critical Care Management of COVID-19. Avaialble at: https://megalabs.global/wp-content/uploads/2020/10/09c-COVID-19-ICU-Care-Guidelines-2.pdf. *Accessed on May, 4 2020*.
15. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. REDCap Consortium. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208.
16. ARDS Definition Task ForceRanieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307(23):2526-2533.
17. Wickham H. ggplot2: Elegant Graphics for Data Analysis, New York: Springer-Verlag, 2016
18. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395 (10229):1054-1062.
19. 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):1574-1581.
20. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020;395(10239):1763-1770.
21. Pan C, Chen L, Lu C, Zhang W, Xia J-A, 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):1294-1297.
22. Kao K-C, Chang K-W, Chan M-C, Liang S-J, Chien Y-C, Hu H-C, et al. Predictors of survival in patients with influenza pneumonia-related severe acute respiratory distress syndrome treated with prone positioning. Ann Intensive Care 2018;8(1):94.
23. 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):1201-1208.
24. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators; Cavalcanti AB, Suzumura EA, Laranjeira LN, de Moraes Paisani D, Damiani LP, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA 2017;318 (14):1335-1345.
25. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004;351(4):327-336.
26. Rice TW, Rubinson L, Uyeki TM, Vaughn FL, John BB, Miller RR III, et al. Critical illness from 2009 pandemic influenza A virus and bacterial coinfection in the United States. Crit Care Med 2012;40 (5):1487-1498.
27. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016;315(8):788-800.
28. Hager DN, Krishnan JA, Hayden DL, Brower RG, ARDS Clinical Trials Network. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med 2005;172(10):1241-1245.
29. Seeley EJ, McAuley DF, Eisner M, Miletin M, Zhuo H, Matthay MA, Kallet RH. Decreased respiratory system compliance on the sixth day of mechanical ventilation is a predictor of death in patients with established acute lung injury. Respir Res 2011;12(1):52.
30. Russotto V, Bellani G, Foti G. Respiratory mechanics in patients with acute respiratory distress syndrome. Ann Transl Med 2018;6(19):382.
31. Jozwiak M, Teboul J-L, Anguel N, Persichini R, Silva S, Chemla D, et al. Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2013;188(12):1428-1433.