Respiratory Mechanics and Gas Exchange in COVID-19–associated Respiratory Failure

To the Editor:

The coronavirus disease (COVID-19) pandemic has dramatically increased the number of patients requiring mechanical ventilation for respiratory failure. Several case series with data on ventilator variables from small cohorts have been reported (1–4). However, differences in respiratory mechanics between those with early mortality and successful extubation have not been explored. In this study, we report physiologic and clinical information from a large group of patients with COVID-19 during the first week of mechanical ventilation.

Methods

This single center cohort study of patients with COVID-19, with a positive RT-PCR for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), treated with mechanical ventilation was performed at New York Presbyterian Hospital–Weill Cornell Medicine from March 1st, 2020 through April 20th, 2020.

Care of the patients was at the discretion of the treating intensivists. Daily briefings were held with critical care leadership to inform best practices as patient load increased. Volume-controlled ventilation was suggested as first choice with a target tidal volume of 6–8 cc/kg of ideal body weight and a plateau pressure ⩽30 cm H_2O (5). Positive end-expiratory pressure (PEEP) was selected by the treating physicians. Neuromuscular blockade was suggested for patients with severe hypoxemia or ongoing ventilator dyssynchrony. Prone positioning was suggested if the partial pressure of O_2:fraction of inspired O_2 (P:F) ratio remained under 150 despite optimization of ventilator settings over the first 48 hours. Pressure-targeted ventilation was considered if patients experienced dyssynchrony when sedation was weaned.

We extracted demographic and chest X-ray findings at baseline. Data were extracted from the electronic medical record from Days 1, 3, and 7 of mechanical ventilation. Set fraction of inspired oxygen, plateau pressure, extrinsic PEEP, set tidal volume, and minute ventilation were recorded. In patients treated with pressure-targeted ventilation, the distending pressure was used to estimate a plateau pressure. Volumetric capnography was not available; therefore, a surrogate of dead space, called the ventilatory ratio, was used (6). The ventilatory ratio is an independent

Table 1. Patient characteristics at hospital presentation ($n = 267$)

Variable	Values	*n*
Age, median (IQR), yr	66 (54–74)	267
Sex, *n* (%)		267
Male	193 (72)	—
Female	74 (28)	—
BMI, median (IQR), kg/m^2	29 (25–33)	264
Race, *n* (%)		216
White	94 (44)	—
Other	58 (27)	—
Asian	35 (16)	—
Black	29 (13)	—
Ethnicity, *n* (%)		166
Not Hispanic or Latino	111 (67)	—
Hispanic or Latino	55 (33)	—
Smoking status, *n* (%)		267
No	187 (70)	—
Former smoker	73 (27)	—
Active smoker	7 (2.6)	—
Comorbidities, *n* (%)		267
CAD	47 (18)	—
DM	86 (32)	—
HTN	167 (63)	—
CVA	18 (6.7)	—
Active cancer	14 (5.2)	—
Cirrhosis	4 (1.5)	—
History of transplant	10 (3.7)	—
Renal disease	26 (9.7)	—
Pulmonary disease	65 (24)	—
Immunosuppressed	7 (2.6)	—
Home medications, *n* (%)		267
Angiotensin-converting enzyme	88 (33)	—
NSAID	77 (29)	—
Statin	108 (40)	—
ED course, *n* (%)		—
Supplemental O_2 in first 3 h in ED	214 (80)	267
Initial chest X-ray, *n* (%)		266
Bilateral infiltrates	228 (86)	—
Unilateral infiltrates	21 (7.9)	—
Clear	13 (4.9)	—
Pleural effusion	2 (0.8)	—
Other	2 (0.8)	—
Laboratory values at presentation, median (IQR)		—
White blood cell count, 1,000/mm^3	8.2 (6.0–11.7)	257
Lymphocyte count, 1,000/mm^3	0.75 (0.53–1.05)	243
D-dimer, ng/ml	494 (306–926)	160
Ferritin, ng/ml	1,018 (569–1,544)	181
Creatine kinase, U/L	200 (102–390)	150
Lactate dehydrogenase, U/L	532 (408–684)	218
C-reactive protein, mg/dl	160 (110–238)	199
ICU interventions, *n* (%)		267
Neuromuscular blockade	161 (60)	—
Prone positioning performed	108 (40)	—
Renal replacement therapy	54 (20)	—
Noninvasive mechanical ventilation	51 (19)	—
Inpatient medications, *n* (%)		267
Antibiotics	240 (90)	—
Steroids	146 (55)	—
Tocilizumab	28 (10)	—
Vasopressors	254 (95)	—
Remdesivir (or placebo)	30 (11)	—
Hydroxychloroquine	246 (92)	—
IVIG in hospital	6 (2.2)	—
Duration of ventilation by outcome, median (IQR)		
Ventilator days (currently intubated)	18 (14–24)	141
Ventilator days (extubated)	10 (6–15)	77
Ventilator days (deceased)	8 (4–13)	49

Definition of abbreviations: BMI = body mass index; CAD = coronary artery disease; CVA = cerebral vascular accident; DM = diabetes mellitus; ED = emergency department; HTN = hypertension; ICU = intensive care unit; IQR = interquartile range; IVIG = intravenous immunoglubulin; NSAID = nonsteroidal antiinflammatory drug.

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predictor of survival in acute respiratory distress syndrome (ARDS) (6, 7).

We compared the distributions of each individual parameter at Days 1 and 3 between those who remained intubated, those successfully extubated, and those who died. We also examined changes over the three time points across the total cohort. We compared the distributions of each individual variable using nonparametric Kruskal-Wallis tests, with a false discovery rate correction for multiple testing. All analyses were performed using *R* (version 3.6.3; R Foundation for Statistical Computing, https://www.R-project.org/). The study was approved by the Institutional Review Board at Weill Cornell Medicine with a waiver of informed consent (no. 20-04021909). Data are presented as median (interquartile range).

Results

Table 1 summarizes demographics, comorbidities, and intensive care unit treatments for this cohort. A total of 267 patients had ventilator data available. The median age was 66 (54–74) years, and men made up 72% of the cohort. Bilateral infiltrates were present on the first available chest film in 86% of patients. A total of 108 (40%) patients was treated with prone positioning, and 161 (60%) patients were treated with neuromuscular blockade during the course of mechanical ventilation. During the observed time period, 77 patients were successfully extubated and 49 died. Among the 140 remaining intubated, the median duration of mechanical ventilation was 18 (14–24) days.

Ventilator variables for the cohort are summarized in Table 2. On Day 1, the median P:F ratio was 103 (82–134). This increased modestly over the first 7 days. The median plateau pressure was 25 (21–29) cm/H_2O on Day 1 and remained constant. The median tidal volumes were 7.01 (6.13, 8.10) ml/kg of ideal body weight on Day 1, and decreased over the observed period. The median driving pressure was 14.0 (11.0–17.2) cm/H_2O, and decreased. The median extrinsic PEEP was 10 (8–12) cm/H_2O, and increased. The median static compliance was 28 (23–38) ml/cm H_2O, and remained constant. The median ventilatory ratio was 1.79 (1.47–2.27), and increased over the observed period. Table 3 displays differences in ventilator variables between those who remained intubated, those successfully extubated, and those who died. There were no differences in any ventilator variables observed on Day 1 in any group. However, on Day 3, the minute ventilation was higher in those who died compared with the other groups (corrected $q < 0.001$). On Day 3 there was a trend for higher ventilator ratio (corrected $q = 0.086$) and a lower P:F ratio (corrected $q = 0.086$) in those who died compared with those who remain intubated or were extubated.

Discussion

This study of 267 patients demonstrates that respiratory failure related to COVID-19 meets the criteria for moderate to severe ARDS, given the initial median P:F ratio of 103. These data compliment other early reports (1, 4, 8). There was also a high use of rescue therapies, such as prone positioning and a prolonged duration of mechanical ventilation. This severe morbidity occurred despite the use of a lung-protective ventilation strategy, as evidenced by the median plateau pressures and tidal volume.

An important question is whether or not COVID-19 is a distinct form of ARDS that requires a different treatment strategy (9). Importantly, ARDS is not a single disease. Rather, patients with ARDS have diverse pathology, and the syndrome's definition is used to identify eligibility for therapeutic trials. In this cohort, the baseline extrinsic PEEP, driving pressure, and static compliance were similar to ARDS Network trials, and the recent worldwide observational study, LUNGSAFE (Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE) (10–12). However, the variability of the respiratory compliance is considerable, as 25% of patients have a compliance greater than 38 ml/cm H_2O, which suggests significant heterogeneity. The duration of mechanical ventilation was prolonged in those that remained intubated, which is longer than in other studies of ARDS (10).

Table 2. Respiratory variables on Days 1, 3, and 7 of mechanical ventilation

Variable	Day 1 (*n* = 267)*	Day 3 (*n* = 252)*	Day 7 (*n* = 206)*	*P* Value†	*q* Value‡
P_{CO_2}	44 (38–52)	46 (41–52)	50 (43–56)	<0.001	<0.001
Pa_{O_2}:$F_{I_{O_2}}$	103 (82–134)	138 (106–177)	138 (109–168)	<0.001	<0.001
Exhaled minute volume, L/min	9.39 (8.13–11.33)	9.99 (8.50–11.70)	10.10 (8.60–12.17)	0.039	0.049
Tidal volume/predicted weight, cc/kg	7.01 (6.13–8.10)	6.38 (6.00–6.97)	6.57 (6.14–7.30)	<0.001	<0.001
Static compliance, cm H_2O	28 (23–38)	31 (25–40)	31 (23–40)	0.11	0.12
Driving pressure, cm H_2O	14.0 (11.0–17.2)	12.0 (9.0–15.2)	13.0 (10.0–16.8)	0.007	0.011
Plateau pressure, cm H_2O	25.0 (21.0–29.0)	24.0 (20.0–28.0)	25.0 (22.0–29.0)	0.2	0.2
PEEP, cm H_2O	10.0 (8.0–12.0)	12.0 (10.0–14.0)	12.0 (8.0–14.0)	0.002	0.003
Ventilatory ratio	1.79 (1.47–2.27)	1.91 (1.55–2.39)	2.08 (1.71–2.52)	<0.001	<0.001

Definition of abbreviations: $F_{I_{O_2}}$ = fraction of inspired oxygen; Pa_{O_2} = arterial oxygen pressure; P_{CO_2} = partial pressure of carbon dioxide; PEEP = positive end-expiratory pressure.
*Data presented as median (interquartile range).
†Statistical test: Kruskal-Wallis.
‡False discovery rate correction for multiple testing.

Table 3. Respiratory variables on Days 1 and 3 between those who remain intubated, those extubated, and those who died

Variables	Currently Intubated	Extubated	Deceased	*P* Value*	*q* Value†
Day 1	*n* = 141‡	*n* = 77‡	*n* = 49‡		
Pa_{CO_2}	44 (38–53)	43 (38–49)	46 (38–53)	0.3	0.8
Pa_{O_2}:F_{IO_2}	105 (81–130)	104 (85–139)	98 (81–133)	0.4	0.8
Tidal volume/predicted weight, cc/kg	7.03 (6.23–8.10)	7.06 (6.17–8.24)	6.30 (5.95–7.57)	0.2	0.8
Static compliance, cm H_2O	28 (20–39)	29 (23–40)	29 (24–37)	0.5	0.8
Driving pressure, cm H_2O	14.0 (11.0–17.8)	13.0 (9.0–16.5)	15.0 (12.0–18.0)	0.3	0.8
Plateau pressure, cm H_2O	26.0 (22.0–29.0)	24.0 (20.0–28.0)	26.0 (22.0–30.0)	0.4	0.8
PEEP, cm H_2O	10.0 (10.0–12.0)	10.0 (8.0–12.0)	10.0 (8.5–10.0)	0.3	0.8
Exhaled minute volume, L/min	9.45 (8.09–11.45)	9.30 (8.10–10.85)	9.95 (8.33–11.38)	0.8	0.9
Ventilatory ratio	1.83 (1.51–2.32)	1.76 (1.45–2.18)	1.82 (1.44–2.58)	0.6	0.8
Day 3	*n* = 131‡	*n* = 73‡	*n* = 43‡		
Pa_{CO_2}	48 (42–52)	46 (40–50)	47 (41–52)	0.4	0.5
Pa_{O_2}:F_{IO_2}	136 (106–168)	153 (122–192)	129 (107–156)	0.028	0.086
Tidal volume/predicted weight, cc/kg	6.43 (6.01–7.01)	6.30 (6.00–6.84)	6.35 (5.97–6.96)	0.6	0.6
Static compliance, cm H_2O	30 (24–42)	31 (26–38)	35 (26–44)	0.2	0.3
Driving pressure, cm H_2O	13.0 (10.0–16.0)	12.0 (9.0–14.2)	12.0 (8.5–15.0)	0.4	0.5
Plateau pressure, cm H_2O	25 (22–28)	23 (19–26)	25 (20–28)	0.090	0.2
PEEP, cm H_2O	12.0 (10.0–14.0)	10.0 (8.0–14.0)	12.0 (10.0–14.0)	0.021	0.086
Exhaled minute volume, L/min	10.20 (8.68–11.85)	9.00 (8.08–10.00)	11.40 (10.00–12.50)	<0.001	<0.001
Ventilatory ratio	1.97 (1.63–2.50)	1.79 (1.48–2.12)	2.26 (1.53–2.50)	0.036	0.086

Definition of abbreviations: F_{IO_2} = fraction of inspired oxygen; Pa_{CO_2} = arterial carbon dioxide pressure; Pa_{O_2} = arterial oxygen pressure; PEEP = positive end-expiratory pressure.
*Statistical test: Kruskal-Wallis.
†False discovery rate correction for multiple testing.
‡Data presented as median (interquartile range).

Surprisingly, there were no observed differences between those with early mortality compared with those that remained intubated or were successfully extubated in this cohort. However, on Day 3, increasing minute ventilation and ventilatory ratio were seen in those who died, along with a P:F ratio that failed to improve. These findings suggest the potential for differential patient trajectories within this disease.

There are a number of limitations of our study. First, the three time points of our study are only snapshots of the dynamic nature of COVID-19 respiratory failure. Moreover, the majority of patients in this cohort were still receiving mechanical ventilation at the time of this analysis. A more definitive comparison of COVID-19 respiratory failure with other forms of ARDS would require rigorous comparison with a contemporary control group. Our analysis of respiratory system compliance does not account for the effects of PEEP titration. Moreover, we lack volumetric capnography, and therefore cannot assess the effects of metabolic rate on gas exchange. We would expect that metabolic rate would vary greatly during fever and neuromuscular blockade (13). A more complete characterization of gas exchange in COVID-19 would require direct measurement of the dead space and shunt fraction. Another limitation of our study is the incomplete standardization of ventilator practice without the use of a formal PEEP titration table.

Conclusions. Patients in this cohort of COVID-19 respiratory failure meet criteria for moderate to severe ARDS, and had baseline respiratory mechanics that were comparable to those in patients enrolled in prior therapeutic trials and observational studies of ARDS. Baseline respiratory mechanics were not different between those who died and those extubated or who remained intubated. Differences in these groups developed over time, suggesting differential trajectories of COVID-19–associated respiratory failure.

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Subphenotyping Acute Respiratory Distress Syndrome in Patients with COVID-19: Consequences for Ventilator Management

To the Editor:

Guidance on the best provision of care for patients with coronavirus disease (COVID-19) is urgently needed. Recently a strong argument in defense of an evidence-based approach was made in *AnnalsATS* (1), and we fully support the given line of reasoning. Most patients in the intensive care unit (ICU) with severe COVID-19 meet the criteria for acute respiratory distress syndrome (ARDS), and proven therapies for ARDS not related to COVID-19 are likely effective in these patients as well. However, ARDS is known to be a heterogeneous syndrome. Over the past decade, several biological, physiological, and morphological subphenotypes have been identified that may predict treatment effects and can be used as treatable traits (2). For example, patients with a focal lung morphology seem to respond better to prone positioning, but their lungs are not as recruitable as those of patients with a nonfocal lung morphology (3).

It has been postulated that patients with COVID-19–related ARDS can develop typical ARDS (recently called "H type," characterized by high elastance, high shunt, and high lung weight) or have an atypical presentation (recently called "L type," characterized by low elastance, low shunt, and low lung weight) (4). As with the abovementioned morphological subphenotypes, some investigators have speculated that these subphenotypes require different ventilator strategies. Patients with H-type ARDS may benefit from lower tidal volumes and higher positive end-expiratory pressure (PEEP), and patients with L-type ARDS may benefit from higher tidal volumes and lower PEEP (5).

Several steps have to be taken before subphenotype-directed treatment can be implemented in clinical practice (6). The ultimate test would be a head-to-head comparison of subphenotype-directed treatment with standard of care in a randomized controlled trial. But before this step can be considered, it is important to validate the basic assumptions underlying the subclassification of patients. We hypothesized that patients with a low elastance (i.e., with a high respiratory system

Table 1. Patient characteristics

N	38
Age, yr, mean (SD)	61.11 (8.18)
Sex, *n* (%)	
Male	26 (68.5)
Female	12 (31.6)
Days of symptoms, median (IQR)	8.00 (5.00–12.00)
PEEP, cm H_2O, median (IQR)	10.00 (9.00–12.00)
Driving pressure cm H_2O, median (IQR)	10.50 (7.25–12.75)
Plateau pressure cm H_2O, median (IQR)	20.50 (17.00–23.00)
Tidal volume, ml, mean (SD)	423.68 (73.46)
Pa_{O_2}/FI_{O_2}, mm Hg, mean (SD)	131.84 (47.92)
Compliance, ml/cm H_2O, mean (SD)	48.96 (24.45)
Severity CT, %, median (IQR)	62.5 (50–75)
Nonfocal morphology, *n* (%)	30 (78.9)

Definition of abbreviations: CT = computed tomography; FI_{O_2} = fraction of inspired oxygen; IQR = interquartile range; Pa_{O_2} = arterial oxygen tension; PEEP = positive end-expiratory pressure; SD = standard deviation.