Respiratory Mechanics and Gas Exchange in COVID-19 Associated Respiratory Failure

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The 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 COVID-19 patients during the first week of mechanical ventilation.

Methods

This single center cohort study of COVID-19 patients, with a positive RTPCR for 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 per kg of ideal body weight and a plateau pressure less than or equal to 30cmH_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 P/F ratio remained < 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 was extracted from the electronic medical record from days 1, 3 and 7 of mechanical ventilation. Set FiO_2,

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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 predictor of survival in ARDS.(6, 7)

We compared the distributions of each individual parameter at day 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 non-parametric Kruskal-Wallis tests, with a false discovery rate correction for multiple testing. All analyses were performed using R (version 3.6.3). The study was approved by the IRB at WCM with a waiver of informed consent IRB# 20-04021909. Data is presented as median (interquartile range, IQR).

Results

Table 1 summarizes demographics, comorbidities and ICU treatments for this cohort. 267 patients had ventilator data available. The median age was 66 (54, 74). Men made up 72 % of the cohort. Bilateral infiltrates were present on the first available chest film in 86% of patients. 108 (40%) patients were 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.

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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 per 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 remain intubated, those successfully extubated and those that 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 that died compared to the other groups, $q<0.001$. 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 that died compared to those that 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. This data compliments 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.

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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.(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 remain intubated which is longer than other studies of ARDS.(10)

Surprisingly, there were no observed differences between those with early mortality compared to 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 that died along with a P:F ratio that failed to improve. These findings suggested 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

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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.

Conclusion

Patients in this cohort of COVID-19 respiratory failure meet criteria for moderate to severe ARDS and had baseline respiratory mechanics which are comparable to 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 remain intubated. Differences in these groups developed over time suggesting differential trajectories of COVID-19 associated respiratory failure.

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Table 1: Patient Characteristics at Hospital Presentation

Variable	N= 267	N
Age (years)[2]	66 (54, 74)	267
Gender[1]		267
Male	193 (72%)	
Female	74 (28%)	
BMI (kg/m^2) [2]	29 (25, 33)	264
Race[1]		216
White	94 (44%)	
Other	58 (27%)	
Asian	35 (16%)	
Black	29 (13%)	
Ethnicity[1]		166
Not Hispanic or Latino	111 (67%)	
Hispanic or Latino	55 (33%)	
Smoking Status[1]		267
No	187 (70%)	
Former Smoker	73 (27%)	
Active Smoker	7 (2.6%)	
Comorbidities[1]		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[1]		267
ACE	88 (33%)	
NSAID	77 (29%)	
Statin	108 (40%)	
ED Course[1]		
Supplemental O2 in first 3 hours in ED	214 (80%)	267
Initial Chest X-Ray[1]		266
Bilateral Infiltrates	228 (86%)	
Unilateral Infiltrates	21 (7.9%)	
Clear	13 (4.9%)	

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Pleural Effusion	2 (0.8%)	
Other	2 (0.8%)	
Lab Values at Presentation[2]		
White Blood Cell count (1000 per mm^3)	8.2 (6.0, 11.7)	257
Lymphocyte count (1000 per mm^3)	0.75 (0.53, 1.05)	243
D-Dimer (ng/mL)	494 (306, 926)	160
Ferritin (ng/mL)	1018 (569, 1544)	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[1]		267
Neuromuscular Blockade	161 (60%)	
Prone Positioning Performed	108 (40%)	
Renal Replacement Therapy	54 (20%)	
Non-invasive Mechanical Ventilation	51 (19%)	
Inpatient Medications[1]		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[2]		
Ventilator Days (Currently Intubated)	18 (14, 24)	141
Ventilator Days (Extubated)	10 (6, 15)	77
Ventilator Days (Deceased)	8 (4, 13)	49

[1]N (%)
[2]Median (Interquartile range)

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Table 2: Respiratory Variables on day 1, 3 and 7 of mechanical ventilation

Variable	**Day 1**, N = 267[1]	**Day 3**, N = 252[1]	**Day 7**, N = 206[1]	p-value[2]	q-value[3]
PCO_2	**44 (38, 52)**	**46 (41, 52)**	**50 (43, 56)**	<0.001	<0.001
PaO_2: FiO_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 (cmH_2O)	**28 (23, 38)**	**31 (25, 40)**	**31 (23, 40)**	0.11	0.12
Driving Pressure (cmH_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 (cmH_2O)	**25.0 (21.0, 29.0)**	**24.0 (20.0, 28.0)**	**25.0 (22.0, 29.0)**	0.2	0.2
PEEP (cmH_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

[1]Data presented as median (Interquartile range)
[2]Statistical test: Kruskal-Wallis
[3]False discovery rate correction for multiple testing

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Table 3: Respiratory Variables on Day 1 and 3 between those who remain intubated, those extubated and those who died

Variables Day 1					
	Currently Intubated, N=141[1]	**Extubated, N=77[1]**	**Deceased, N=49[1]**	**p-value[2]**	**q-value[3]**
$PaCO_2$	**44 (38, 53)**	**43 (38, 49)**	**46 (38, 53)**	0.3	0.8
PaO_2: FiO_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 (cmH_2O)	**28 (20, 39)**	**29 (23, 40)**	**29 (24, 37)**	0.5	0.8
Driving Pressure (cmH_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 (cmH_2O)	**26.0 (22.0, 29.0)**	**24.0 (20.0, 28.0)**	**26.0 (22.0, 30.0)**	0.4	0.8
PEEP (cmH_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
Variables Day 3					
	Currently Intubated, N=131[1]	**Extubated, N=73[1]**	**Deceased, N=43[1]**	**p-value[2]**	**q-value[3]**
$PaCO_2$	**48 (42, 52)**	**46 (40, 50)**	**47 (41, 52)**	0.4	0.5
PaO_2: FiO_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 (cmH_2O)	**30 (24, 42)**	**31 (26, 38)**	**35 (26, 44)**	0.2	0.3
Driving Pressure (cmH_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 (cmH_2O)	**25 (22, 28)**	**23 (19, 26)**	**25 (20, 28)**	0.090	0.2

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PEEP (cmH_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

[1]Data presented as median (Interquartile range)
[2]Statistical test: Kruskal-Wallis
[3]False discovery rate correction for multiple testing

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