Respiratory Pathophysiology of Mechanically Ventilated Patients with COVID-19: A Cohort Study

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To the Editor:

Five to twenty percent of hospitalized patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection are admitted to the intensive care unit (ICU), with mortality reported between 26% and 61.5% (1-3). Nearly all ICU patients present with respiratory failure and up to 88% are managed with invasive mechanical ventilation (1-3).

Descriptions of the pathophysiological characteristics of COVID-19 respiratory failure are limited. Reports of preserved respiratory system mechanics despite severe hypoxemia in early small series have led some to hypothesize that a significant proportion of COVID-19 respiratory failure is not the typical acute respiratory distress syndrome (ARDS) and warrants alternative management (4, 5).

Detailed characterization of COVID-19 respiratory failure and its response to established ARDS therapies are needed before rigorous comparisons of established and new strategies are contemplated. We describe the respiratory pathophysiology of patients with COVID-19 respiratory failure treated with invasive mechanical ventilation at two tertiary care hospitals in Boston, Massachusetts, USA.

Methods

Population and Setting

We studied all adult inpatients with SARS-CoV-2 infection and respiratory failure managed with invasive mechanical ventilation at Massachusetts General Hospital (MGH) and Beth Israel Deaconess Medical Center (BIDMC) between March 11 and

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March 30, 2020. The studies were granted exemption by the hospital institutional review boards. Informed consent was waived.

Clinical management occurred at the discretion of the treating physician. Hospital treatment guidelines recommended ventilation with tidal volumes less than 6 mL/kg predicted body weight, early consideration of prone ventilation for partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2:FiO_2) < 200, and conservative fluid management. Positive end-expiratory pressure (PEEP) was titrated per institutional protocols and included use of the lower PEEP / higher FiO_2 ARDS network table, titration by best tidal compliance, and esophageal manometry (6). Both institutions recommended against the routine use of high-flow nasal cannula or non-invasive positive pressure ventilation.

Data Collection and Definitions

Data were collected from the electronic medical record. ARDS was defined according to the Berlin criteria (7). We estimated physiological dead space fraction using the unadjusted Harris-Benedict estimate of resting energy expenditure and the rearranged Weir equation for CO_2 production (8). We calculated the ventilatory ratio as previously described (9).

Statistical Analysis

We used descriptive statistics to summarize clinical data. Results are reported as medians and interquartile ranges (IQR). Categorical variables are reported as counts

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and percentages. We report all available data without imputation. We performed analyses with GraphPad Prism v7.0 software.

Results

Demographic and Clinical Characteristics

From March 11 to March 30, 2020, 66 patients with laboratory-confirmed COVID-19 were intubated and admitted to MGH and BIDMC ICUs. Demographics, clinical characteristics, therapies, and outcomes are summarized in Table 1. Median age was 58 years (range, 23-87) and 43 patients (65%) were male. Eight patients (12%) had pre-existing pulmonary disease and 22 patients (34%) were current or former smokers.

Respiratory Failure and Respiratory System Indices

Gas exchange and respiratory system mechanics are shown in Figure 1. On ICU admission, 56 patients (85%) met Berlin criteria for ARDS and most patients had mild to moderate ARDS (7). On intubation, median PEEP was 10 cm H_2O (IQR, 8-12), plateau pressure was 21 cm H_2O (IQR, 19-26), and driving pressure was 11 cm H_2O (IQR, 9-12). Static compliance of the respiratory system was 35 mL per cm H_2O (IQR, 30-43). Estimated physiologic dead space ratio was 0.45 (IQR, 0.38-0.58).

Response to Prone Ventilation

Of the 31 patients who underwent prone ventilation, median PaO_2:FiO_2 in the supine position was 150 (IQR, 125-183) and compliance was 33 mL per cm H_2O (IQR, 26-46) immediately prior to prone positioning. After prone positioning, PaO_2:FiO_2

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increased to 232 (IQR, 174-304) and compliance increased to 36 mL per cm H_2O (IQR, 33-44). After returning to the supine position, PaO_2:FiO_2 was 217 (IQR, 149-263) and compliance was 35 mL per cm H_2O (IQR 31-41). Seventy-two hours after initial prone ventilation, patients had a PaO_2:FiO_2 while supine of 233 (IQR, 167-265) and compliance of 42 mL per cm H_2O (IQR, 34-47). Over these 72 hours, patients underwent prone ventilation for a median of two sessions (range, 1-3), with a median of 18 hours (IQR, 16-22) per session. Twelve patients (38.7%) received concurrent neuromuscular blockade. Median PEEP was 13 cm H_2O (IQR, 12-15) while supine at all timepoints and 14 cm H_2O (IQR, 12-15) in the prone position.

Outcomes

As of data censoring on April 28, 2020, median patient follow-up was 34 days (range 30-49; Table 1). Forty-one patients (62.1%) were successfully extubated, among whom the median duration of mechanical ventilation was 16.0 days (IQR, 10.0-21.0). Fourteen patients (21.2%) underwent tracheostomy. Fifty patients (75.8%) were discharged from the ICU. Eleven patients (16.7%) died.

Discussion

We characterize COVID-19 respiratory failure in 66 patients managed with mechanical ventilation and established ARDS protocols. Almost all patients presented with dyspnea and were intubated on the day of hospital presentation. Upon initiation of mechanical ventilation, patients had a median PaO_2:FiO_2 of 182, dead space fraction of 0.45, and compliance of 35 mL per cm H_2O, findings consistent with prior large cohorts of patients with ARDS (6, 8, 10). Patients exhibited a spectrum of impaired gas

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exchange and respiratory system mechanics, and very few patients had near normal compliance (Figure 1). Improvements in oxygenation and compliance with prone positioning were consistent with prior studies of prone ventilation in early ARDS (10). Prone ventilation improves gas exchange in ARDS by increasing aerated areas of lung, among other mechanisms (11). Our findings thus differ from earlier series describing near-normal respiratory system compliance and lack of recruitability in early presentations of COVID-19 respiratory failure (4, 5). Patients in our cohort were managed with established ARDS therapies including low tidal volume ventilation, conservative fluid administration, and, in many cases, prone ventilation. With a minimum follow-up of 30 days, overall mortality was 16.7% and the majority of patients were successfully extubated and discharged from the ICU.

Our study has important limitations. The limited duration of patient follow-up in this retrospective study was driven by a focus on respiratory pathophysiology as opposed to clinical outcomes. Further, it is possible that some patients were not intubated on the basis of goals and preferences and thus not included in our cohort.

Patients with COVID-19 respiratory failure in our series exhibit similar gas exchange, respiratory system mechanics, and response to prone ventilation as prior large cohorts of patients with ARDS. While further study is needed to elucidate the biology and unique features of this disease, our findings provide a pathophysiologic justification for the use of established ARDS therapies, including low tidal volume and early prone ventilation, for COVID-19 respiratory failure.

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Figure Legends

Figure 1. Respiratory Indices During the First Five Days of Mechanical Ventilation. Respiratory indices including the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FiO_2), plateau pressure (P_{plat}), positive end-expiratory pressure (PEEP), and static compliance of the respiratory system ($Cstat_{RS}$) were obtained daily in intubated patients with COVID-19 respiratory failure. The number of patients with recorded values is shown below the x-axis. The solid line indicates the median value.

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Table 1. Patient Characteristics and Laboratory Values on Hospital Presentation

	All patients	
Characteristics	% patients (n = 66)	# patients
Site		
Massachusetts General Hospital	73%	(48/66)
Beth Israel Deaconess Medical Center	27%	(18/66)
Demographics		
Age, year, median (range)	58 (23-87)	(66/66)
Gender, n (%)		
Male	65%	(43/66)
Body mass index, median (IQR)	30 (27-35)	(66/66)
Co-morbidities		
Pulmonary disease	12%	(8/66)
Current smoker or former smoker	34%	(22/64)
Hypertension	44%	(29/66)
Diabetes mellitus	26%	17/66)
Chronic kidney disease	6%	(4/66)
Immunocompromise	9%	(6/66)
Malignancy	8%	(5/66)
Home Medications		
ACEi or ARB	27%	(18/66)
Statin	34%	(21/62)
Presentation		
Median symptom onset to admission (days, IQR)	7 (6-10)	(66/66)

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Median symptom onset to intubation (days, IQR)	8 (6-10)	(66/66)
Presenting symptoms		
Fever	86%	(57/66)
Cough	88%	(58/66)
Dyspnea	91%	(60/66)
Congestion	15%	(10/65)
Nausea/vomiting	22%	(14/65)
Diarrhea	28%	(18/65)
Myalgias	55%	(36/66)
Fatigue	67%	(44/66)
Presenting Laboratory Values	**Median (IQR)**	
White blood cell count, 1000 per mm^3	7.6 (5.7-9.7)	(65/66)
Lymphocyte count, 1000 per mm^3	0.93 (0.66-1.16)	(65/66)
C-reactive protein, mg/L	159 (88-233)	(57/66)
Ferritin, µg/L	923 (590-1548)	(52/66)
D-dimer, ng/mL	1144 (789-2440)	(50/66)
Lactate dehydrogenase, IU/liter	442 (351-584)	(54/66)
Creatine kinase, U/liter	210 (107-395)	(42/66)
IL-6, pg/mL	126.7 (65.0-343.0)	(46/66)
Respiratory Parameters on Intubation	**Median (IQR)**	
Bilateral infiltrates on chest x-ray	97%	(64/66)
PaO_2:FiO_2	182 (135-245)	(65/66)
Estimated physiological dead space fraction	0.45 (0.38-0.58)	(65/66)

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Ventilatory ratio	1.25 (1.06-1.44)	(65/66)
Ventilator parameters on intubation		
Positive end-expiratory pressure, cm H_2O	10 (8-12)	(66/66)
Plateau pressure, cm H_2O	21 (19-26)	(48/66)
Driving pressure, cm H_2O	11 (9-12)	(48/66)
Static compliance, ml per cm H_2O	35 (30-43)	(48/66)
Resistance, cm H_2O per liters per second	5 (4-7)	(48/66)
ICU Therapies		
High-flow nasal cannula	2%	(1/66)
Non-invasive positive pressure ventilation	2%	(1/66)
Invasive mechanical ventilation	100%	(66/66)
Invasive mechanical ventilation, median HD initiated (IQR)	1 (1-2)	
Prone position	47%	(31/66)
Prone position, median HD initiated (IQR)	3 (2-5)	
Neuromuscular blockade	42%	(28/66)
Neuromuscular blockade, median HD initiated (IQR)	2 (1-2)	
Inhaled pulmonary vasodilator	27%	(18/66)
Inhaled pulmonary vasodilator, median HD initiated (IQR)	3 (1-3)	
Extracorporeal membrane oxygenation	5%	(3/66)
Extracorporeal membrane oxygenation, median HD initiated (range)	2 (2-5)	
Renal replacement therapy	20%	(13/66)
Renal replacement therapy, median HD initiated (IQR)	9 (5-13)	
Vasopressors	95%	(63/66)
Selected Inpatient Medications	**% patients**	
Antibiotics	98%	(65/66)
Glucocorticoids	8%	(5/66)

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Statins	82%	(54/66)
Hydroxychloroquine	91%	(60/66)
Azithromycin	97%	(64/66)
Remdesevir (or placebo)	26%	(17/66)
Lopinavir / Ritonavir	3%	(2/66)
Anti-Interleukin-6 antibody	11%	(7/66)
Outcomes		
Median patient follow-up (days, range)	34 (30-49)	66/66
Successful extubation	62.1%	41/66
Median duration of mechanical ventilation (days, IQR)*	16.0 (10.0-21.0)	
Tracheostomy	21.2%	14/66
Median time to tracheostomy (days, IQR)	22.5 (18.0-27.0)	
Thrombotic event	22.7%	15/66
ICU discharge	75.8%	50/66
Median ICU length of stay (days, IQR)**	17.5 (13.0-25.0)	
Death	16.7%	11/66

Interesting when compared to Geneva where mortality was 19%. Also the too used Hydroxy/Azithro! Also NB that they rarely used steroids (8%) and they had an RRT of 20% despite limiting fluids.

Abbreviations: interquartile range (IQR), angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), interleukin-6 (IL-6), intensive care unit (ICU), partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2:FiO_2), hospital day (HD).

*Among patients who did not have tracheostomy placement
**Among patients discharged from ICU

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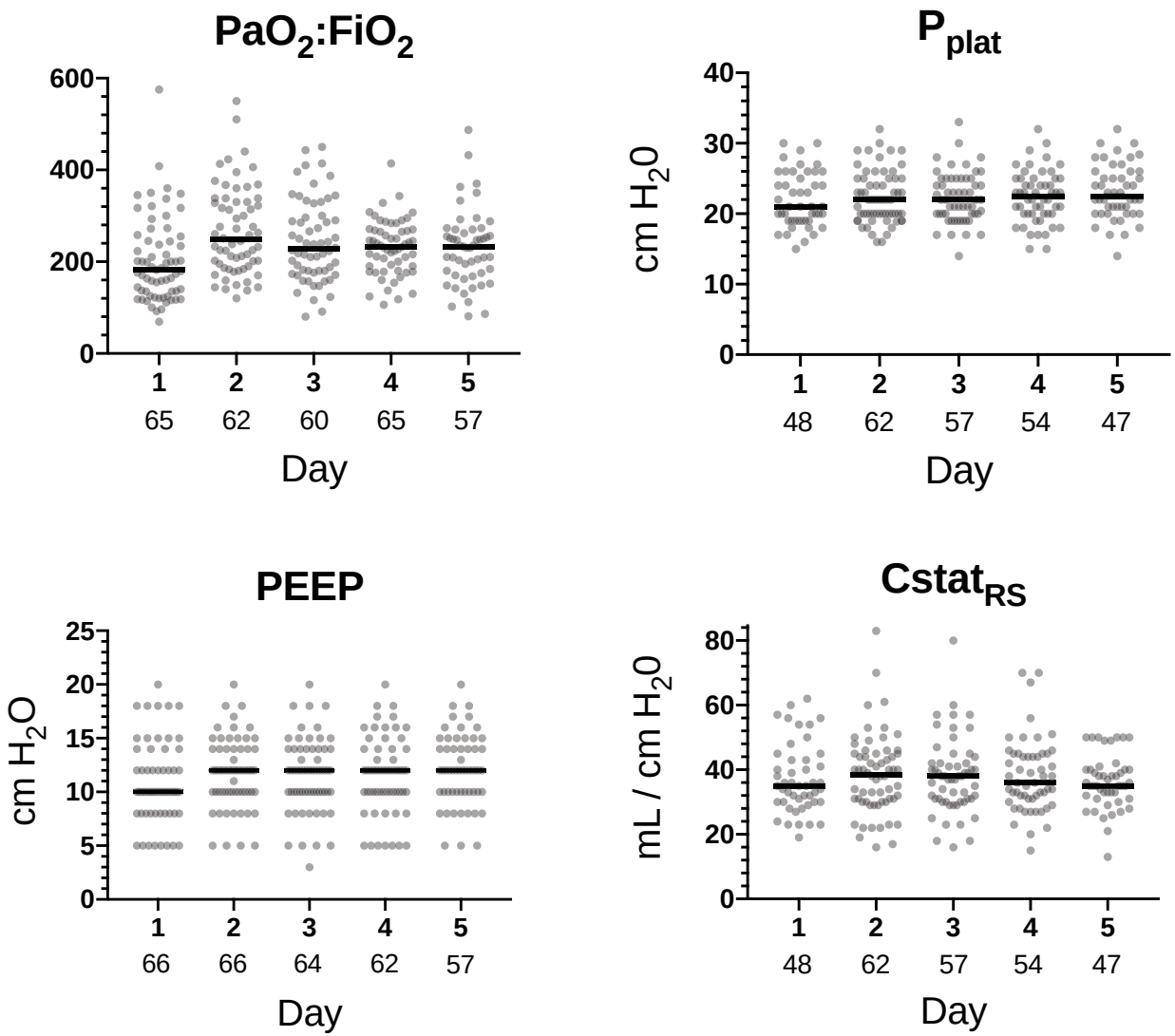

Figure 1

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