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

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 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 coronavirus disease (COVID-19) respiratory failure are limited. Reports of preserved respiratory system mechanics despite severe hypoxemia in early small series have led some investigators 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).

A detailed characterization of COVID-19 respiratory failure and its response to established ARDS therapies is needed before rigorous comparisons of established and new strategies can be 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.

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 and Beth Israel Deaconess Medical Center between March 11 and 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 V_Ts of <6 ml/kg predicted body weight, early consideration of prone ventilation for Pa_{O_2}:$F_{I_{O_2}} < 200$, and conservative fluid management. Positive end-expiratory pressure (PEEP) was titrated per institutional protocols and included use of the lower-PEEP/higher-$F_{I_{O_2}}$ 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 noninvasive positive-pressure ventilation.

Data collection and definitions. Data were collected from the electronic medical records. ARDS was defined according to the Berlin criteria (7). We estimated the 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 the clinical data. The results are reported as medians and interquartile ranges (IQRs). Categorical variables are reported as counts 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 ICUs at Massachusetts General Hospital and Beth Israel Deaconess Medical Center. The patients' demographics, clinical characteristics, therapies, and outcomes are summarized in Table 1. The median age was 58 years (range, 23–87 yr), and 43 patients (65%) were male. Eight patients (12%) had preexisting 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 the Berlin criteria for ARDS, and most patients had mild-to-moderate ARDS (7). On intubation, the 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). The static compliance of the respiratory system was 35 ml/cm H_2O (IQR, 30–43). The estimated physiologic dead-space ratio was 0.45 (IQR, 0.38–0.58).

Response to prone ventilation. Among the 31 patients who underwent prone ventilation, the median Pa_{O_2}:$F_{I_{O_2}}$ ratio in the supine position was 150 (IQR, 125–183) and compliance was 33 ml/cm H_2O (IQR, 26–46 ml/cm H_2O) immediately before prone positioning. After prone positioning, Pa_{O_2}:$F_{I_{O_2}}$ increased to 232 (IQR, 174–304) and compliance increased to 36 ml/cm H_2O (IQR, 33–44 ml/cm H_2O). After the patients returned to the supine position, Pa_{O_2}:$F_{I_{O_2}}$ was 217 (IQR, 149–263) and compliance was 35 ml/cm H_2O (IQR, 31–41 ml/cm H_2O). Seventy-two hours after initial prone ventilation, the patients had a Pa_{O_2}:$F_{I_{O_2}}$ while supine of 233 (IQR, 167–265) and compliance of 42 ml/cm H_2O (IQR, 34–47 ml/cm H_2O). Over these 72 hours, the patients underwent prone ventilation for a median of two sessions (range, 1–3), with a median of 18 hours (IQR, 16–22 h) per session. Twelve patients (38.7%) received concurrent neuromuscular blockade. The median PEEP was 13 cm H_2O (IQR, 12–15 cm H_2O) while supine at all time points, and 14 cm H_2O (IQR, 12–15 cm H_2O) in the prone position.

Outcomes. As of data censoring on April 28, 2020, the median patient follow-up was 34 days (range, 30–49 d;

Supported in part by NIH grant U01 HL123009. J.A. is supported by NIH grant T32 HL116275.

Author Contributions: Conception and design: D.R.Z., J.A., C.R.P., J.H.M., A.M., and C.C.H. Analysis and interpretation of data: D.R.Z., J.A., C.R.P., J.H.M., K.A.H., B.T.T., and C.C.H. Drafting of the manuscript: D.R.Z., J.A., C.R.P., J.H.M., A.M., B.D.M., K.A.H., B.T.T., and C.C.H.

Originally Published in Press as DOI: 10.1164/rccm.202004-1163LE on April 29, 2020

Table 1. Patient Characteristics and Laboratory Values on Hospital Presentation

Characteristics	All Patients	
	Percentage of Patients* (*N* = *66*)	Number of Patients
Site		
Massachusetts General Hospital	73%	48/66
Beth Israel Deaconess Medical Center	27%	18/66
Demographics		
Age, yr, median (range)	58 (23–87)	66/66
Sex, *n* (%)		
Male	65%	43/66
Body mass index, median (IQR)	30 (27–35)	66/66
Comorbidities		
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		
Symptom onset to admission, d, median (IQR)	7 (6–10)	66/66
Symptom onset to intubation, d, median (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, 1,000/mm^3	7.6 (5.7–9.7)	65/66
Lymphocyte count, 1,000/mm^3	0.93 (0.66–1.16)	65/66
C-reactive protein, mg/L	159 (88–233)	57/66
Ferritin, μg/L	923 (590–1,548)	52/66
D-dimer, ng/ml	1,144 (789–2,440)	50/66
Lactate dehydrogenase, IU/L	442 (351–584)	54/66
Creatine kinase, U/L	210 (107–395)	42/66
IL-6, pg/ml	126.7 (65.0–343.0)	46/66
Respiratory parameters on intubation		
Bilateral infiltrates on chest X-ray	97%	64/66
Pa_{O_2}:$F_{I_{O_2}}$, median (IQR)	182 (135–245)	65/66
Estimated physiological dead-space fraction, median (IQR)	0.45 (0.38–0.58)	65/66
Ventilatory ratio, median (IQR)	1.25 (1.06–1.44)	65/66
Ventilator parameters on intubation, median (IQR)		
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/cm H_2O	35 (30–43)	48/66
Resistance, cm H_2O/L/s	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, HD initiated, median (IQR)	1 (1–2)	
Prone position	47%	31/66
Prone position, HD initiated, median (IQR)	3 (2–5)	

(Continued)

Table 1. (*Continued*)

Characteristics	All Patients	
	Percentage of Patients* (*N* = 66)	Number of Patients
Neuromuscular blockade	42%	28/66
Neuromuscular blockade, HD initiated, median (IQR)	2 (1–2)	
Inhaled pulmonary vasodilator	27%	18/66
Inhaled pulmonary vasodilator, HD initiated, median (IQR)	3 (1–3)	
Extracorporeal membrane oxygenation	5%	3/66
Extracorporeal membrane oxygenation, HD initiated, median (range)	2 (2–5)	
Renal replacement therapy	20%	13/66
Renal replacement therapy, HD initiated, median (IQR)	9 (5–13)	
Vasopressors	95%	63/66
Selected inpatient medications		
Antibiotics	98%	65/66
Glucocorticoids	8%	5/66
Statins	82%	54/66
Hydroxychloroquine	91%	60/66
Azithromycin	97%	64/66
Remdesevir (or placebo)	26%	17/66
Lopinavir/ritonavir	3%	2/66
Anti–IL-6 antibody	11%	7/66
Outcomes		
Patient follow-up, d, median (range)	34 (30–49)	66/66
Successful extubation	62.1%	41/66
Duration of mechanical ventilation, d, median (IQR)†	16.0 (10.0–21.0)	
Tracheostomy	21.2%	14/66
Time to tracheostomy, d, median (IQR)	22.5 (18.0–27.0)	
Thrombotic event	22.7%	15/66
ICU discharge	75.8%	50/66
ICU length of stay, d, median (IQR)‡	17.5 (13.0–25.0)	
Death	16.7%	11/66

Definition of abbreviations: ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; HD = hospital day; IQR = interquartile range.
*Unless otherwise indicated.
†Among patients who did not have tracheostomy placement.
‡Among patients who were discharged from the ICU.

Table 1). Forty-one patients (62.1%) were successfully extubated, and among these patients the median duration of mechanical ventilation was 16.0 days (IQR, 10.0–21.0 d). Fourteen patients (21.2%) underwent tracheostomy. Fifty patients (75.8%) were discharged from the ICU. Eleven patients (16.7%) died.

Discussion

We characterized COVID-19 respiratory failure in 66 patients managed with mechanical ventilation and established ARDS protocols. Almost all of the patients presented with dyspnea and were intubated on the day of hospital presentation. Upon initiation of mechanical ventilation, the patients had a median Pa_{O_2}:FI_{O_2} of 182, dead-space fraction of 0.45, and compliance of 35 ml/cm H_2O—findings that are consistent with previously described large cohorts of patients with ARDS (6, 8, 10). The patients exhibited a spectrum of impaired gas 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 the lung, among other mechanisms (11). Our findings thus differ from earlier series describing near-normal respiratory system compliance and a lack of recruitability in early presentations of COVID-19 respiratory failure (4, 5). The patients in our cohort were managed with established ARDS therapies, including low V_T 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 the 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. Furthermore, it is possible that some patients were not intubated for reasons related to goals and preferences, and thus were not included in our cohort.

Patients with COVID-19 respiratory failure in our series exhibited gas exchange values, respiratory system mechanics, and responses to prone ventilation similar to those observed in large cohorts of patients with ARDS. Although 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

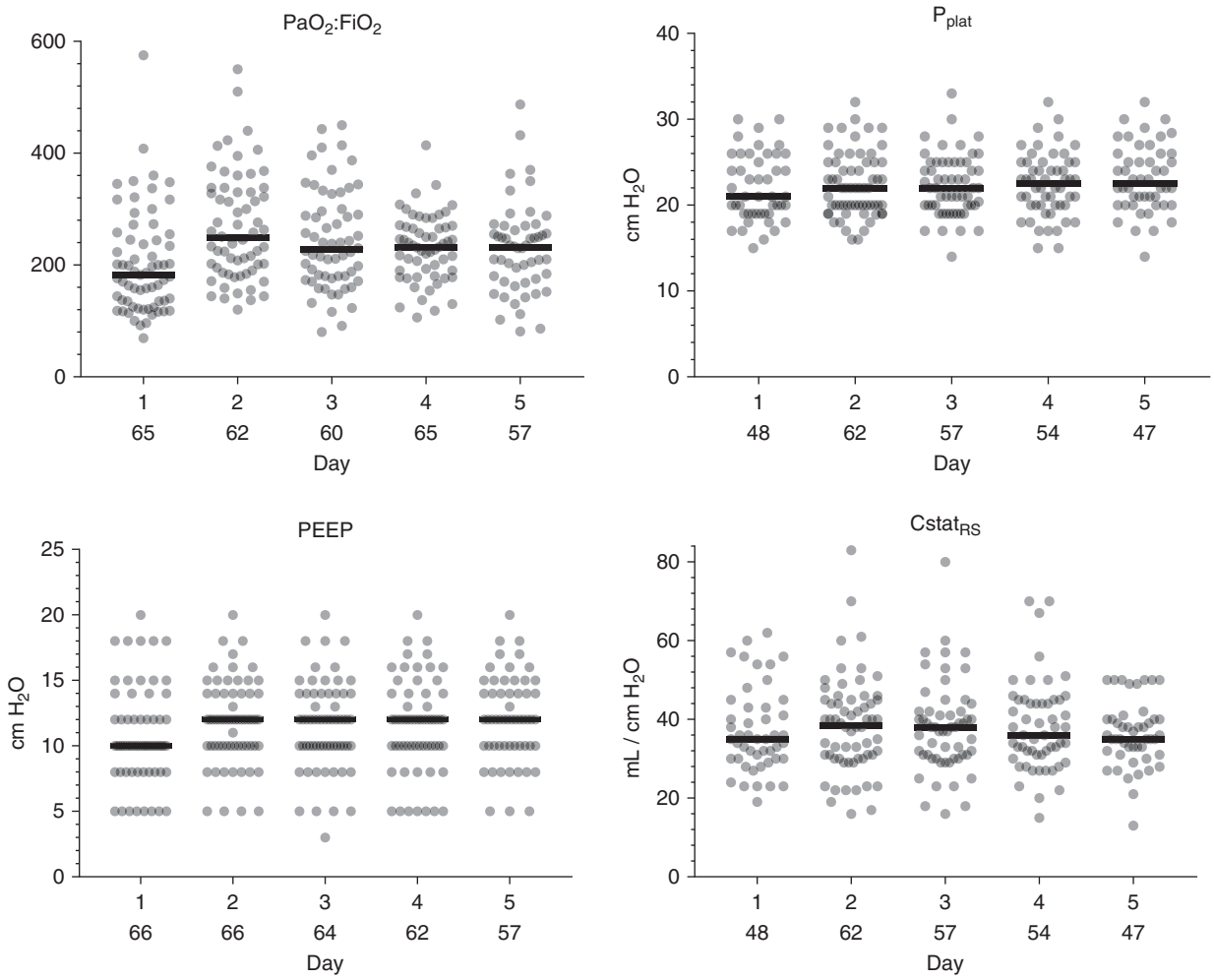

Figure 1. Respiratory indices during the first 5 days of mechanical ventilation. Respiratory indices, including the Pa_{O_2}:$F_{I_{O_2}}$ ratio, plateau pressure (Pplat), positive end-expiratory pressure (PEEP), and static compliance of the respiratory system ($Cstat_{RS}$), were obtained daily in intubated patients with coronavirus disease (COVID-19) respiratory failure. The number of patients with recorded values is shown below the *x*-axis. The solid line indicates the median value.

ARDS therapies, including low VT and early prone ventilation, for COVID-19 respiratory failure. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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§B.T.T. is Associate Editor of *AJRCCM*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

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Bedaquiline-Resistant Tuberculosis: Dark Clouds on the Horizon

To the Editor:

Emergence of drug resistance is challenging the control of tuberculosis (TB). The World Health Organization (WHO) estimated that approximately 5.6% of the 10 million new TB cases in 2017 were caused by *Mycobacterium tuberculosis* complex (MTBC) strains showing resistance against rifampicin (RR-TB) or against rifampicin and isoniazid (multidrug-resistant tuberculosis [MDR-TB]) (1). After the demonstration of higher cure rates in a phase IIb trial and decreased death rates in programmatic data from South Africa, the new WHO consolidated guidelines on drug-resistant TB treatment list bedaquiline (BDQ) together with later-generation fluoroquinolones and linezolid (LZD) among the prioritized group A drugs for the treatment of MDR/RR-TB (2–4). The three group A drugs should be complemented by one or two of the group B drugs, clofazimine (CFZ) and D-cycloserine (DCS)/terizidone, for the design of MDR/RR-TB treatment regimens (4). This recommendation has also been adopted in the recent official clinical practice guideline on treatment of drug-resistant tuberculosis jointly published by the American Thoracic Society, the CDC, the European Respiratory Society, and the Infectious Diseases Society of America (5).

BDQ inhibits the mycobacterial ATP synthase by targeting its c-ring AtpE (ATP synthase subunit c, *Mycobacterium tuberculosis*), leading to rapid depletion of intracellular ATP levels (6). Accordingly, mutations in *atpE*, which to date have very rarely been observed in clinical isolates, can confer BDQ resistance (7). In addition, mutations in *rv0678*, a transcriptional repressor of the MmpS5-MmpL5 efflux pump, have been described after exposure to BDQ in clinical isolates and in *in vitro* selection experiments (8). Mutations in *rv0678* also affect CFZ and result in minimum inhibitory concentrations (MICs) ranging around the critical concentrations (CCs) (8). In light of the new WHO recommendations, concerns have been raised regarding the global preparedness to detect resistance to BDQ, CFZ, and companion drugs (4, 9). In the present study, we investigated BDQ/CFZ resistance in a cohort of consecutive patients with MDR-TB. We aimed to *1*) determine the incidence of BDQ/CFZ resistance, *2*) identify the underlying mechanisms, and *3*) describe patients at risk for developing resistance under therapy.

Methods

In June 2018, BDQ and CFZ were added to the second-line phenotypic drug susceptibility testing (pDST) panel at the National and WHO Supranational Reference Center for Mycobacteria in Borstel, Germany, which processes about three-fourths of all new MDR-TB cultures in Germany annually. In addition to all initial MDR-MTBC isolates, selected follow-up isolates were tested in patients treated with BDQ or CFZ at least every 2 months to monitor the emergence of resistance under therapy. Testing was performed using a mycobacteria growth indicator tube (MGIT) 960 system (Becton Dickinson) with CC of 1 μg/ml for both BDQ and CFZ, which corresponds to the tentative epidemiological cutoff value for both agents; that is, isolates with MIC greater than CC are phenotypically non–wild type (pNWT) and assumed to be resistant (7). For all isolates showing growth at the CC, BDQ and CFZ MICs were determined by testing at 0.125, 0.25, 0.5, 0.75, 1.0, 2.0, 4.0, and 8.0 μg/ml in MGITs using EpiCenter TB eXiST software (Becton Dickinson). In addition, selected preceding and follow-up isolates were subjected to MIC testing. MIC data for all isolates showing resistance to BDQ and/or CFZ and for a subset of susceptible isolates were reproduced at the WHO Supranational Reference Laboratory in Munich-Gauting, Germany. Whole-genome sequencing of all drug-resistant isolates and, if available, at least one preceding susceptible isolate was performed as previously described (10). In addition to routine molecular drug resistance testing (mDST), each genome was investigated for mutations in *atpE*, *rv0678*, *mmpS5*, *mmpL5*, *Rv1979c*, *pepQ*, and *serB2*, including 30–180 bp of the respective upstream regions (10).

Supported by internal funding. In addition, C.L., J.H., S.N., and M.M. are supported by the German Center for Infection Research (DZIF); B.K., S.N., and C.L. are supported by the Cluster of Excellence "Precision Medicine in Chronic Inflammation"; S.N. and M.M. are supported by the Leibniz Science Campus Evolutionary Medicine of the Lung (EvoLUNG); and F.P.M. is supported by a research grant from Joachim Herz Foundation.

Originally Published in Press as DOI: 10.1164/rccm.201909-1819LE on February 13, 2020