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Inspiratory Airway Resistance in Respiratory Failure Due to COVID-19

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OBJECTIVES: To measure inspiratory airflow resistance in patients with acute respiratory distress syndrome (ARDS) due to COVID-19.

DESIGN: Observational cohort of a convenience sample.

SETTING: Three community ICUs.

SUBJECTS: Fifty-five mechanically ventilated patients with COVID-19.

INTERVENTIONS: Measurements of ventilatory mechanics during volume control ventilation.

MEASUREMENTS: Flow-time and pressure-time scalars were used to measure inspiratory airways resistance.

RESULTS: The median inspiratory airflow resistance was 12 cm H_2O/L/s (interquartile range, 10–16). Inspiratory resistance was not significantly different among patients with asthma or chronic obstructive pulmonary disease compared with those without a history of obstructive airways disease (median 12.5 vs 12 cm H_2O/L/s, respectively; $p = 0.66$). Survival to 90 days among patients with inspiratory resistance above 12 cm H_2O/L/s was 68% compared with 60% for patients below 12 cm H_2O/L/s ($p = 0.58$). Inspiratory resistance did not correlate with C-reactive protein, ferritin, Pao_2/Fio_2 ratio, or static compliance.

CONCLUSIONS: Inspiratory airflow resistance was normal to slightly elevated among mechanically ventilated patients with ARDS due to COVID-19. Airways resistance was independent of a history of obstructive airways disease, did not correlate with biomarkers of disease severity, and did not predict mortality.

KEY WORDS: acute respiratory distress syndrome; airways resistance; COVID-19; mechanical ventilation

Most descriptions of the pulmonary physiology of COVID-19 acute respiratory distress syndrome (ARDS) have focused on static respiratory system compliance and lung recruitability. Because autopsies of patients with COVID-19 show evidence of airway injury (1), we hypothesized that patients with ARDS due to COVID might have elevated airflow resistance.

To test this hypothesis, we measured inspiratory airway resistance in a convenience sample of 55 intubated and mechanically ventilated COVID patients meeting the Berlin criteria for ARDS (2) in three ICUs between March and September 2020. The study was approved with a waiver of informed consent by the Institutional Review Boards (IRBs) and Research Committees of Louisiana State University, University Medical Center of New Orleans, and Ochsner Medical Center (IRB protocol 1224). Patients were identified based solely on the availability of one of the investigators to photograph ventilator waveforms during the routine assessments of ventilatory mechanics.

All patients were intubated with an oral endotracheal tube greater than or equal to 7.0 mm internal diameter and were ventilated in the volume-assist-control mode with a target tidal volume of 6 mL/kg predicted body weight. Positive

DOI: 10.1097/CCE.0000000000000669

end-expiratory pressure (PEEP) and FIO_2 combinations were protocolized (3). Sedation, analgesia, and neuromuscular blockade were controlled by the primary treatment team. Patients were suctioned prior to the measurements, and the heat and moister exchanger (HME) was changed regularly. During a period of passive ventilation, photographs were obtained of pressure-time and flow-time scalars for offline analysis using a HIPAA compliant software program (Haiku, Epic Systems, Verona, WI). During each assessment, inspiratory flow (F_{inspir}) was set to 60 L/min using a square-wave flow pattern with an end-inspiratory pause of 0.3 seconds. Waveforms that demonstrated active or reverse triggering were excluded from analysis (approximately 5% of the sample). Measurements of peak inspiratory airway pressure (P_{peak}) and plateau airway pressure (P_{plat}) were used to calculate inspiratory airflow resistance (R_{inspir}) using the following formula:

$$R_{inspir} = P_{peak} - P_{plat} / F_{inspir}$$

Deidentified patient demographics, smoking status, history of chronic lung disease, admission laboratory, COVID-specific treatments, vital status at 90 days, and dates of first positive severe acute respiratory syndrome coronavirus-2 test, intubation, ventilator liberation, and hospital discharge were captured.

Baseline characteristics are described as means ± SD, medians (interquartile range [IQR]), or percentages. R_{inspir} was compared between patients with and without chronic obstructive pulmonary disease (COPD)/asthma using Mann-Whitney *U* test. Spearman correlation was used to determine associations between R_{inspir} and inflammatory markers (C-reactive protein [CRP] and ferritin) as well as PaO_2/FIO_2 ratio and static respiratory system compliance (C_{stat}). Survival to 90 days was calculated, and the proportion of survivors above or below the median R_{inspir} was compared.

Patient characteristics are displayed in the table. The time from intubation to the waveform was 7 days (IQR, 2–12 d). The median R_{inspir} was 12 cm H_2O/L/s (IQR, 10–16). R_{inspir} was not significantly different between patients with asthma or COPD compared with those without these diagnoses (median 12.5 vs 12 cm H_2O/L/s, respectively; $p = 0.66$) or between patients who received either remdesivir or steroids and those who did not (13 vs 12 cm H_2O/L/s, respectively; $p = 0.83$). Furthermore, R_{inspir} did not correlate with CRP, ferritin, PaO_2/FIO_2, or C_{stat}. Thirty-nine percent of the cohort survived to 90 days. Survival among patients with R_{inspir} greater than 12 cm H_2O/L/s was 68% compared with 60% among patients with R_{inspir} less than 12 cm H_2O/L/s ($p = 0.58$).

Our investigation has shown that inspiratory airflow resistance was normal to only slightly elevated (12 cm H_2O/L/s; IQR, 10–16) among a convenience sample of critically ill, mechanically ventilated patients with COVID-19 ARDS compared with reported normal values (4). Our study can be compared with two prior investigations of inspiratory airways resistance in ARDS. In the first, Wright and Bernard (5) reported a mean inspiratory airflow resistance of 6.15 cm H_2O/L/s in 10 patients with non-COVID ARDS versus 0.88 in three control subjects. However, this previous study measured airway pressures below the tip of the endotracheal tube and referenced them to pleural pressure.

In a second more recent study of patients with COVID-19 ARDS, Koppurapu et al (6) used methods similar to ours. They reported a higher mean inspiratory airflow resistance (20 cm H_2O/L/s) than that observed in our study. Although our study is larger and, therefore, perhaps less susceptible to sampling error than that of Koppurapu et al (6), approximately 50% of our patients were receiving remdesivir, systemic glucocorticoids, beta-agonists, and/or anticholinergics. In addition, the median time from intubation to assessment was only 1.7 days in the study by Koppurapu et al (6) versus 7 days in our study, which could have led to reduced airways resistance in our cohort.

There are limitations to our study. First, we did not measure expiratory airways resistance that would have required a measurement of intrinsic PEEP. In addition, similar to the study by Koppurapu et al (6), we were unable to determine the small contribution of the endotracheal tube and HME to R_{inspir}.

We conclude that patients with COVID-19 ARDS generally have only minimally increased airways resistance and that inspiratory airflow resistance was not correlated with a history of asthma or COPD, the duration of mechanical ventilation, or mortality.

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Drs. Kantrow, Lammi, and deBoisblanc conceived the original idea and developed the methods. Drs. Tran, Zamora, Lowery,

TABLE 1.
Demographics, Baseline Laboratory Data, Treatments, and Pulmonary Physiology of the Enrolled Patients

Patient Characteristics	Value
Age, yr (median ± SD)	57 ± 14
Male/female (%)	60/40
Race/ethnicity (%)	
Non-Hispanic White	25
Black	40
Hispanic	31
Body mass index, kg/m^2 (mean ± SD)	34 ± 9
Hx of asthma or chronic obstructive pulmonary disease (%)	24
Admit laboratory values	
C-reactive protein, mg/L (mean ± SD)	157 ± 108
Ferritin, ng/mL (median [IQR])	1,086 (396–2,155)
D-dimer, mg/L (median [IQR])	1.14 (0.56–4.67)
ICU therapies (% of cohort)	
Remdesivir	42
Systemic corticosteroids	53
Inhaled b-agonists	46
Inhaled antimuscarinics	35
Proning	24
Neuromuscular blockade	35
Vasopressors	73
Renal replacement therapy	35
Full anticoagulation	82
Pulmonary physiology on date of waveform	
Pao_2/Fio_2 (median [IQR])	135 (94–182)
Static compliance of respiratory system, mL/cm H_2O (median [IQR])	21 (17–30)
Dynamic compliance of respiratory system, mL/cm H_2O (median [IQR])	12 (10–17)
Driving pressure, cm H_2O (mean ± SD)	21 ± 8

IQR = interquartile range.

Kantrow, and deBoisblanc captured and interpreted the waveforms. Drs. Nezami and Lammi performed the analyses. Drs. Nezami, Tran, Zamora, Lowery, Kantrow, Lammi, and deBoisblanc wrote and edited the article.

The authors have disclosed that they do not have any potential conflicts of interest.

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