Adherence to Lung Protective Ventilation in Patients With Coronavirus Disease 2019

Elizabeth Levy, MD[1]

Stefania Scott, MS[2]

Teresa Tran, MPH[2]

Wei Wang, PhD[2]

Mark E. Mikkelsen, MD, MSCE[1–3]

Barry D. Fuchs, MD[1,3]

Meeta Prasad Kerlin, MD, MSCE[1–3]

OBJECTIVES: Prior studies have demonstrated suboptimal adherence to lung protective ventilation among patients with acute respiratory distress syndrome. A common barrier to providing this evidence-based practice is diagnostic uncertainty. We sought to test the hypothesis that patients with acute respiratory distress syndrome due to coronavirus disease 2019, in whom acute respiratory distress syndrome is easily recognized, would be more likely to receive low tidal volume ventilation than concurrently admitted acute respiratory distress syndrome patients without coronavirus disease 2019.

DESIGN: Retrospective cohort study.

SETTING: Five hospitals of a single health system.

PATIENTS: Mechanically ventilated patients with coronavirus disease 2019 or noncoronavirus disease 2019 acute respiratory distress syndrome as identified by an automated, electronic acute respiratory distress syndrome finder in clinical use at study hospitals.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Among 333 coronavirus disease 2019 patients and 234 noncoronavirus disease 2019 acute respiratory distress syndrome patients, the average initial tidal volume was 6.4 cc/kg predicted body weight and 6.8 cc/kg predicted body weight, respectively. Patients had tidal volumes less than or equal to 6.5 cc/kg predicted body weight for a mean of 70% of the first 72 hours of mechanical ventilation in the coronavirus disease 2019 cohort, compared with 52% in the noncoronavirus disease 2019 cohort (unadjusted $p < 0.001$). After adjusting for height, gender, admitting hospital, and whether or not the patient was admitted to a medical specialty ICU, coronavirus disease 2019 diagnosis was associated with a 21% higher percentage of time receiving tidal volumes less than or equal to 6.5 cc/kg predicted body weight within the first 72 hours of mechanical ventilation (95% CI, 14–28%; $p < 0.001$).

CONCLUSIONS: Adherence to low tidal volume ventilation during the first 72 hours of mechanical ventilation is higher in patients with coronavirus disease 2019 than with acute respiratory distress syndrome without coronavirus disease 2019. This population may present an opportunity to understand facilitators of implementation of this life-saving evidence-based practice.

KEY WORDS: coronavirus disease 2019; implementation science; intensive care units; mechanical ventilation; respiratory distress syndrome; tidal volume

Coronavirus disease 2019 (COVID-19) is associated with high rates of respiratory failure and acute respiratory distress syndrome (ARDS). Up to 20% of hospitalized COVID-19 patients are admitted to an ICU, with up to 88% of these patients requiring mechanical ventilation (1). Clinical practice guidelines for mechanically ventilated patients with COVID-19 include a strong recommendation for lung protective ventilation (LPV), defined as low tidal volume ventilation (tidal volumes 4–8 cc/kg predicted body weight [PBW]) and

targeting plateau pressures (Pplat) less than or equal to 30 cm H_2O (2). Prior to the COVID-19 pandemic, LPV was underutilized in ARDS despite these strong recommendations (3). We sought to compare mechanical ventilation practices in ARDS patients with and without COVID-19 to test the hypothesis that patients with COVID-19, in whom ARDS is easily recognized, would be more likely to receive low tidal volume ventilation than ARDS patients without COVID-19.

METHODS

We performed a retrospective cohort study of ARDS patients with and without COVID-19 who underwent mechanical ventilation in five University of Pennsylvania Health System (UPHS) hospitals from March 16, 2020, to July 14, 2020, including the first COVID-19 case admitted to the health system and the first period of peak COVID-19 admissions. All data were collected from the electronic health record. For the COVID-19 population, we included all patients diagnosed with COVID-19 requiring mechanical ventilation. The non-COVID-19 ARDS cohort was identified by the health system's ARDS Finder (4). We excluded patients who were mechanically ventilated for less than 12 hours, as these patients were likely either patients without respiratory failure or patients who had a rapid change in goals of care, and LPV may not be appropriate. We also excluded patients exclusively on spontaneous breathing trial settings (defined at UPHS as positive end-expiratory pressure ≤ 8, pressure support ≤ 10, and F_{IO_2} ≤ 50%). We calculated initial ventilator parameters using the initial documented ventilator settings and the initial arterial blood gas after intubation, and at 24 hours using the documented settings and arterial blood gas closest to 24 hours after intubation, including only those values within 6 hours of the 24-hour mark. To calculate the percentage of time during the first 72 hours with tidal volume less than or equal to 6.5 or 8 cc/kg PBW, we assumed that a patient was on the tidal volume documented in the ventilator flowsheet from the time of documentation until the time of the next documented tidal volume. The total time at tidal volumes below the threshold was divided by the total eligible ventilation time during the first 72 hours. If a patient was on minimal settings during any part of the first 72 hours of mechanical ventilation, that part was excluded from analyses.

We performed unadjusted comparisons using chi-square and rank-sum tests, as appropriate. We performed multivariable analyses to adjust for potential confounders identified a priori: gender, height, and $Pao_2:F_{IO_2}$ (P:F ratio). Because of baseline variability in adherence to LPV, we included admitting hospital as a fixed effect. Because of pre-pandemic differences in exposure to ARDS and mechanical ventilation practices in medical specialty ICUs compared with other ICUs, we included a variable for medical versus other ICUs. We performed two sensitivity analyses: we excluded patients admitted to cardiovascular ICUs because of the known high false positive rate of the ARDS Finder© in those units, and we excluded the variable for P:F ratio because of missingness in 107 patients. The study protocol was approved under expedited review by the University of Pennsylvania institutional review board using a waiver of informed consent (Protocol No. 833400).

RESULTS

During the study period, there were 333 COVID-19 patients requiring mechanical ventilation and 234 non-COVID ARDS patients identified by the ARDS Finder. **Table 1** summarizes patient characteristics and outcomes. Patients with COVID-19 had more severe hypoxemia at start of mechanical ventilation (P:F 148 vs 214), longer duration of mechanical ventilation (10.6 vs 4.2 d) and ICU length of stay (15 vs 9.7 d), and higher inhospital mortality (45% vs 34%). **Table 2** summarizes mechanical ventilation parameters during the first 72 hours. The average initial tidal volume was 6.4 cc/kg in the COVID-19 population and 6.8 cc/kg in the non-COVID-19 population ($p < 0.001$). Patients had tidal volumes less than or equal to 6.5 cc/kg PBW for a mean of 70% of the first 72 hours of mechanical ventilation in the COVID-19 cohort compared with 52% in the non-COVID-19 cohort ($p < 0.001$) and less than 8 cc/kg PBW for a mean of 93% of the time in the COVID-19 cohort compared with 88% in the non-COVID-19 cohort ($p = 0.001$). COVID-19 patients were less likely to have Pplat less than 30 at start of mechanical ventilation than non-COVID ARDS patients (89% vs 95%, respectively).

In the primary multivariable analysis, patients with COVID-19 had significantly higher proportion of

TABLE 1.
Patient Characteristics and Outcomes

Characteristic	COVID-19 (n = 333)	Non-COVID-19 Acute Respiratory Distress Syndrome (n = 234)	p
Age, yr, median (range)	64 (54–74)	62 (49–71)	0.01
Male gender, n (%)	185 (56)	126 (54)	0.69
Race, n (%)			< 0.001
Asian	25 (8)	6 (3)	
Black or African American	175 (53)	92 (39)	
Native Hawaiian or other Pacific Islander	1 (0.3)	0 (0)	
Other	12 (4)	6 (3)	
Unknown	9 (3)	18 (8)	
White	111 (33)	114 (48)	
Elixhauser comorbidity categories, n (%)			
Congestive heart failure	79 (24)	97 (41)	< 0.001
Chronic pulmonary disease	101 (30)	68 (29)	0.75
Cancer	14 (4)	26 (11)	0.002
Chronic kidney disease	114 (34)	68 (29)	0.19
Chronic liver disease	55 (17)	49 (21)	0.18
Chronic neurologic disorder	42 (13)	33 (14)	0.61
Hypertension	226 (67)	136 (58)	0.02
Body mass index, median (range)[a]	29.8 (25.1–35.9)	27.1 (22.5–33.5)	< 0.001
Initial P:F ratio, median (range)[b]	148 (94–258)	214 (138–320)	< 0.001
P:F ratio at 24 hr, median (range)[c]	176 (124–260)	250 (183–340)	< 0.001
Duration of mechanical ventilation, hr, median (range)	254 (126–434)	101 (44–211)	< 0.001
Duration of mechanical ventilation, d, median (range)	10.6 (5.3–18.1)	4.2 (1.8–8.8)	< 0.001
ICU length of stay, d, median (range)	15.0 (7.7–22.7)	9.7 (5.0–19.7)	< 0.001
Hospital length of stay, d, median (range)	21.1 (12.8–35.4)	18.6 (9.2–32.0)	< 0.001
Inhospital mortality, n (%)	150 (45)	79 (34)	0.007

COVID-19 = coronavirus disease 2019, P:F = Pao_2:Fio_2.
[a]Body mass index available in 329 COVID-19 patients and 234 patients with non-COVID-19 acute respiratory distress syndrome (ARDS).
[b]Available for 270 COVID-19 patients and 188 patients with non-COVID-19 ARDS.
[c]Available for 231 COVID-19 patients and 170 patients with non-COVID-19 ARDS.

time during the first 72 hours of mechanical ventilation with tidal volume less than or equal to 6.5 cc/kg PBW (mean difference, 22.4%; 95% CI, 15–29.8%; p < 0.001). Sensitivity analyses excluding patients admitted to cardiovascular ICUs and excluding the P:F ratio from analyses yielded similar results (mean differences, 25.0% and 21.2%, respectively).

DISCUSSION

LPV using low tidal volumes and low Pplat is known to improve mortality in patients with ARDS (5); however, adoption of this practice has been incomplete (3). Most COVID-19 patients requiring ICU care meet the Berlin definition of ARDS (1, 6). Despite controversy

TABLE 2.
Mechanical Ventilation Parameters

Parameter	COVID-19 (*n* = 333)	Non-COVID-19 Acute Respiratory Distress Syndrome (*n* = 234)	*p*
Initial tidal volume, mean mL/kg PBW (SD)	6.4 (1.2)	6.8 (1.1)	< 0.001
Percentage time during first 72 hr with tidal volume < 6.5 mL/kg PBW, mean percentage (SD)			
All hospitals	70 (40)	52 (45)	< 0.001
Hospital A	43 (44)	62 (45)	0.51
Hospital B	59 (46)	21 (39)	0.02
Hospital C	75 (36)	53 (45)	0.005
Hospital D	70 (42)	37 (44)	0.03
Hospital E	77 (36)	54 (45)	0.02
Percentage time during first 72 hr with tidal volume < 8 mL/kg PBW, mean percentage (SD)	93 (21)	88 (26)	0.001
Initial positive end-expiratory pressure, median cm H_2O (interquartile range)	10 (8–14)	5 (5–10)	< 0.001
Initial Pplat, mean cm H_2O (SD)[a]	24 (6)	21 (6)	< 0.001
Patients with initial Pplat ≤ 30, *n* (%)	291 (89)	218 (95)	0.01
Pplat at 24 hr, mean cm H_2O (SD)[b]	25 (6)	21 (6)	< 0.001
Patients with 24 hr Pplat ≤ 30, *n* (%)[b]	224 (88)	165 (94)	0.02
Initial driving pressure, mean cm H_2O (SD)[b]	13 (5)	14 (5)	0.18
Driving pressure at 24 hr, mean cm H_2O (SD)[c]	14 (5)	14 (5)	0.88
Initial static compliance, mean mL/cm H_2O (SD)[b]	35 (16)	33 (36)	0.61
Static compliance at 24 hr mean mL/cm H_2O (SD)[c]	33 (17)	34 (14)	0.36

COVID-19 = coronavirus disease 2019, PBW = predicted body weight, Pplat = plateau pressure.

[a]Initial Pplat, driving pressure, and compliance available for 326 patients with COVID-19 and 229 patients without COVID-19.

[b]Pplat at 24 hr available for 256 patients with COVID-19 and 175 patients without COVID-19.

[c]Compliance and driving pressure at 24 hr available for 255 patients with COVID-19 and 173 patients without COVID-19.

regarding the physiology of respiratory failure in COVID-19, LPV is the mainstay of supportive care for COVID-19 patients requiring mechanical ventilation (2). In this observational study of patients with ARDS with and without COVID-19 during the initial regional peak of the pandemic, we observed higher adherence to low tidal volume ventilation among patients with COVID-19.

The level of adherence to LPV seen in both cohorts is higher than in historical cohorts of ARDS patients prior to the COVID-19 pandemic. For example, in the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure, 35% of patients received tidal volumes of more than 8 cc/kg PBW (3), and in another study, only 19% of ARDS patients received tidal volumes less than 6.5 cc/kg PBW in one U.S. hospital (7). Our findings are consistent with two recent

observational studies in Europe, which found high adherence to LPV at the start of ventilation in COVID-19 patients (1, 6). We add to the literature by directly comparing LPV adherence in a concurrent non-COVID-19 ARDS cohort and by reporting sustained adherence through examination of ventilator settings beyond the initiation of mechanical ventilation.

The average duration of mechanical ventilation for our COVID-19 cohort was 10.6 days, similar to other large cohorts of patients with COVID-19 respiratory failure (1, 6). Despite the prolonged duration of mechanical ventilation in patients with COVID-19, we focused on the first 72 hours of invasive mechanical ventilation because existing studies of ARDS have demonstrated that early administration of low tidal volume ventilation is associated with improved mortality (8, 9) and that many patients do not receive tidal

volumes less than 6.5 cc/kg PBW when initially managed with higher tidal volumes (9).

Delayed and missed diagnosis of ARDS and erroneous knowledge about what LPV entails are two commonly identified barriers of LPV use in ARDS (10). We believe several complementary factors helped rapidly overcome these barriers in COVID-19 patients. First, the diagnosis of ARDS is common and easily recognized in this population. Second, our health system's response planning for the initial COVID-19 surge brought with it several complementary strategies to disseminate knowledge about what LPV entails, including rapid education and clinical protocols to support a broad array of clinicians who would step into critical care clinical roles, use of the ARDS Finder alongside real-time data dashboards to provide visual prompts for LPV settings, and daily dashboard reviews by an integrated ICU telemedicine team.

Our study has a few notable limitations. First, the ARDS Finder used to identify non-COVID-19 ARDS patients is a surveillance tool known to have high sensitivity with moderate specificity (4). We addressed this limitation through our sensitivity analyses, which confirmed our findings. Second, the use of clinical decision support like the ARDS Finder may be uncommon in other institutions, potentially limiting the generalizability of our findings. Third, we conducted this study in a single health system, which may further limit generalizability to other populations. Last, ARDS was the anticipated outcome of patients with COVID-19 developing respiratory failure, whereas ARDS due to other etiologies has more variability in clinical presentation and thus variability in management. We analyzed the first 72 hours of mechanical ventilation in all patients for consistency, but if ARDS developed later in the course, patients may not have been prescribed low tidal volumes immediately.

In conclusion, we have shown that in one multihospital health system, during the COVID-19 pandemic, clinicians practiced with strong adherence to evidence-based LPV in patients with COVID-19 respiratory failure. The pandemic provided heightened awareness of ARDS and emphasized the importance of LPV. More research is needed to determine if increased awareness during the pandemic leads to sustained adherence to LPV in other populations of patients with ARDS.

1 Department of Medicine, Perelman School of Medicine at The University of Pennsylvania, Philadelphia, PA.

2 Palliative and Advanced Illness (PAIR) Center, Department of Medicine, Perelman School of Medicine at The University of Pennsylvania, Philadelphia, PA.

3 Division of Pulmonary and Critical Care Medicine, Department of Medicine, Perelman School of Medicine at The University of Pennsylvania, Philadelphia, PA.

For information regarding this article, E-mail: Elizabeth.Levy@pennmedicine.upenn.edu

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