Prolonged Prone Positioning for COVID-19–induced Acute Respiratory Distress Syndrome: A Randomized Pilot Clinical Trial

To the Editor:

Prone ventilation is among the only interventions shown in a randomized controlled trial to decrease mortality in acute respiratory distress syndrome (ARDS). There remain questions about the optimal duration of each proning session, and implementation is often limited by concerns about staff burden (1). The landmark trial on prone positioning demonstrated a mortality benefit in patients with severe ARDS using 16-hour prone sessions (1); however, there is observational evidence of a dose–response relationship, with longer periods of prone positioning conferring greater benefit than shorter periods (2, 3). Furthermore, increased duration of prone positioning may decrease prone–supine position transitions, which subsequently may reduce staffing demands and decrease cumulative staff exposure to coronavirus disease (COVID-19).

Methods
This study was performed in three closed medical intensive care units (ICUs) within a 1,157-bed academic medical center. Enrollment occurred between November 10, 2020, and January 12, 2021. Patients with COVID-19–induced ARDS were screened if the treating team planned to prone. Patients were eligible if they 1) were ≥18 years of age, 2) were endotracheally intubated, and 3) had an arterial oxygen tension/pressure (PaO2) to fraction of inspired oxygen (FiO2) (P:F) ratio of <150 on at least 0.6 FiO2 and 10 cm H2O of positive end-expiratory pressure. Patients were excluded if they 1) had a do not attempt resuscitation order, 2) were a prisoner or pregnant, 3) had been intubated for >48 hours at the time of screening, or 4) had a contraindication to prone positioning.

Patients were block-randomized to receive either 16-hour traditional or 24-hour prolonged prone positioning followed by a supine session. Arterial blood gas sampling was recommended 4–6 hours after supination. Return to the prone position was recommended within 8 hours if the P:F ratio was <150 on 0.6 FiO2 and 10 cm H2O. The primary outcome of the study was duration proned; secondary outcomes included pulmonary mechanics and patient outcomes.

Central tendency was measured with means and standard deviation or medians and interquartile range (IQR). Categorical variables were compared using chi-square test, and continuous variables were compared using Wilcoxon rank-sum test. This study was approved under waiver of informed consent by the University of Alabama at Birmingham Institutional Review Board. This study was registered on clinicaltrials.gov before the first patient enrollment (NCT04581811).

Results
Sixty-three patients were potentially eligible during the study period, of whom six were proned before screening. Of the 57 patients screened, 52 were eligible and randomized (Table 1). The median age of subjects was 62 years (IQR, 54–73.5), 61.5% were male, 48.1% were non-Hispanic White, and 44.2% were non-Hispanic Black. Median body mass index was 32.1 (IQR, 27.9–37.4). Overall, mortality was high (55.8%).

At 96 hours, patients randomized to prolonged prone positioning had a higher total duration proned (56.6 vs. 45.7 h; P = 0.02) (Table 2). Those in the prolonged prone positioning arm had higher mean duration of prone sessions (23.1 vs. 14.9 h; P < 0.01) and similar duration of supine sessions (9.0 vs. 11.5 h; P = 0.46). Patients in the prolonged prone positioning arm underwent fewer position changes (4.7 vs. 5.7 turns; P = 0.05). Respiratory mechanics were similar across groups. There were very few adverse events at 96 hours with no obvious differences between groups.

The traditional proning group had six pressure ulcers whereas the prolonged proning group had four pressure ulcers at 30 days. Patients in the traditional proning group had 5.81 ICU-free, 4.15 ventilator-free, and 2.58 hospital-free days; patients in the prolonged proning group had 6.27 ventilator-free, 4.35 ICU-free, and 2.25 hospital-free days. Mortality was 57.4% in patients who received traditional proning and 53.8% in the prolonged prone positioning group.

Discussion
In this single-center randomized controlled study, prolonged prone positioning was feasible. Importantly, allocation to prolonged prone positioning was associated with fewer position changes, which may reduce staff workload, decrease the risk of infectious disease transmission to medical personnel, and decrease the need for personal protective equipment. Furthermore, prolonged prone positioning did not appear to increase the risk of adverse events including tube dislodgement or pressure ulcers, although these events were rare, and our study was underpowered to detect these differences. Although underpowered to detect all but extreme differences, our study did not demonstrate massive differences in gas exchange, respiratory mechanics, or patient outcomes between groups.

Because of the pilot nature of our study, we cannot comment in a meaningful way on the safety or efficacy of the intervention, although, importantly, we were able to demonstrate the feasibility. As such, this study may serve as the foundation for future work evaluating variable duration of prone positioning. Two key requirements in the success of this study’s feasibility were institutional review board approval for waiver of informed consent and potential for decreased nursing requirements.

Our study is the first to prospectively evaluate variable durations of prone positioning in ARDS. To date, only two nonrandomized, retrospective studies describe the use of prolonged duration of prone positioning in patients with
COVID-19–induced ARDS (4, 5). The first study of 10 patients found that P:F ratios in the supine position after prolonged prone positioning improved relative to traditional duration prone position sessions (4). The second and larger (N = 61) single-center study examined the outcomes of continuous prone positioning after it was adopted as standard of care (5). This cohort had a much higher rate of pressure ulcer development than we observed (70.5% vs. 15.4%). We suspect this is related to the fact that our patients continued to receive interrupting supine periods. Mortality in this study was also lower than we observed (31.1% vs. 55.8%), perhaps due to our population’s older age (62.7 vs. 56.7 yr) and higher proportion of Black patients (44.2% vs. 8.2%), both independent predictors of mortality in COVID-19 (6, 7).

The primary limitations of our study are the small sample size and its unblinded and single-center design.

Conclusions
A prolonged prone positioning strategy for patients with COVID-19–induced ARDS was feasible. This strategy resulted in increased

| Table 1. Baseline characteristics of included patients |
|---------------------------------|-----------------|-----------------|
| **Characteristic**              | **Traditional Proning (N = 26)** | **Prolonged Proning (N = 26)** |
| Age, mean ± SD, yr              | 62 ± 12          | 64 ± 14         |
| Male sex, n (%)                 | 17 (65.4)        | 15 (53.6)       |
| Race, n (%)                     |                  |                 |
| White                           | 13 (50.0)        | 12 (46.2)       |
| Black                           | 12 (46.2)        | 11 (42.3)       |
| Other/declined to disclose      | 1 (3.8)          | 3 (11.5)        |
| Height, mean ± SD, cm           | 168.6 ± 16.4     | 172.1 ± 9.7     |
| Weight, mean ± SD, kg           | 95.9 ± 18.0      | 101.3 ± 20.8    |
| BMI, mean ± SD, kg/m²           | 32.0 ± 5.7       | 34.5 ± 8.5      |
| Tidal volume, mean ± SD, ml     | 389 ± 50         | 388 ± 65        |
| Tidal volume, mean ± SD, ml/kg IBW | 6.1 ± 1.1       | 5.9 ± 0.9       |
| PEEP, mean ± SD, cm H₂O        | 11.8 ± 2.1       | 12.8 ± 2.7      |
| FIO₂, mean ± SD, %              | 87.7 ± 17.0      | 86.5 ± 15.7     |
| Plateau pressure, mean ± SD, cm H₂O | 26.2 ± 3.5     | 27.5 ± 4.4      |
| Compliance, mean ± SD, ml/cm H₂O | 28.8 ± 8.7     | 28.9 ± 11.8     |
| PaO₂, mean ± SD, mm Hg         | 81.9 ± 20.5      | 82.7 ± 17.8     |
| PaO₂/FIO₂ ratio, mean ± SD, mm Hg | 93.2 ± 25.0    | 99.0 ± 27.2     |

**Definition of abbreviations:** BMI = body mass index; FIO₂ = fraction of inspired oxygen; IBW = ideal body weight; PaO₂ = arterial oxygen tension/pressure; PEEP = positive end-expiratory pressure; SD = standard deviation.

| Table 2. Outcomes |
|------------------|------------------|------------------|
| **Characteristics**, mean ± SD* | **Traditional Proning (N = 26)** | **Prolonged Proning (N = 26)** |
| Total duration prone, h          | 45.7 ± 20.8      | 56.6 ± 20.6      |
| Mean duration prone session, h   | 14.9 ± 4.3       | 23.1 ± 5.9       |
| Mean duration supine session, h  | 9.0 ± 4.7        | 11.5 ± 6.0       |
| Number of position changes       | 5.7 ± 2.6        | 4.6 ± 1.6        |
| 96-hour safety outcomes, n (%)   |                  |                 |
| Loss of central venous line      | 1 (3.8)          | 0 (0)            |
| Loss of arterial line            | 0 (0)            | 0 (0)            |
| Pressure ulcer development       | 0 (0)            | 1 (3.8)          |
| New initiation of pulmonary vasodilator | 1 (3.8)        | 0 (0)            |
| Loss of endotracheal tube        | 1 (3.8)          | 0 (0)            |
| 96-hour pulmonary outcomes, mean ± SD |                 |                 |
| PaO₂/FIO₂ ratio, mm Hg           | 143.0 ± 61.4     | 145.7 ± 40.0     |
| PEEP, cm H₂O                     | 10.5 ± 2.8       | 10.7 ± 2.8       |
| Plateau pressure, cm H₂O         | 26.6 ± 4.4       | 25.4 ± 4.3       |
| Drive pressure, cm H₂O           | 15.4 ± 5.3       | 14.7 ± 3.2       |
| Compliance, ml/cm H₂O            | 26.1 ± 8.5       | 26.9 ± 8.5       |
| Change in PaO₂/FIO₂ ratio         | 44.3 ± 63.7      | 46.6 ± 39.9      |
| Change in drive pressure          | 0.88 ± 4.95      | 0.16 ± 3.26      |
| Change in compliance, ml/cm H₂O  | -3.12 ± 4.71     | -2.21 ± 8.54     |
| 30-day outcomes                  |                 |                 |
| Alive and liberated from ventilator, n (%) | 8 (30.7)        | 9 (34.6)         |
| Ventilator-free days, mean ± SD  | 5.81 ± 9.28      | 6.27 ± 9.15      |
| ICU-free days, mean ± SD         | 4.15 ± 7.52      | 4.35 ± 7.14      |

(Continued)
duration in prone positioning and decreased number of turns and was not associated with large differences in the rate of pressure ulcers. Implementation of a prolonged proning strategy may be reasonable in the context of overburdened and resource-strained health systems.

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

Table 2. (Continued)

| Characteristic                      | Traditional Proning (N = 26) | Prolonged Proning (N = 26) |
|-------------------------------------|-----------------------------|---------------------------|
| Hospital-free days, mean ± SD       | 2.58 ± 5.40                 | 2.26 ± 4.98               |
| Mortality, n (%)                    | 15 (57.7)                   | 14 (53.8)                 |
| Location, n (%)                     |                             |                           |
| Dead                                | 15 (57.7)                   | 14 (53.8)                 |
| ICU                                 | 4 (15.4)                    | 3 (11.5)                  |
| Hospitalized (not ICU)             | 0 (0)                       | 2 (7.7)                   |
| Rehab facility                      | 5 (19.2)                    | 6 (23.1)                  |
| Home                                | 2 (7.7)                     | 1 (3.8)                   |
| Performance of tracheostomy, n (%)  | 3 (11.5)                    | 6 (23.1)                  |
| Pressure ulcer, n (%)               | 6 (23.1)                    | 4 (15.4)                  |
| Location of ulcer, n (%)            |                             |                           |
| Torso                               | 5 (19.2)                    | 2 (7.7)                   |
| Extremity                           | 1 (3.8)                     | 1 (3.8)                   |
| Head/face                           | 0 (0.0)                     | 1 (3.8)                   |
| Depth, n (%)                        |                             |                           |
| Superficial/partial thickness       | 5 (19.2)                    | 3 (11.5)                  |
| Full thickness                      | 1 (3.8)                     | 1 (3.8)                   |
| ECMO, n (%)                         | 1 (3.8)                     | 0 (0)                     |

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; FIO2 = fraction of inspired oxygen; ICU = intensive care unit; PaO2 = arterial oxygen tension/pressure; PEEP = positive end-expiratory pressure; SD = standard deviation.

*Median time from endotracheal intubation to prone positioning: 6 hours (interquartile range, 2.83–12.02 h).

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