ventilator shortages, after exhausting alternatives, ventilator sharing is a reasonable stopgap to support potentially rescuable patients for at least 2 days in centers with appropriate expertise. This approach may be most useful when additional time is needed to relocate ventilators or patients to match supply with demand. The safety and utility of prolonged ventilator sharing, when ventilators or patients cannot be relocated, is unknown. ■

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Prone Positioning of Nonintubated Patients with COVID-19

To the Editor:

Epidemiological data on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease it causes, coronavirus

Author Contributions: M.D., S.Z., S.N., S.M., A.N.-A., B.B., and N.P. were involved in data acquisition or analysis; M.D., S.Z., and N.P. wrote the manuscript or provided substantial involvement in its revision. No authors have published, posted, or submitted any related papers from this study.

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disease (COVID-19), are quickly emerging. As the pandemic progresses, scarce resources (e.g., ICU beds and mechanical ventilators) may become a rate-limiting factor in the care for these patients. Therefore, therapies to prevent the need for intubation and mechanical ventilation are desperately needed.

A recent study describing the respiratory physiology of mechanically ventilated patients with COVID-19–associated acute respiratory distress syndrome (ARDS) showed low respiratory system compliance in the supine position; however, prone positioning increased lung recruitment and improved oxygenation (1). Given the physiological benefits of prone positioning, we hypothesized that patients with COVID-19 and respiratory distress, not yet intubated but at high risk for intubation, might benefit from prone positioning. We conducted a retrospective review of our experience proning a clinical series of nonintubated patients.

Methods

Patients. Between March 23, 2020, and April 15, 2020, nine adult patients at an academic medical center with confirmed positive PCR testing results for SARS-CoV-2 RNA, with rapidly increasing oxygen requirements necessitating ICU admission but not yet requiring intubation, were determined to be appropriate clinical candidates for proning. One additional patient on the medical floor, who required an ICU consult because of increased work of breathing, was also included. Patients requiring urgent mechanical intubation were not eligible for proning.

Proning. Patients were asked to alternate every 2 hours between a prone and supine position during the day and sleep in a prone position at night, as tolerated. A physician provider supervised the first episode of proning. Patients were asked to self-prone, and nursing staff reminded patients.

Outcome measures. Primary outcome measures were the change in oxygen saturations and respiratory rate before proning and approximately 1 hour after initial proning compared with preproning. The secondary outcome was the incidence of intubation within 2 weeks of the first prone-positioning trial. All patients were followed for 28 days for hospital discharge status. Outcomes were collected retrospectively via chart review. The retrospective data for this case series were determined to be exempt by the institutional review board at the Johns Hopkins University School of Medicine.

Results

Three of the 10 patients (30%) were female, and the median age was 56 years (range, 40–80 yr). Before prone positioning, the median oxygen requirement was 40%, with four patients requiring high-flow nasal cannula (HFNC) and five patients requiring nasal cannula. The median time from onset of symptoms to ICU consultation/admission was 8.5 days (range, 5–11 d), and median time from ICU admission to prone positioning was 5 hours (interquartile range [IQR], 2.25–13.25 h). All patients received empirical antimicrobial therapy for possible community-acquired pneumonia. One patient was enrolled in a randomized clinical trial of remdesivir or placebo. Eight patients had bilateral lower-lobe infiltrate on chest imaging, two with an alveolar pattern, three with an interstitial pattern, and three with a mixed alveolar and interstitial pattern.

Oxygenation rapidly improved after prone positioning, and at 1 hour after assuming a prone position, median oxygen saturations had increased from 94% (IQR, 91–95%) to 98% (IQR, 97–99%) (Figure 1). Interestingly, after prone positioning, work of breathing had improved, as evidenced by a reduced median respiratory rate from 31 (IQR, 28–39) to 22 (IQR, 18–25) breaths/min (Figure 2). There were no adverse events with prone positioning. Patients endorsed improved dyspnea with prone positioning. Seven of the 10 patients did not require escalation of respiratory care. Eight of the 10 patients did not require intubation. The two patients who required intubation were intubated ~24 hours after the initial prone positioning. In addition, these two patients also had the highest respiratory support on admission to the ICU, with an $F_{I_{O_2}}$ of 0.50 and 0.60 on HFNC. At 28 days of follow-up, all patients had been discharged from the hospital to their homes.

Discussion

Although the value of prone positioning in mechanically ventilated patients with moderate-to-severe ARDS is compelling (2), less is known about the effects of prone positioning in spontaneously breathing, nonintubated adult patients. Case reports and retrospective reviews have demonstrated safety and improvements in oxygenation with prone positioning in patients with ARDS (3–5). In nonintubated patients with COVID-19, prone positioning together with a combined strategy of HFNC and restrictive fluid (6) or noninvasive ventilation (7) improved oxygenation. The effects of prone positioning, without positive pressure ventilation, were not isolated.

In this case series, all patients experienced significant improvement in respiratory status during the initial prone-positioning period. Five of the 6 patients on nasal cannula or room air did not require escalation of respiratory care, and 8 of 10 patients did not require invasive mechanical ventilation. The potential mechanism of benefit of prone positioning in nonintubated patients is unlikely to be related solely to improved oxygenation, as past studies have not associated improved oxygenation with survival in ARDS. Homogenous lung aeration with prone positioning (8) could result in reduced respiratory effort and lead to a lower incidence of intubation.

Although the data presented herein are intriguing, many questions remain. How long does the effect of proning last? Does the beneficial effect of proning continue after supination? Does proning prevent the need for intubation or merely delay it? Could prone positioning accelerate recovery?

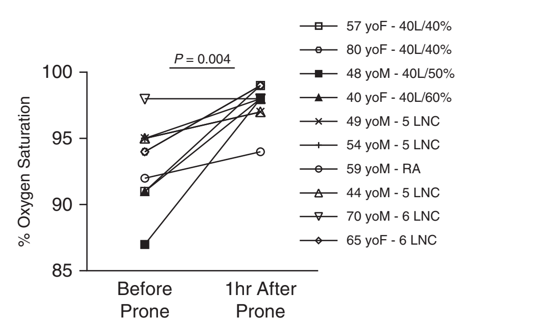

Figure 1. Oxygen saturations before prone positioning and 1 hour after prone positioning of individual patients. Solid symbols represent patients that required intubation. The *P* value was determined by using the Wilcoxon matched-pairs signed rank test. LNC = liters of nasal cannula; RA = room air; yoF = year-old female; yoM = year-old male.

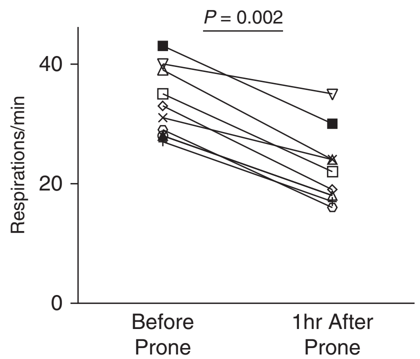

Figure 2. Respiratory rate before prone positioning and 1 hour after prone positioning of individual patients. Solid symbols represent patients who required intubation. The *P* value was determined by using the Wilcoxon matched-pairs signed rank test.

There are several limitations in the data from this case series. First, as is common with case series, selection bias is possible. Second, there was no control intervention, and the study sample was small. Third, it is uncertain whether these patients would have improved without prone positioning, although the rapid change, within 1 hour, after proning is suggestive of a favorable impact. Fourth, measures of patient dyspnea or comfort after prone positioning were not collected. Fifth, to minimize the documentation burden on nursing-staff workflow, data on patient adherence to the prone-positioning recommendation beyond the first episode of proning were not collected.

Given the potential of prone positioning as a low-cost, easily implemented, and scalable intervention, particularly in low- and middle-income countries, expeditious yet thorough testing of prone positioning in patients at risk for intubation is warranted (e.g., W. Al-Hazzani and colleagues, unpublished results [clinicaltrials.gov identifier NCT 04350723], among others). ■

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COVID-19 Severity Correlates with Weaker T-Cell Immunity, Hypercytokinemia, and Lung Epithelium Injury

To the Editor:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic that continues to wreak havoc on people's lives and livelihoods. As of June 16, 2020, the number of coronavirus disease (COVID-19) cases surpassed 8 million, and the death toll stood at more than 400,000 (1). Although the majority of the patients developed mild symptoms and eventually recovered from this disease, a significant proportion suffered from serious pneumonia and developed acute respiratory distress syndrome, septic shock, and/or multiorgan failure (2, 3). The degree of the disease severity should result from direct viral damages on epithelial surface layer and the host immune response. SARS-CoV-2 infection may trigger a dysfunctional response leading to an overproduction of cytokines (cytokine storm) and the recruitment of more immune cells into the lungs, resulting in greater damages (4). However, the immune effectors that determine or influence the severity of the disease and the reason why immune response mediates recovery in some individuals (5), but not in others, are far from clear. In this study, we addressed these issues by analyzing the blood samples of patients with COVID-19 with varying degrees of disease severity

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