A Multicenter Trial of Prolonged Prone Ventilation in Severe Acute Respiratory Distress Syndrome


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Rationale: Ventilation in the prone position for about 7 h/d in patients with acute respiratory distress syndrome (ARDS), acute lung injury, or acute respiratory failure does not decrease mortality. Whether it is beneficial to administer prone ventilation early, and for longer periods of time, is unknown.

Methods: We enrolled 136 patients within 48 h of tracheal intubation for severe ARDS, 60 randomized to supine and 76 to prone ventilation. Guidelines were established for ventilator settings and weaning. The prone group was targeted to receive continuous prone ventilation treatment for 20 h/d.

Results: The intensive care unit mortality was 58% (35/60) in the patients ventilated supine and 43% (33/76) in the patients ventilated prone (p = 0.12). The latter had a higher simplified acute physiology score II at inclusion. Multivariate analysis showed that simplified acute physiology score II at inclusion (odds ratio [OR], 1.07; p < 0.001), number of days elapsed between ARDS diagnosis and inclusion (OR, 2.83; p < 0.001), and randomization to supine position (OR, 2.53; p = 0.03) were independent risk factors for mortality. A total of 718 turning procedures were done, and prone position was applied for a mean of 17 h/d for a mean of 10 d. A total of 28 complications were reported, and most were rapidly reversible.

Conclusion: Prone ventilation is feasible and safe, and may reduce mortality in patients with severe ARDS when it is initiated early and applied for most of the day.

Keywords: prone position; respiratory distress syndrome, adult; respiration, artificial

Supportive treatment for acute respiratory distress syndrome (ARDS) usually requires tracheal intubation and mechanical ventilation with positive end-expiratory pressure (PEEP) and high concentrations of inspired oxygen. Although these measures are thought to be life-saving, there is increasing concern that mechanical ventilation itself can injure the lungs as a result of overdistension and/or cyclical airspace opening and closing, and possibly cause or contribute to multisystem organ failure in these patients (1–6).

Ventilating patients with ARDS in the prone position has repeatedly been shown to improve arterial oxygenation and to have few untoward side effects (7–13). Improvement in arterial oxygenation could allow the use of lower, less toxic, inspired oxygen concentrations and lower inflation pressures, and might also help in earlier liberation from mechanical ventilation. The vertical gravitational gradient in pleural pressure is more evenly distributed in prone position than in supine (14), thus implying a better distribution of ventilation in the dorsal areas of the lung (15) where the most impressive morphologic lung lesions are predominantly located (16). The reduction in the gravitational pleural pressure gradient that occurs on turning prone could result in less overdistension and less airspace opening and closing, thereby reducing the incidence of ventilator-induced lung injury and multisystem organ failure (17–20).

Gattinoni and colleagues (21) found no improvement in survival in a randomized trial of prone ventilation applied in the course of ARDS or acute lung injury for an average of 7 h/d for 10 d. On post hoc analysis, however, 10-d mortality was found to be significantly lower in the prone group as compared with the supine group in the quartile with the lowest Pao2/Fio2 ratio (i.e., ≈ 88 mm Hg), the quartile with the highest Vt/Fio2 ratio (i.e., > 12 ml/kg), and the quartile with the highest (i.e., > 49) simplified acute physiology score II (SAPS II). In patients with a variety of causes of acute respiratory failure, Guérin and colleagues (22) observed no improvement in survival using prone ventilation instituted shortly after intubation and applied for a mean of 8.6 h/d for a mean of 4.1 d. We hypothesized that prone ventilation would decrease mortality if it were implemented early in the course of ARDS, applied for most of the day, and maintained for a prolonged period of time. Preliminary data have been published in abstract form (23, 24).

METHODS

Patients and Randomization

The study was conducted between December 1998 and September 2002. Patients were recruited from 13 intensive care units: 12 in Spain and 1 in Mexico. This study was approved by the Comité Ético de Investigación Clínica of Hospital de Sant Pau (which served as the coordinating center). Informed signed consent was obtained from patients’ next of kin.

Inclusion criteria were intubation, mechanical ventilation, over 18 yr of age, and meeting the American–European consensus conference

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definition for ARDS (25). In addition, diffuse bilateral infiltrates on the chest X-ray had to be present. Noninclusion criteria are mentioned in the online supplement.

A sequence of random numbers was computer-generated. This sequence was partitioned into blocks of different size according to the expected number of inclusions at each participating center. Blocks had an equal number of supine and prone position assignments; one center had a block of 30 patients, one center had a block of 24 patients, five centers had blocks of 20 patients each, and six centers had blocks of 16 patients each. Concealment was performed using sealed opaque envelopes prepared by an independent person. All centers had experience in implementing prone ventilation.

The treatment guidelines, including mechanical ventilation settings (maximal VT = 10 ml/kg and maximal plateau airway pressure = 35 cm H₂O, or up to 40 cm H₂O when chest wall stiffness was clinically suspected), weaning (using T-piece trials or pressure support ventilation), sedation, and data collection are available in the online supplement.

Outcomes and Statistics

Our primary outcome variable was intensive care unit mortality. Secondary endpoints were hospital mortality, associated complications, and length of stay. On the basis of previous experience (26), we estimated that the mortality in patients ventilated supine would be 50%, and calculated a need to enroll 200 patients, 100 in each arm, to detect a decrease in mortality rate from 50% (supine group) to 30% (prone group) using a two-sided test, a type I error of 0.05, and a power of 80%. Estimates were a compromise between clinical importance (decrease in mortality rate) and feasibility (number of patients to be enrolled).

Analysis was by intention-to-treat. Categorical data were compared by means of the χ² or Fisher’s exact test, and the Student’s t test was used for quantitative data. The time course of respiratory variables in the two groups was compared using a two-way analysis of variance for repeated measures. Intensive care unit cumulative survival plots for supine and prone groups were constructed using the Kaplan-Meier method, and the log-rank test was used to determine significance. We also looked for independent risk factors for mortality by entering variables into a multivariate analysis using logistic regression. SAPS IIIs were used as a continuous variable in the logistic regression. Like other authors (21), we analyzed our findings for dichotomized SAPS IIIs (i.e., SAPS II < 50 and SAPS II > 50 at randomization).

All data presented are means (± SD). Additional details are available in the online supplement.

RESULTS

Because of a marked decrease in the number of patients enrolled in the last year, the study was aborted after 142 participants had been randomized (62 supine and 80 prone). Of these, 136 (60 supine and 76 prone) were evaluated (Figure 1). Five patients allocated to the supine group were crossed-over to prone position immediately after randomization due to hemodynamic instability, and the pulmonary capillary wedge pressure (PCWP) was 33 mm Hg. This patient was transferred to a referral hospital for possible open heart surgery due to the suspicion of acute mitral regurgitation. *Five patients allocated to the supine group were crossed over to the prone group. **This patient was lost to follow-up.
Conjunctival hemorrhage and pressure sores were observed in patients, but rapidly improved when patients were turned supine. Edema (facial, limbs, thorax) was observed in 14 patients, but did not differ between the supine and the prone groups. Five patients needed to be reintubated (one allocated to prone) was diagnosed with ventilator-associated pneumonia after reintubation. None of the patients who had an unplanned extubation died. The results of multiple logistic regression analysis indicated two patients each, and one patient exhibited a vascular catheter malfunction during continuous veno-venous hemofiltration.

Outcome variables are summarized in Table 3. Intensive care unit mortality was 58% (35/60) in the patients ventilated supine and 43% (33/76) in the patients ventilated prone—a 15% absolute and 25% relative decrease that was not statistically significant (p = 0.12). A similar trend was observed for hospital mortality. No statistical difference (p = 0.27, log-rank test) was observed in the cumulative intensive care unit survival Kaplan-Meier plots between the two groups (Figure 5). Intensive care unit length of stay was shorter in nonsurvivors compared with survivors, but did not differ between the supine and the prone groups. With respect to unplanned extubations, only one occurred during the turn. Five patients needed to be reintubated (one allocated to supine, four allocated to prone). Only one patient (allocated to prone) was diagnosed with ventilator-associated pneumonia after reintubation. None of the patients who had an unplanned extubation died.

Complications related to prone position per se were few and clinically mild. Edema (facial, limbs, thorax) was observed in 14 patients, but rapidly improved when patients were turned supine. Conjunctival hemorrhage and pressure sores were observed in were not followed in 6 patients. These data are reported in the online supplement.

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### TABLE 1. CHARACTERISTICS OF THE PATIENTS AT INCLUSION

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Supine Group (n = 60)</th>
<th>Prone Group (n = 76)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>54 ± 16</td>
<td>54 ± 17</td>
<td>0.98</td>
</tr>
<tr>
<td>Male/Female, n</td>
<td>42/18</td>
<td>44/32</td>
<td>0.10</td>
</tr>
<tr>
<td>SAPS II</td>
<td>38 ± 14</td>
<td>43 ± 16</td>
<td>0.08</td>
</tr>
<tr>
<td>ARDS etiology, n</td>
<td></td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>25</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Aspiration</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>16</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Multiple trauma</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other causes</td>
<td>11</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Comorbidities, n</td>
<td></td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Immunosupression</td>
<td>11</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>HIV infection</td>
<td>2</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Nonpulmonary organ/system failures*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular, n (%)</td>
<td>21 (35)</td>
<td>22 (29)</td>
<td>0.50</td>
</tr>
<tr>
<td>Gastrointestinal, n (%)</td>
<td>22 (37)</td>
<td>16 (21)</td>
<td>0.06</td>
</tr>
<tr>
<td>Renal, n (%)</td>
<td>8 (13)</td>
<td>20 (26)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hematologic, n (%)</td>
<td>7 (12)</td>
<td>17 (22)</td>
<td>0.10</td>
</tr>
<tr>
<td>Hepatic, n (%)</td>
<td>6 (10)</td>
<td>6 (8)</td>
<td>0.80</td>
</tr>
<tr>
<td>Neurologic, n (%)</td>
<td>2 (3)</td>
<td>3 (4)</td>
<td>1</td>
</tr>
<tr>
<td>No. of nonpulmonary organ failures</td>
<td>1.1 ± 1.2</td>
<td>1.1 ± 1.1</td>
<td>0.98</td>
</tr>
<tr>
<td>No. of patients with vasopressors, n (%)</td>
<td>44 (73)</td>
<td>63 (83)</td>
<td>0.21</td>
</tr>
<tr>
<td>No. of patients who received non-invasive ventilation, n (%)</td>
<td>25 (42)</td>
<td>31 (41)</td>
<td>1</td>
</tr>
<tr>
<td>No. of patients with chest wall stiffness, n (%)</td>
<td>14 (23)</td>
<td>14 (18)</td>
<td>0.60</td>
</tr>
<tr>
<td>Respiratory variables†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P_{acO_2}$, mm Hg</td>
<td>126 ± 94</td>
<td>107 ± 65</td>
<td>0.19</td>
</tr>
<tr>
<td>$F_{O_2}$, %</td>
<td>0.79 ± 0.21</td>
<td>0.84 ± 0.19</td>
<td>0.13</td>
</tr>
<tr>
<td>$P_{acO_2}$/$F_{O_2}$, mm Hg</td>
<td>161 ± 94</td>
<td>132 ± 74</td>
<td>0.06</td>
</tr>
<tr>
<td>$P_{acO_2}$, mm Hg</td>
<td>43 ± 11</td>
<td>45 ± 9</td>
<td>0.25</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>19 ± 4</td>
<td>20 ± 4</td>
<td>0.14</td>
</tr>
<tr>
<td>$V_t$, ml/kg</td>
<td>8.6 ± 1.6</td>
<td>8.3 ± 1.7</td>
<td>0.20</td>
</tr>
<tr>
<td>PEEP, cm H$_2$O</td>
<td>12.3 ± 2.4</td>
<td>12.4 ± 1.9</td>
<td>0.89</td>
</tr>
<tr>
<td>Plateau airway pressure, cm H$_2$O</td>
<td>32 ± 4</td>
<td>32 ± 5</td>
<td>0.61</td>
</tr>
<tr>
<td>Arterial pH, units</td>
<td>7.35 ± 0.1</td>
<td>7.35 ± 0.08</td>
<td>0.77</td>
</tr>
<tr>
<td>$Crs$, ml/cm H$_2$O</td>
<td>32 ± 10</td>
<td>31 ± 11</td>
<td>0.60</td>
</tr>
<tr>
<td>$Crs$/kg, ml/cm H$_2$O/kg</td>
<td>0.47 ± 0.16</td>
<td>0.44 ± 0.15</td>
<td>0.28</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** ARDS = acute respiratory distress syndrome; $Crs$ = respiratory system compliance; PEEP = positive end-expiratory pressure; SAPS = simplified acute physiology score.

* Some patients had more than one organ/system failure at inclusion.

† All measurements in supine position in both groups and obtained 30–60 min after randomization.

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risk of mortality: the SAPS II at inclusion (odds ratio [OR], 1.07; 95% confidence interval [CI], 1.04–1.11; p < 0.001), the number of days elapsed between ARDS diagnosis and inclusion (OR, 2.83; 95% CI, 1.63–4.90; p < 0.001) and random allocation to supine position (OR, 2.53, 95% CI, 1.09–5.89; p = 0.03).

The post hoc analysis performed in the 103 patients with a SAPS II of less than 50 showed an intensive care unit mortality of 53% (26/49) in the patients ventilated supine and 33% (18/54) in the patients ventilated prone (p = 0.049). The SAPS II in the two groups at the time of randomization tended to be higher in the prone group (33 ± 10 supine, 36 ± 9 prone; p = 0.10). The 33 patients with a SAPS II of 50 or greater showed an intensive care unit mortality of 82% (9/11) in the patients ventilated supine and 68% (15/22) in the patients ventilated prone (p = 0.68). The SAPS II was similar in both groups at the time of randomization (60 ± 10 supine, 62 ± 15 prone; p = 0.67). Intensive care unit length of stay for the 24 nonsurvivors with SAPS IIs of 50 or greater was 4 ± 3.7 d.

The use of opiates, sedatives, and neuromuscular blocking agents is reported in the online supplement.

DISCUSSION

The important finding in this study was that patients with ARDS who received mechanical ventilation in the prone position within 48 h of meeting entry criteria, and who remained prone for most of the day and until preset weaning criteria were met, had a 15% absolute and a 25% relative reduction in intensive care unit mortality compared with those who were ventilated supine. Although this improvement did not reach statistical significance, the patients randomized to receive prone ventilation showed a trend toward a higher severity score in comparison with those ventilated supine. The multiple logistic regression analysis
shown, however, that supine position was an independent risk factor for mortality (OR, 2.53). The post hoc analysis indicating a subset of patients that benefited from prone position treatment should be interpreted very cautiously.

Two previous trials (21, 22) failed to find improved survival in adult patients ventilated prone compared with those ventilated supine. Both had design issues limiting the strength of their conclusions.Gattinoni and colleagues (21) only applied prone ventilation for a mean of 8.6 h/d for a mean of 10 d, and many of the patients were likely not enrolled until late in the course of ARDS (i.e., nearly 25% had pressure sores at entry). Ventilation and weaning guidelines were not employed, and although 304 patients were enrolled, the study was underpowered and was stopped early because caregivers were unwilling to continue randomizing patients to supine ventilation. On the basis of post hoc analysis, Gattinoni and colleagues (21) suggested that prone ventilation had a lower risk of death at Day 10 in patients with the highest quartile of SAPS II (i.e., > 49). Our post hoc analysis led to a different conclusion. Such a discrepancy can be explained by a number of factors: (1) Gattinoni and colleagues only found a significant difference when they analyzed the 10-d mortality rate; (2) the patients we studied were probably enrolled earlier in the course of ARDS than those studied by Gattinoni and colleagues, as suggested by the high percentage (∼23%) of pressure sores at study entry; (3) our patients were treated with prone positioning over a longer period; (4) routine care (for instance, antibiotic policy, strategies to implement other supportive treatment, such as dialysis or vasoactive drugs, decisions to withdraw treatment, etc.) could have differed between these studies; and (5) in the study by Gattinoni and colleagues, the VT decreased over time in patients allocated to supine and increased over time in patients allocated to prone (an average change that was statistically significant). This may have been deleterious, and such a change did not arise in our study. VT was about 655 ml at baseline in the trial by Gattinoni and coworkers (and increased over time), and about 574 ml in our trial (and remained virtually constant over time). These differences, alone or in combination, could account for the differences in the results. From a clinical point of view, a plausible explanation is that prone position works like any other treatment when it is: instituted as early as possible (as probably occurred in our study in comparison to that of Gattinoni and coworkers); given at appropriate doses (our dose per day was higher than that of Gattinoni and colleagues); and given for a sufficient period of time—our treatment was delivered until a major improvement in gas exchange was observed and weaning was envisaged.

Guérin and colleagues (22) enrolled patients earlier, but only applied prone ventilation for a mean of 8.6 h/d for a mean of

**TABLE 2. PRONE POSITION IMPLEMENTATION**

<table>
<thead>
<tr>
<th>Day</th>
<th>Patients in Prone Position (n)</th>
<th>Hours in Prone Position (Mean ± SD)</th>
<th>Patients Undergoing Weaning from the Ventilator (n)</th>
<th>Deaths in the ICU (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>14 ± 7.1</td>
<td>—</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>20.4 ± 3.4</td>
<td>—</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>18.7 ± 4.8</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>23</td>
<td>19.4 ± 4</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>10</td>
<td>16</td>
<td>18.3 ± 5</td>
<td>33</td>
<td>21</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
<td>12.6 ± 9.9</td>
<td>21</td>
<td>29</td>
</tr>
</tbody>
</table>

*Definition of abbreviation: ICU = intensive care unit.

* Cumulative number of patients.

**TABLE 3. OUTCOME VARIABLES**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Supine Group (n = 60)</th>
<th>Prone Group (n = 76)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU mortality, n (%)</td>
<td>35 (58)</td>
<td>33 (43)</td>
<td>0.12</td>
</tr>
<tr>
<td>95% CI</td>
<td>45–71%</td>
<td>32–55%</td>
<td></td>
</tr>
<tr>
<td>Hospital mortality, n (%)</td>
<td>37 (62)</td>
<td>38 (50)</td>
<td>0.22</td>
</tr>
<tr>
<td>95% CI</td>
<td>48–74%</td>
<td>38–62%</td>
<td></td>
</tr>
<tr>
<td>ICU length of stay, d</td>
<td>19.1 ± 23.1</td>
<td>20.5 ± 18.2</td>
<td>0.70</td>
</tr>
<tr>
<td>Survivors</td>
<td>22 ± 14.1</td>
<td>27.9 ± 18.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>17 ± 27.9</td>
<td>10.9 ± 12.5</td>
<td></td>
</tr>
<tr>
<td>Pneumothorax, n (%)</td>
<td>4 (6.7)</td>
<td>7 (9.2)</td>
<td>0.76</td>
</tr>
<tr>
<td>Unplanned tracheal extubation, n (%)</td>
<td>1 (1.7)</td>
<td>6 (7.9)*</td>
<td>0.13</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia, n (%)</td>
<td>9 (15)</td>
<td>14 (18.4)</td>
<td>0.65</td>
</tr>
<tr>
<td>Days under vasopressors†</td>
<td>6.35 ± 5.03</td>
<td>5.43 ± 5.22</td>
<td>0.32</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: CI = confidence interval; ICU = Intensive care unit.

Unless otherwise specified, all values presented are mean ± SD.

* Includes one patient accidentally extubated during the turning procedure.

† A total of 54 supine patients and 70 prone patients received vasopressors for at least 1 d.
with ARDS (at least in the early phase) show normal PaCO₂ ratio (27), and, on average, spontaneously breathing patients had an average respiratory system compliance of 1238 AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 173 2006

ance in comparison with normal subjects (our patients, at inclu-

patients with ARDS exhibit a lower respiratory system compli-

We speculate that a potentially harmful scenario may occur.

ative treatment with mechanical ventilation was delayed in these

patients, as they were intubated at a later stage in their illness.

We found that the number of days elapsed between ARDS

onset and study entry was an independent risk factor for mortal-

ity. This might be attributed to the fact that institution of support-

ive treatment with mechanical ventilation was delayed in these

patients, as they were intubated at a later stage in their illness.

We speculate that a potentially harmful scenario may occur.

Patients with ARDS exhibit a lower respiratory system compli-

ance in comparison with normal subjects (our patients, at inclu-

nation with PEEP and prone positioning in these patients, the

mortality rates exceed 50% (32, 33), in line with our data. An-

other factor that could have contributed to the mortality rate

in our study is excessive Vt and/or excessive end-inspiratory

plateau airway pressure. Nevertheless, only 4 patients in the

supine group and 12 in the prone group received VtS and/or
developed end-inspiratory plateau airway pressures above the

preset limits of our recommended guidelines. The more frequent
occurrence of patients receiving a potentially injurious ventila-
tion in the prone group, if anything, negatively biased our results.

In a randomized trial performed in patients with ARDS and

comparing conventional ventilation with high-frequency oscilla-
tory ventilation (34), the ventilator settings in the conventional
ventilation group were similar to ours, and the mortality at Day
30 was 52%.

Our study is limited by the facts that it was stopped due to
decreased patient accrual and is underpowered. This may have
occurred because of difficulties associated with enrolling patients
within the narrow randomization window. Having to evaluate
and enroll patients within 48 h of meeting entry criteria required
continuous motivation and considerable effort from investiga-
tors, and this may have worn with time. In addition, we had
only limited funding available to conduct the trial (€9616) at a
time when heavily funded pharmaceutical studies were compet-
ing for similar patients. Finally, although there were few compli-
cations related to prone position per se and to the turning proce-
dures, it was unfortunate that the study design did not foresee
the need to record complications occurring during routine supine
position treatment. The relevance of complications attributable
to prone positioning should therefore be interpreted with
cautiousness.

In conclusion, using prone ventilation for prolonged periods
of time is both feasible and safe. It may reduce mortality in
ARDS patients. To date, none of the three trials designed to
evaluate the effect of prone ventilation on mortality in adult
patients with ARDS have been sufficiently powered to confirm
a benefit or the lack thereof. Our results suggest that the duration
of prone positioning may be an important determinant of its
effectiveness, as may the interval between the onset of ARDS
and its application. An appropriately powered trial is needed
to reevaluate whether prone ventilation reduces mortality in
patients with ARDS.

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