Prone position: the time of certainty*

Décubitus ventral : le temps des certitudes

C. Guérin

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Abstract

After four negative randomized controlled trials testing the effects of prone positioning on patient outcome, a fifth randomized controlled trial (PROSEVA trial) has been able to show a significant reduction in mortality in patients with acute respiratory distress syndrome (ARDS). In this trial including patients with ARDS severity criteria (PaO$_2$/FiO$_2$ ratio less than 150 mmHg with positive end expiratory pressure of 5 cmH$_2$O or more, FiO$_2$ of 0.6 or more, and tidal volume around 6 ml/kg of predicted body weight) confirmed 12 to 24 h after the onset of ARDS, the day 28 mortality in the supine group (229 patients) was 32.8% versus 16% in the prone group (237 patients) ($p < 0.001$). The same significant reduction in mortality was confirmed at day 90. The reasons for this result that contrasted with the previous ones as well as the refinements that were introduced in the trials over time are discussed in this review article. From the results of the two meta-analyses and the last randomized controlled trial, there is a strong signal to use prone position in patients suffering from ARDS with severity criteria. More data are needed about the effects of prone position on ventilation-induced lung injury in humans.

Keywords

Acute respiratory distress syndrome · Prone position · Ventilator-induced lung injury · Mechanical ventilation

Résumé

Après quatre essais randomisés contrôlés ayant testé l’effet du décubitus ventral sur la survie des patients avec syndrome de détresse respiratoire aiguë (SDRA) ou insuffisance respiratoire aiguë hypoxémique et qui se sont avérés négatifs, un cinquième, l’essai PROSEVA, a finalement mis en évidence un net bénéfice du décubitus ventral chez des malades avec SDRA sévère. Dans cet essai, des patients ayant un SDRA avec des critères de sévérité (PaO$_2$/FiO$_2$ inférieure à 150 mmHg avec une pression en fin d’expiration [PEP] supérieure ou égale à 5 cmH$_2$O, FiO$_2$ supérieure ou égale à 60 % et volume courant à 6 ml/kg de poids prédit par la taille et le sexe), confirmés 12 à 24 heures après le diagnostic de SDRA, la mortalité à j28 du groupe décubitus dorsal (229 patients) était de 32,8 % versus 16,0 % dans le groupe décubitus ventral (237 patients) [$p < 0.001$]. La même différence significative a été mise en évidence à j90. Les raisons que l’on peut avancer pour expliquer ces résultats qui contrastent, surtout dans leur intensité plus que dans leur nature, avec les essais précédents sont discutées dans cette revue. En prenant en considération les résultats des deux méta-analyses et de l’essai PROSEVA, nous avons maintenant des arguments forts pour proposer l’usage routinier du décubitus ventral chez les patients avec SDRA sévère. D’autres études sont nécessaires pour affiner nos connaissances quant à l’effet du procubitus sur les lésions induites par la ventilation mécanique.

Mots clés

Syndrome de détresse respiratoire aiguë · Décubitus ventral · Lésions pulmonaires induites par la ventilation mécanique

Introduction

Prone positioning patients with acute respiratory distress syndrome (ARDS) has been used for many years, but no single randomized controlled trial until recently had been able to demonstrate any benefit to patient outcome. In this review, we will not cover the pathophysiological rationale for using prone position in ARDS patients. Briefly, prone position is an attractive tool for its capacity to improve...
oxygenation, sometimes dramatically, in the large majority of patients with ARDS, which is a relevant property for patients with severe hypoxemia. Furthermore, there are some evidence in humans that prone position can promote alveolar recruitment without overdistension and, hence, can reduce or prevent ventilator-induced lung injury (VILI) and minimize the lung strain at no pressure and volume cost. The goal of this review is to briefly summarize the evidence-based medicine and discuss the results of the last randomized controlled trial that demonstrates a significant benefit in terms of mid-term patient survival. Furthermore, the reasons for this result will also be discussed, highlighting the refinements done in the trials in this field over time.

Previous trials on prone position in ARDS

Four randomized controlled trials comparing prone to supine position were completed in the last decade [1–4]. Each failed to demonstrate a benefit to patient survival (Table 1). In the post-hoc analysis of the first Italian trial [1], patients with the most severe hypoxemia (\( \text{PaO}_2/\text{FiO}_2 \leq 88 \text{ mmHg} \)) significantly benefited from proning with a 50% relative reduction of mortality at day 10 (from 47.2% in the supine group to 23.1% in the prone group). The first meta-analysis on grouped data [5] found that prone positioning improved survival significantly (relative risk reduction of 16%) in those patients with the most severe hypoxemia at the threshold of 100 mmHg \( \text{PaO}_2/\text{FiO}_2 \) ratio. Interestingly, this result was consistently found in the individual [6] meta-analysis that included only the four trials discussed previously. Also interesting was the lack of significant statistical heterogeneity across the trials [5], even though some clinical heterogeneity among these was expected and acknowledged. From this basis, an experts’ panel decided that prone position was a proven beneficial strategy and should be recommended in severe ARDS (\( \text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mmHg} \)) [7] according to the Berlin definition [8]. It should be noted that in the post-hoc analysis of the meta-analysis on grouped data, prone position could benefit to patient survival above that threshold of \( \text{PaO}_2/\text{FiO}_2 \) ratio in the range of 100 to 130 mmHg [5].

The PROSEVA trial. Implementation and main results

With the aim to further refine the previous trials, we designed and completed a fifth trial in 26 intensive care units (ICUs) in France and one ICU in Spain [9]. Its design brought up specific new features. First, lung-protective mechanical ventilation was used (tidal volume at 6 ml/kg of predicted body weight as starting setting and plateau pressure maintained below 30 cmH\(_2\)O) and weaning from mechanical ventilation including the interruption of sedation was standardized. Second, neuromuscular blockade use was strongly recommended, as this intervention was shown to improve survival in severe ARDS [10]. Third, 12–24 h stabilization period before randomization was mandated. This approach was thought to select the most severe ARDS patients by discarding those with atelectasis or hydrostatic pulmonary edema as important contributors to the acute hypoxemia [11]. Fourth, patients with severe ARDS were included. Severe ARDS was defined as \( \text{PaO}_2/\text{FiO}_2 < 150 \text{ mmHg} \) with positive end expiratory pressure (PEEP) and FiO\(_2\) of at least 5 cmH\(_2\)O and 0.6, respectively. The study was first designed in the years 2005–2006 and, hence, the criteria for ARDS severity were not the same as those used in the Berlin definition released in 2012 [8]. Fifth, proning sessions lasting 16 consecutive hours or more were mandated and the first prone position session had to start within one hour after randomization. Sixth, crossover was not allowed except for life-threatening hypoxemia defined by strict criteria. Seventh, stopping criteria for proning

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<tbody>
<tr>
<td>( n ) patients (SP/PP)</td>
<td>152/152</td>
<td>378/413</td>
<td>60/76</td>
<td>174/168</td>
<td>229/237</td>
</tr>
<tr>
<td>% of ARDS (SP/PP)</td>
<td>93.3/94.7</td>
<td>28/33.9</td>
<td>100/100</td>
<td>100/100</td>
<td>100/100</td>
</tr>
<tr>
<td>( \text{PaO}_2/\text{FiO}_2 ) (mmHg)*</td>
<td>127</td>
<td>150</td>
<td>147</td>
<td>113</td>
<td>100</td>
</tr>
<tr>
<td>Tidal volume (ml/kg)*</td>
<td>10.3</td>
<td>8</td>
<td>8.4</td>
<td>8</td>
<td>6.1</td>
</tr>
<tr>
<td>MBW</td>
<td>MBW</td>
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<td>MBW</td>
<td>PBW</td>
<td>PBW</td>
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<tr>
<td>PEEP (cmH(_2)O)*</td>
<td>10</td>
<td>8</td>
<td>12</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>PP session duration (average hours per session)</td>
<td>7</td>
<td>8</td>
<td>17</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Mortality (SP/PP) (%)</td>
<td>25/21.1</td>
<td>31.5/32.4</td>
<td>58/43</td>
<td>32.8/31</td>
<td>32.8/16</td>
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*computed from the arithmetic mean values of the average values in each group

were based on improvement of oxygenation and complications due to the procedure.

The main end-point was day 28 mortality and secondary end-point was day 90 mortality.

The trial demonstrated a 50%-reduction in the relative risk of mortality favoring the prone position group (Table 1). The day 28 mortality in the supine position group was 32.8% versus 16% in the prone position group (p < 0.001). The day 90 mortality was 41% and 23.6% in the supine and prone groups (p < 0.001), respectively. Interestingly, both day 28 and day 90 mortality rates measured in the interim analysis, which was planned by study design, achieved similar significant results as these in the final analysis. Therefore, the results were consistent throughout the trial. The benefit of prone position was observed at each quartile of PaO₂/FIO₂ ratio over the range of 45 to 149 mmHg PaO₂/FIO₂.

The PROSEVA trial. Possible reasons for the positive result

The result of present trial is actually not surprising as it is in line with the two previous meta-analyses and the trend shown in the previous trials by Mancebo et al. [3] and Taccone et al. [4] The effect size is large: 16% in absolute and 50% in relative reduction in mortality. It is larger than that found in the two previous meta-analyses. Furthermore, the reduction of the relative risk ratio in the experimental group (prone position) was the lowest ever reported in the largest trials (more than 100 patients enrolled per arm) testing ventilator or non-ventilator strategies in ARDS patients (Table 2). It should be noted that there is any trend in the mortality over time among these trials.

The main reason why prone position was able to significantly reduce mortality could be ascribed to the prevention of VILI. However, we don’t have data to support this from our trial as we did not measure biomarkers nor perform lung imaging for instance. Therefore, additional data are required to explain the results of the trial.

The second reason for the positive result is that the groups were not completely balanced (by chance) for SOFA score and use of vasopressors and neuromuscular blocking agents. Even after controlling for these confounding factors, the effect of prone position on mortality remained statistically significant.

Third, the rate of complications was not different between the two groups, contrary to what had happened in the previous trials. This argument may be not an explanation to the

<table>
<thead>
<tr>
<th>Trial’s acronym or intervention tested</th>
<th>Experimental group</th>
<th>Control group</th>
<th>Relative risk (95% CI)</th>
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<tbody>
<tr>
<td>ARMA [13]</td>
<td>432</td>
<td>429</td>
<td>0.68 (0.51–0.90)</td>
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<tr>
<td>FACTT [14]</td>
<td>503</td>
<td>497</td>
<td>0.90 (0.69–1.10)</td>
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<td>ALVEOLI [15]</td>
<td>276</td>
<td>25.1</td>
<td>0.88 (0.60–1.29)</td>
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<td>EXPRESS [16]</td>
<td>385</td>
<td>45.4</td>
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<tr>
<td>LOVS [17]</td>
<td>475</td>
<td>35.4</td>
<td>0.85 (0.65–1.10)</td>
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<tr>
<td>ACURASYS [10]</td>
<td>178</td>
<td>31.6</td>
<td>0.68 (0.48–0.98)</td>
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<tr>
<td>Aerosolized albuterol [18]</td>
<td>152</td>
<td>23.0</td>
<td>1.30 (0.83–1.77)</td>
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<tr>
<td>BALTI-2 [19]</td>
<td>162</td>
<td>34.0</td>
<td>1.47 (1.03–2.08)</td>
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<tr>
<td>OSCILLATE [7]</td>
<td>275</td>
<td>40.0</td>
<td>1.41 (1.12–1.61)</td>
</tr>
<tr>
<td>OSCAR [20]</td>
<td>398</td>
<td>41.7</td>
<td>1.03 (0.75–1.40)</td>
</tr>
<tr>
<td>PROSEVA [9]</td>
<td>237</td>
<td>16.0</td>
<td>0.39 (0.25–0.63)</td>
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</table>
result but reveals that the caregivers and teams were experts in doing the maneuver safely. This is an important point to take into account. Furthermore, there was a lower rate of cardiac arrest in the prone position group as compared to the other group. The reason for this finding was not clear. It should be noted that the mortality in the control group was in the range of that reported in the largest trials done in ARDS patients (Table 2) and was the same as in the trial done by Taccone et al. (Table 3).

Fourth, the prone position was applied early in the ARDS course, for long sessions and the rate of crossover was the lowest reported across the five trials (Table 2). Finally, a 12–24 h period was mandated for the ARDS to be confirmed. This was an inclusion criterion into the trial. This feature might have played a role in the result. Villar et al. [11] showed that this strategy would select patients with the greater severity. Furthermore, Costa et al. [12] found that increasing ARDS severity according to the Berlin definition was associated to a worsened prognosis if the assessment of oxygenation (PaO2/FiO2 ratio) was taken into account at 24 h. The effect of ARDS stage on mortality was not significant when oxygenation was assessed at baseline.

### Refinements of the trials over time

The story of the randomized controlled trials in the field of prone positioning in ARDS is interesting because five large trials have been done totaling 2039 patients (1476 “true” ARDS), which is substantial for a treatment that was early seen as cosmetic or irrelevant and potentially harmful. Also of interest is to consider the refinements that have been done in the implementation of the mechanical ventilation and the procedure, in particular the lung-protective mechanical ventilation and the duration of the prone sessions. The early trials [1,2] did not provide with any of these (Table 1). The third trial [3] featured for the first time long proning sessions and showed that this was not harmful. The fourth trial [4] aimed to apply both strategies, i.e., lung-protective ventilation and long proning sessions. In our trial this was also true and even more as the tidal volume was maintained between 6 and 7 ml/kg of predicted body weight and plateau pressure lower than 30 cmH2O during the first days.

Another refinement was the patient selection. In the trial by Taccone et al., the randomization was stratified according to the level of hypoxemia at the threshold of 100 mmHg PaO2/FiO2 ratio. However, the patients were included from the level of PaO2/FiO2 of 200 mmHg. In our trial we were straightforward in including severe ARDS below 150 mmHg PaO2/FiO2 ratio.

### Conclusion

There are now several lines of evidence that strongly support the early use of long prone position sessions in patients with severe ARDS defined as PaO2/FiO2 ratio less than 150 mmHg. Further studies are required to better understand the mechanisms subtending the observed improvement in patient outcome and also the pathophysiological events that may occur during the first 24 h after having defined the ARDS.

### Conflict of interest

C. Guerin do not have any conflict of interest to declare.

### References