SESSION THÉMATIQUE

Prone position: the time of certainty*

Décubitus ventral : le temps des certitudes

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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 (PaO2/FiO2 ratio less than 150 mmHg with positive end expiratory pressure of 5 cmH2O or more, FiO2 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 hypoxémiantes 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 (PaO2/FiO2 inférieure à 150 mmHg avec une pression en fin d’expiration [PEP] supérieure ou égale à 5 cmH2O, FiO2 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 (PaO₂/FiO₂ ≤ 88 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 PaO₂/FiO₂ 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 (PaO₂/FiO₂ ≤ 100 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 PaO₂/FiO₂ 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 cmH₂O) 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 PaO₂/FiO₂ < 150 mmHg with positive end expiratory pressure (PEEP) and FiO₂ of at least 5 cmH₂O 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>
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<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>
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<td>PaO₂/FiO₂ (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>PEEP (cmH₂O)*</td>
<td>MBW</td>
<td>MBW</td>
<td>PBW</td>
<td>PBW</td>
<td>PBW</td>
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<tr>
<td>PP session duration (average hours per session)</td>
<td>7</td>
<td>8</td>
<td>12</td>
<td>10</td>
<td>10</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