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 (PaO_2/FiO_2 ratio less than 150 mmHg with positive end expiratory pressure of 5 cmH_2O 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 hypoxémiante 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_2O, $FiIO_2$ 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

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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 ($PaO_2/FiO_2 \leq 88$ 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 PaO_2/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 ($PaO_2/FiO_2 \leq 100$ 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 PaO_2/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 $PaO_2/FiO_2 < 150$ 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*, cross-over was not allowed except for life-threatening hypoxemia defined by strict criteria. *Seventh*, stopping criteria for proning

Table 1 Ventilator settings, prone position duration and mortality in the five completed trials

First author	Gattinoni [1]	Guerin [2]	Mancebo [3]	Taccone [4]	Guerin [9]
n patients (SP/PP)	152/152	378/413	60/76	174/168	229/237
% of ARDS (SP/PP)	93.3/94.7	28/33.9	100/100	100/100	100/100
PaO$_2$/FIO$_2$ (mmHg)*	127	150	147	113	100
Tidal volume (ml/kg)*	10.3	8	8.4	8	6.1
	MBW	MBW	PBW	PBW	PBW
PEEP (cmH$_2$O)*	10	8	12	10	10
PP session duration (average hours per session)	7	8	17	18	17
Mortality (SP/PP) (%)	25/21.1	31.5/32.4	58/43	32.8/31	32.8/16

*computed from the arithmetic mean values of the average values in each group

SP: supine position, PP: prone position group, MBW: measured body weight, PBW: predicted body weight computed from patient's height and gender, PEEP: positive end-expiratory pressure, FiO$_2$: fraction of oxygen in air

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 PaO_2/FIO_2 ratio over the range of 45 to 149 mmHg PaO_2/FIO_2.

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 2 Mortality rate in large trials in ARDS

Trial's acronym or intervention tested	Experimental group			Control group			Relative risk (95% CI)
	n patients	Definition	Mortality rate	n patients	Definition	Mortality rate	
ARMA [13]	432	Lower VT	31.0	429	Higher VT	39.8	0.68 (0.51–0.90)
FACTT [14]	503	Restrictive fluid strategy	25.5	497	Liberal fluid strategy	28.4	0.90 (0.69–1.10)
ALVEOLI [15]	276	Higher PEEP	25.1	273	Lower PEEP	27.5	0.88 (0.60–1.29)
EXPRESS [16]	385	Recruitment augmented	35.4	382	Minimal distension	39.0	0.85 (0.64–1.15)
LOVS [17]	475	Higher PEEP	36.4	508	Lower PEEP	40.4	0.85 (0.65–1.10)
ACURASYS [10]	178	Neuromuscular blockade	31.6	162	Placebo	40.7	0.68 (0.48–0.98)
Aerosolized albuterol [18]	152	Inhaled β-2 agonist	23.0	130	Placebo	17.7	1.30 (0.83–1.77)
BALTI-2 [19]	162	Intravenous (IV) β-2 agonist	34.0	164	Placebo	23.0	1.47 (1.03–2.08)
OSCILLATE [7]	275	High frequency oscillatory ventilation	40.0	273	Conventional ventilation	29.0	1.41 (1.12–1.61)
OSCAR [20]	398	High frequency oscillatory ventilation	41.7	397	Conventional ventilation	41.1	1.03 (0.75–1.40)
PROSEVA [9]	237	Prone position	16.0	229	Supine position	32.8	0.39 (0.25–0.63)

Table 3 Limitations in the trials on prone position

First author	Gattinoni [1]	Guerin [2]	Mancebo [3]	Taccone [4]	Guerin [9]
Protective lung ventilation according to ARMA trial [13]	No	No	No	Yes	Yes
Long proning sessions	No	No	Yes	Yes	Yes
Population	ALI/ARDS	Hypoxemic acute respiratory failure	ARDS	ARDS	ARDS with severity criteria
Crossover allowed in the protocol (patients allocated to supine group who were turned prone)	Yes	Yes	Yes	No (rescue)	No (rescue)
Rate of crossover	Not reported	81/378 (21.4%)	5/62 (8.1%)	20/174 (11.5%)	17/229 (7.4%)

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 (PaO$_2$/FiO$_2$ 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 totalizing 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 ventila-

tion 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 cmH$_2$O 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 PaO$_2$/FIO$_2$ ratio. However, the patients were included from the level of PaO$_2$/FIO$_2$ of 200 mmHg. In our trial we were straightforward in including severe ARDS below 150 mmHg PaO$_2$/FIO$_2$ 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 PaO$_2$/FIO$_2$ 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.

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