Prone ventilation in acute respiratory distress syndrome

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ABSTRACT Prone positioning has been used for many years in patients with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), with no clear benefit for patient outcome. Meta-analyses have suggested better survival in patients with an arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2}) ratio <100 mmHg. A recent randomised controlled trial was performed in ARDS patients after a 12–24 h stabilisation period and severity criteria (P_{aO_2}/F_{IO_2} <150 mmHg at a positive end-expiratory pressure ⩾5 cmH_2O). This trial has demonstrated a significant reduction in mortality from 32.8% in the supine group to 16% in the prone group ($p<0.001$). The reasons for this dramatic effect are not clear but probably involves a reduction in ventilator-induced lung injury due to prone positioning, for which there is ample evidence in experimental and clinical studies.

The aims of this article are to discuss: the rationale of prone positioning in patients with ALI/ARDS; the evidence of its use based on trial analysis; and the limitations of its use as well as the current place of prone positioning in the management of patients with ALI/ARDS.

From the currently available data, prone positioning should be used as a first-line therapy in patients with severe ALI/ARDS.

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Introduction

It took almost 40 years from the early recommendation by Bryan [1] to use prone positioning in patients with acute respiratory distress syndrome (ARDS) to the demonstration of its beneficial effect on patient survival (fig. 1) [2]. Meanwhile, research has explored the mechanisms by which prone positioning could improve oxygenation and reduce ventilator-induced lung injury (VILI). Furthermore, several randomised controlled trials (RCTs) have been performed to test the effect of prone positioning on patient outcome. Of interest over these 40 years was the continuous interaction between pathophysiological advances and the search for clinical evidence of efficiency, and the continuous refinement in trial design. The aims of this article are to summarise the rationale for prone positioning, the level of evidence supporting its use, its limitations and its place in the current management of ARDS.

For editorial comments see page 157.

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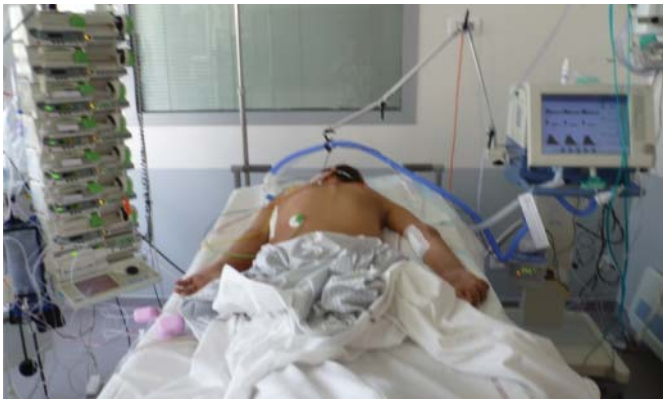

FIGURE 1 A patient with acute respiratory distress syndrome receiving mechanical ventilation in the intensive care unit while in the prone position.

Rationale

Oxygenation

From an historical point of view, the first rationale for using prone positioning in ARDS patients is improvement in oxygenation. We now know that this goal is less important than other rationale that will be discussed later. A large number of reports have shown that the improvement in oxygenation in ARDS was frequent, observed in ~75% of the cases, and sometimes dramatic, *i.e.* during a prone session. The oxygenation response is commonly defined as an increase in the arterial oxygen tension (P_{aO_2}) by 20% or an increase in the P_{aO_2}/inspiratory oxygen fraction (F_{IO_2}) ratio by $\geqslant$20 mmHg from the supine position. Therefore, from the onset prone positioning has mainly been thought of and used as a rescue therapy to relieve life-threatening hypoxaemia. For instance, in 1997 MURE *et al.* [3] reported on 13 ARDS patients, mostly secondary lung injury (indirect lung injury stemming from nonrespiratory severe sepsis/septic shock), who received low positive end-expiratory pressure (PEEP) and high F_{IO_2}. 11 of the patients had a P_{aO_2}/F_{IO_2} ratio of $<$100 mmHg in the supine position and in four patients this ratio was $<$50 mmHg. In six patients, the P_{aO_2}/F_{IO_2} ratio increased by a factor of at least four in the prone position. From their results, the authors concluded that prone positioning should be used as a first-line therapy before the use of nitric oxide and extracorporeal membrane oxygenation (ECMO). Moving forward into the RCT era, the effects on oxygenation were then assessed for prone positioning using a group, not just as a single session. Therefore, the effects on oxygenation in the prone position group were compared to the supine position group. Meta-analyses showed a significantly greater risk, ~30–40%, for better oxygenation in the prone position group [4, 5].

In 1988, LANGER *et al.* [6] reported on the effects of prone positioning on oxygenation in 13 ARDS patients, mostly primary lung injury (direct lung injury mainly stemming from pneumonia or aspiration), who received higher PEEP and lower F_{IO_2}. Furthermore, the authors performed lung computed tomography (CT) scans in two patients, not only in the supine position but also in the prone position. In patient 4, P_{aO_2} increased from 76 mmHg in the supine position to 141 mmHg in the prone position, with a similar PEEP of 10 cmH_2O and F_{IO_2} of 0.60. The lung densities observed on the lung CT scan redistributed from the dorsal to the ventral regions with the corresponding body position change. In contrast, in patient 9, for an almost similar redistribution of the dorsal lung densities towards the ventral regions when in prone position, P_{aO_2} decreased from 101 mmHg to 64 mmHg from the supine to the prone position, with the same PEEP of 10 cmH_2O and F_{IO_2} of 0.60. These unexpected findings have not been previously observed. Thus, the authors performed a systematic investigation of lung CT scans in the supine and prone position in normal subjects and in patients with acute respiratory failure [7]. The patients received, on average, PEEP of 11 cmH_2O, F_{IO_2} of 0.58 and tidal volume (V_T) of 10 $mL \cdot kg^{-1}$ measured body weight. The gas/tissue ratio assessed on the CT scan decreased progressively across the ventral to dorsal gradient in the supine position, indicating a progressive loss of aeration. With the prone position, the gas/tissue ratio increased towards the dorsal regions, reflecting more aeration in these regions, but was decreased in the ventral regions, which were dependent on the gravitational force. Accordingly, the improvement in oxygenation in the prone position is due to a reduction in intrapulmonary shunt [8] and results from the concomitant effect of the increase in aeration in the dorsal lung regions, which was greater than the loss of aeration in the ventral regions, and the prevalence of lung perfusion into those dorsal regions. The fact that blood continues to flow towards the dorsal regions in the prone position has been demonstrated in many studies. Therefore, the reduction in intrapulmonary shunt is due to more ventilation in well-perfused lung areas.

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Ventilator-induced lung injury

The second rationale to use prone positioning is in the prevention of VILI [9]. Preventing VILI has been established as the primary goal of mechanical ventilation after the ARDS network demonstrated that lower V_T improved survival compared to higher V_T in ARDS patients [10]. This trial was the ultimate demonstration, after decades of research [11, 12], that lung overdistension was detrimental not only to lung healing but also to patient outcome. Lung overdistension is the first component of VILI and, thus, preventing lung overdistension is the main concern of intensivists when setting mechanical ventilation. As it has become clear that lung overdistension pertains to volutrauma [13], not barotrauma (fig. 2), the relevant measurement should not be airway pressure but transpulmonary pressure determination. Transpulmonary pressure is the difference between alveolar pressure (airway pressure at zero airflow when the alveoli and conducting airways are communicating) and pleural pressure. Transpulmonary pressure can even be high if airway pressure is low. The typical example is pressure support ventilation when mechanical breaths are synchronised with a patient's inspiratory effort, a combination that may promote very high V_T, causing a risk for volutrauma [14]. Active research is currently dedicated to spontaneous breathing in ARDS patients.

The second component of VILI is called atelectrauma (fig. 2), which results from the repeated opening and closing of the small airways [15]. When V_T is reduced, atelectrauma may be less important than overdistension as three large RCTs failed to demonstrate a beneficial effect on patient outcome of higher PEEP compared to lower PEEP [16–18]. However, individual meta-analysis found a statistically significant lower mortality rate in the higher PEEP group in the subgroup of patients with a P_{aO_2}/F_{IO_2} ratio $\leqslant$200 mmHg [19].

A clear and direct demonstration that prone positioning can prevent VILI was reported by BROCCARD *et al.* [20] who ventilated normal dogs with 77 $mL \cdot kg^{-1}$ measured body weight V_T to reach a transpulmonary plateau pressure of 35 cmH_2O. During 6 h of such mechanical ventilation in the supine position the lungs were macroscopically and microscopically severely injured. When the dogs received the same ventilator settings for 6 h in the prone position the lung injury was markedly reduced. Furthermore, the histological lung injury due to high V_T was more homogeneously distributed throughout the lungs in the prone position.

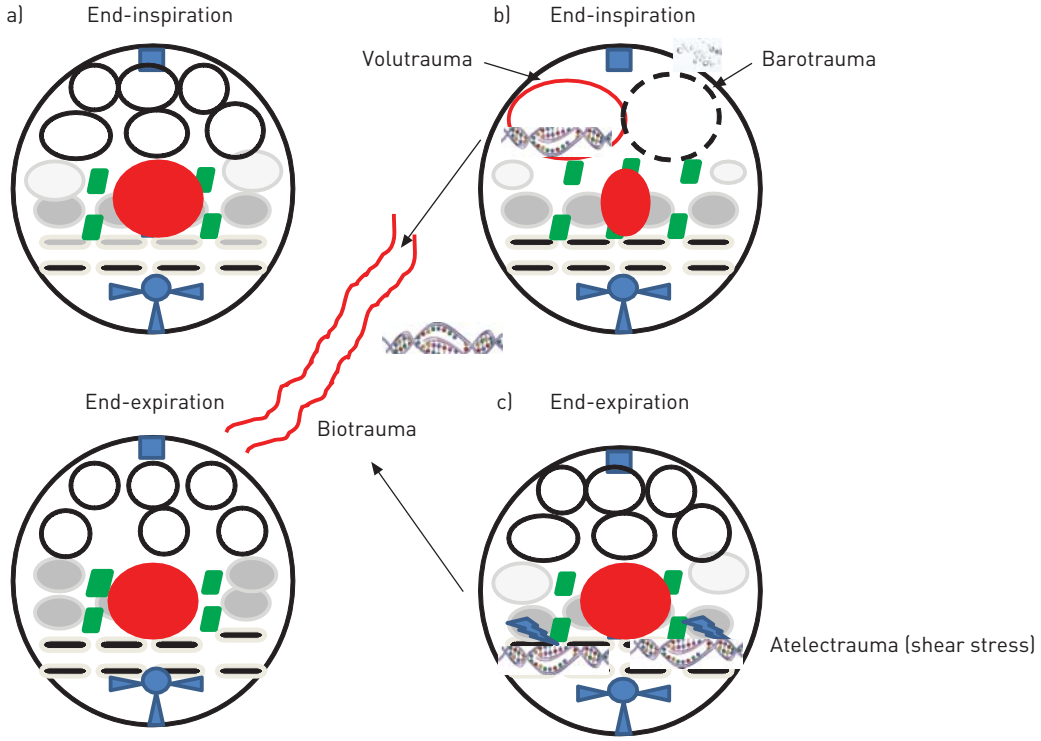

FIGURE 2 a) The distribution of normally aerated (white circles), poorly aerated (grey circles), non-aerated (black rectangle) and consolidated (green rectangle) lung areas during acute respiratory distress syndrome while in the supine position during end-inspiration and end-expiration. b) Barotrauma (alveolar rupture with air leaks) and volutrauma (overdistension in the normally aerated lung areas). c) Atelectrauma, *i.e.* shear stress in the poorly aerated lung areas close to the consolidated non-recruitable lung areas. Biotrauma (biochemical and biological response) results from volutrauma and/or atelectrauma with activation of pro-inflammatory mediators within the lungs and distant end organs. The red circle represents the heart.

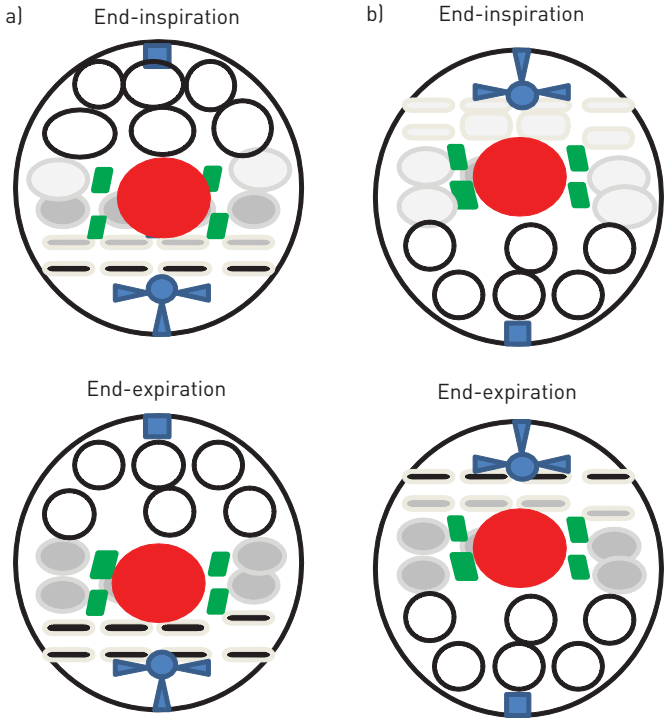

FIGURE 3 Homogenisation of the distribution of lung aeration as a result of moving from a) the supine to b) the prone position during acute respiratory distress syndrome. The red circle represents the heart. White circles: normally aerated lung areas; grey circles: poorly aerated lung areas; black rectangle: non-aerated lung areas; green rectangle: consolidated lung areas.

Further findings pertaining to VILI prevention using prone positioning have increased over time in the literature. Prone positioning makes the following more homogeneously distributed in the anterior-to-posterior direction throughout the lungs: lung densities (fig. 3) [7, 21], as previously discussed; intrapulmonary shunt [22]; lung ventilation [23]; and transpulmonary pressure [24]. By favouring such a homogenisation, prone positioning prepares the lung to receive the strain imposed by mechanical ventilation [25], and hence makes the distribution of the resulting stress more homogeneous across the lung. Stress/strain homogenisation is associated with less risk for VILI. Furthermore, the global lung stress and strain is reduced in the prone position. MENTZELOPOULOS *et al.* [26] found that transpulmonary pressure, *i.e.* lung stress, and V_T to end-expiratory lung volume ratio, *i.e.* lung strain, were lower in the prone position than in the supine position. GALIATSOU *et al.* [27] performed a lung CT scan in ARDS patients in the supine position and then in the prone position, same patient restricted to different interventions. The authors found that the prone position was associated with significant alveolar recruitment and less hyperinflation compared to the supine position, and that these effects were more important in lobar than diffuse ARDS anatomical pattern. These findings were confirmed and even expanded on by CORNEJO *et al.* [28], who assessed the lung recruitability in the supine position. The prone position promoted lung recruitment and reduced overdistension in patients in both categories of low and high recruitability at either low or high PEEP in the prone position. However, tidal recruitment and derecruitment, *i.e.* cyclic opening and closing of the small airways (atelectrauma), and tidal hyperinflation were significantly reduced in the prone position in only the subgroup of ARDS patients who had high recruitability in the supine position and who were receiving higher PEEP in the prone position.

VILI is subtended by biochemical and biological events implicated in the regulation of lung inflammation, a process termed biotrauma (fig. 2). PAPAZIAN *et al.* [29] found that the prone position was associated with lower lung concentration of interleukin (IL)-8, IL-6 and IL-1β compared to the supine position in ARDS patients ventilated with 6 mL·kg^{-1} predicted body weight V_T and higher PEEP. In rodents subjected to injurious mechanical ventilation (V_T 18 mL·kg^{-1} and PEEP 0 cmH_2O), prone ventilation has been shown to maintain the expression of mitogen-activated protein kinase (MAPK)-phosphatase 1, a pivotal regulator in VILI, while the supine position was associated with a significant downregulation [30]. Mice deficient in MAPK-phosphatase 1 were more susceptible to VILI [30].

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TABLE 1 Characteristics of the five largest randomised controlled trials testing the role of prone positioning in patient survival

	First author [ref.]				
	Gattinoni [31]	Guérin [32]	Mancebo [33]	Taccone [34]	Guérin [2]
Patients n					
Supine position	152	378	60	174	229
Prone position	152	413	76	168	237
Patients with ARDS %					
Supine position	93.3	28	100	100	100
Prone position	94.7	33.9	100	100	100
Pa_{O_2}/F_{IO_2} at inclusion mmHg	127	150	147	113	100
Tidal volume at inclusion mL·kg^{-1}	10.3 MBW	8 MBW	8.4 PBW	8 PBW	6.1 PBW
PEEP at inclusion cmH_2O	10	8	12	10	10
Prone position session duration# h	7	8	17	18	17
Mortality %					
Supine position	25	31.5	58	32.8	32.8
Prone position	21.1	32.4	43	31	16

ARDS: acute respiratory distress syndrome; Pa_{O_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; PEEP: positive end-expiratory pressure; MBW: measured body weight; PBW: predicted body weight. #: average hours per session.

So, there is large body of evidence supporting the fact that prone position ventilation has relevant beneficial physiological effects in ARDS. These benefits were progressively discovered together with major advances in mechanical ventilation. Whether these physiological benefits can translate into improvement in patient outcome will be discussed in the next section.

Evidence

To date, five large RCTs (table 1), as well as some smaller ones, have tested the role of prone positioning in patient survival. Over time there has been a continuous refinement of the design of the RCTs taking into account the advances made in mechanical ventilation (table 2). For example, protective lung ventilation was only applied in the two most recent trials [2, 34], the duration of prone sessions was increased from the third trial onwards [2, 33, 34], and the targeted population focused on the most severe ARDS patients in terms of hypoxaemia, and crossover was not allowed for patients allocated to the supine position group except as a rescue therapy in the two most recent trials [2, 34]. The four largest RCTs performed meta-analyses on both study and patient levels [31–34]. Both analyses consistently found that prone positioning was associated with a significant reduction in mortality in the subgroup of patients with a Pa_{O_2}/F_{IO_2} ratio $<$100 mmHg.

We designed, performed and published the fifth large RCT on prone positioning in a specific ARDS subgroup, termed severe ARDS [2]. This was defined according to local criteria before the Berlin definition was released [35]. We found a significant reduction in 28-day mortality (the primary end-point) with 32.8% mortality in the supine group *versus* 16% mortality in the prone group ($p<0.001$). At 90 days, mortality in the supine and prone groups was 41% and 23.6%, respectively ($p<0.001$).

Our RCT included 10 specific features (table 3), which, in addition to the physiological benefits of prone positioning discussed previously, may explain this result. The stabilisation period of 12–24 h we mandated had previously been used by Villar *et al.* [36] to select the most severe ARDS patients. It could be that this stabilisation period in our RCT included selected patients who may have benefited from prone positioning. However, it remains unclear whether this had occurred and what could be the mechanisms underlying this hypothesis. It should be stressed that the PROSEVA (Proning Severe ARDS Patients) trial [2] included highly selected patients by study design: severity criteria, stabilisation period, and several noninclusion criteria. Therefore, one issue for a wider use of prone positioning may be related to the capability to select the right patients. Furthermore, the skills of the caregivers are essential for the safety of the procedure. This important point will be discussed below.

The PROSEVA trial [2] and the second Italian RCT (PSII: Prone Supine II) [34] were very close in their design to the five largest RCTs (table 4), as they implemented most of the advances achieved in mechanical ventilation, prone positioning and adjunct therapies. The reasons why PROSEVA succeeded and PSII did not are unclear but may be related to the items presented in table 4, in particular strict lung protective ventilation, concentrated prone period, less complications and larger sample size in the former study.

TABLE 2 Limitations in randomised controlled trials

	First author [ref.]				
	Gattinoni [31]	Guérin [32]	Mancebo [33]	Taccone [34]	Guérin [2]
Year of trial	2001	2004	2006	2009	2013
Protective lung ventilation	No	No	No	Yes	Yes
Long prone sessions	No	No	Yes	Yes	Yes
Target population	ALI/ARDS	Hypoxaemic acute respiratory failure	ARDS	ARDS	ARDS with severity criteria
Crossover allowed	Yes	Yes	Yes	No (rescue)	No (rescue)
Rate of crossover	Not reported	81 (21.4%) out of 378	5 (8.1%) out of 62	20 (11.5%) out of 174	17 (7.4%) out of 229

ALI: acute lung injury; ARDS: acute respiratory distress syndrome.

It should also be highlighted that, for a greater severity of patients enrolled in the PROSEVA trial, the outcome in the control group was similar to that in the PSII trial (table 1). This finding may reflect the continuous improvement in the patient's care and the skills in performing prone positioning in the participating intensive care units in the PROSEVA trial. This latter argument is supported by the fact that the same rate of complications between the two groups was observed in the PROSEVA trial contrary to the previous RCTs, including PSII.

Limitations

Our trial has some limitations as the two groups were not completely balanced (by chance) at the time of randomisation. In particular, the Sequential Organ Function Assessment score was lower in the prone group. This was observed even though in order to be included the patients had to have a mean arterial blood pressure $\geqslant$65 mmHg. Even though this criterion was met by every patient in both groups, the rate of patients receiving vasopressors was greater in the supine group. However, in the multivariate analysis the effect of the prone position was still highly significant.

From the onset it was pointed out that the procedure of prone positioning exposes serious complications, in particular those related to airways, such as endotracheal tube displacement (main stem intubation or non-scheduled extubation), endotracheal tube obstruction or kinking, and vascular access kinking or removal. In our trial [32], as in others [31, 33], the rate of complications was significantly greater in the prone group compared to the supine group [4]. However, the mortality was not higher in the prone group. The same was true in the PSII RCT, in which the use of rotoprone was implicated in the observed higher rate of complications in the prone group. Therefore, the caregivers were very reluctant to expand the use of prone positioning in their intensive care unit given the lack of a clear significant benefit. The benefit/risk ratio was judged to not be in favour of extensive use of prone positioning. In the PROSEVA trial, for the first time, the rate of serious complications was similar between the two groups. This finding is probably the result of the expertise and skills of the centres involved in the trial that performed the procedure safely. Following the PROSEVA trial the benefit/risk ratio has greatly improved due to the significant increase in survival.

TABLE 3 Key features in the PROSEVA trial on prone positioning in severe acute respiratory distress syndrome (ARDS) patients

1. ARDS criteria confirmed after 12–24 h
2. ARDS with severity criteria:
   $Pa_{O_2}/F_{I_{O_2}}$ <150 mmHg with $F_{I_{O_2}}$ $\geqslant$0.6 + PEEP $\geqslant$5 cmH_2O + V_T 6 $ml \cdot kg^{-1}$ predicted body weight
3. Several noninclusion criteria
4. Strict lung protective mechanical ventilation (in both groups)
5. First prone position session started within 1 h after randomisation
6. Prone sessions of at least 16 h consecutively
7. Predetermined stopping criteria of prone position
8. Crossover not allowed except as a lifesaving procedure in the supine group
9. Neuromuscular blockade in both groups
10. Centres with expertise in prone positioning for many years

PROSEVA: Proning Severe ARDS Patients; Pa_{O_2}: arterial oxygen tension; $F_{I_{O_2}}$: inspiratory oxygen fraction; PEEP: positive end-expiratory pressure; V_T: tidal volume.

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TABLE 4 Characteristics of the PSII and PROSEVA randomised controlled trials on prone positioning in acute respiratory disease syndrome patients

	PSII [34]	PROSEVA [2]
Centres n	25	27
Support	Rotoprone in 20 centres	Standard bed
Patients n		
Supine position	168	229
Prone position	174	237
Inclusion criteria	P_{aO_2}/F_{IO_2} ⩽200 mmHg + PEEP 5–10 cmH_2O	P_{aO_2}/F_{IO_2} <150 mmHg + PEEP ⩾5 cmH_2O + F_{IO_2} ⩾0.60
Stratification of randomisation	Yes	No
Stabilisation period	No	Yes
Stopping prone criteria	Resolution of ARF	Improvement in oxygenation (P_{aO_2}/F_{IO_2} >150 mmHg + PEEP <10 cmH_2O + F_{IO_2} <0.60)
Target tidal volume mL·kg^{-1}	8 PBW	6 PBW
PEEP management	Local PEEP/F_{IO_2} table	PEEP/F_{IO_2} table used in the ARMA trial
Target oxygenation	P_{aO_2} 70–90 mmHg	P_{aO_2} 55–80 mmHg
Target plasma pH	7.30–7.45	7.20–7.45
SAPS II	41±15	46±16
SOFA score	6.8±3.9	10.0±3.3
P_{aO_2}/F_{IO_2} at inclusion mmHg	113±39	104±25
PEEP at inclusion cmH_2O	10±3	10±4
Tidal volume at inclusion mL·kg^{-1}	8.0±1.7 PBW	6.1±0.6 PBW
P_{plat} at inclusion cmH_2O	Not available	24±5
Average prone session duration h	18±4	17±4
Time in prone# %	50	73
Average prone position sessions per patient in the prone position group	8±6	4±4

Data are presented as mean±SD, unless otherwise stated. PSII: Prone Supine II: PROSEVA: Prone Severe ARDS Patients; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; PEEP: positive end-expiratory pressure; ARF: acute respiratory failures; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Function Assessment; P_{plat}: plateau pressure; PBW: predicted body weight. #: time spent in the prone position between the start of the first session and the end of the last session.

However, there is another side-effect of prone positioning that may cause some concern to the patients, their family and the caregivers, namely pressure ulcers. Previous trials and meta-analyses, also reported a greater incidence of pressure ulcers with the use of prone positioning. Furthermore, the facial location of pressure ulcers may have a psychological impact on the patients and their family. In the PROSEVA trial, as an ancillary study, the location and stage of pressure ulcers at time of inclusion, 7 days after inclusion and at intensive care unit discharge was prospectively reported in both groups. A greater incidence of new pressure ulcers was found in the prone position group during the first week and at the time of intensive care unit discharge [37]. However, in the logistic regression analysis the position group was no longer significantly associated with new pressure ulcers. An unresolved issue was the role of prone position *per se* and greater survival in the prone group with the subsequent greater risk for pressure ulcers. At any rate, preventive means should be tested in the prone position.

Place of prone positioning in the management of ARDS patients

Three interventions have proven beneficial in ARDS: lower V_T [10], neuromuscular blocking agents (ACURASYS (ARDS et Curarisation Systématique) trial) [38], and prone positioning [2]. Lower V_T is the common strategy that must be applied to any ARDS patient regardless of the level of hypoxaemia [39]. Two recent meta-analyses have been published, which included PROSEVA in addition to the previous RCTs. Both found that prone positioning improves survival irrespective of the level of hypoxaemia provided a lower V_T is set [40, 41].

Neuromuscular blocking agents and prone positioning were investigated in ARDS patients with a P_{aO_2}/F_{IO_2} ratio <150 mmHg at PEEP ⩾5 cmH_2O. An F_{IO_2} of at least 0.60 and a 12–24-h stabilisation period were added to the inclusion criteria. Clearly, these two interventions are tightly linked and should be used together as first-line therapy in patients exhibiting the criteria mentioned above. The recent Berlin proposal split ARDS patients into mild, moderate and severe categories at 300, 200 and 100 mmHg P_{aO_2}/F_{IO_2} ratio

thresholds, respectively. It is unclear whether mortality does regularly increase from the mild to the severe ARDS category in the Berlin definition [42].

Based on the positive results of the ACURASYS and PROSEVA trials, it would be more appropriate to split ARDS patients into only two categories, a P_{aO_2}/F_{IO_2} ratio of $<$150 mmHg and $>$150 mmHg assessed at PEEP $\geqslant$5 cmH_2O. In ARDS patients with an P_{aO_2}/F_{IO_2} ratio $<$150 mmHg, the mechanical ventilation should start with the following settings: lower V_T, neuromuscular blockade for the first 48 h and prone positioning for long sessions until P_{aO_2}/F_{IO_2} is $>$150 mmHg.

Large multicentre trials are ongoing to investigate the effects of the following interventions on patient outcome: PEEP set according to end-expiratory transpulmonary pressure, ECMO and spontaneous ventilation. It is worth noting that in the control group, *i.e* traditional lung protective ventilation, the use of prone positioning is not mandated. These trials were, however, designed before the release of the results of the PROSEVA trial.

In conclusion, there is now a large body of evidence supporting the fact that prone positioning improves mortality in patients with severe ARDS. Accordingly, prone positioning should be used as a first-line therapy in this setting.

References

1 Bryan AC. Conference on the scientific basis of respiratory therapy. Pulmonary physiotherapy in the pediatric age group. Comments of a devil's advocate. *Am Rev Respir Dis* 1974; 110: 143–144.
2 Guérin C, Reignier J, Richard JC, *et al.* Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; 368: 2159–2168.
3 Mure M, Martling CR, Lindahl SG. Dramatic effect on oxygenation in patients with severe acute lung insufficiency treated in the prone position. *Crit Care Med* 1997; 25: 1539–1544.
4 Sud S, Sud M, Friedrich JO, *et al.* Effect of mechanical ventilation in the prone position on clinical outcomes in patients with acute hypoxemic respiratory failure: a systematic review and meta-analysis. *CMAJ* 2008; 178: 1153–1161.
5 Abroug F, Ouanes-Besbes L, Elatrous S, *et al.* The effect of prone positioning in acute respiratory distress syndrome or acute lung injury: a meta-analysis. Areas of uncertainty and recommendations for research. *Intensive Care Med* 2008; 34: 1002–1011.
6 Langer M, Mascheroni D, Marcolin R, *et al.* The prone position in ARDS patients. A clinical study. *Chest* 1988; 94: 103–107.
7 Gattinoni L, Pelosi P, Pesenti A, *et al.* CT scan in ARDS: clinical and physiopathological insights. *Acta Anaesthesiol Scand Suppl* 1991; 95: 87–94.
8 Albert RK, Leasa D, Sanderson M, *et al.* The prone position improves arterial oxygenation and reduces shunt in oleic-acid-induced acute lung injury. *Am Rev Respir Dis* 1987; 135: 628–633.
9 Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med* 2013; 369: 2126–2136.
10 Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342: 1301–1308.
11 Tobin MJ. Culmination of an era in research on the acute respiratory distress syndrome. *N Engl J Med* 2000; 342: 1360–1361.
12 Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. *Am Rev Respir Dis* 1974; 110: 556–565.
13 Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med* 1998; 157: 294–323.
14 Leray V, Bourdin G, Flandreau G, *et al.* A case of pneumomediastinum in a patient with acute respiratory distress syndrome on pressure support ventilation. *Respir Care* 2010; 55: 770–773.
15 Muscedere JG, Mullen JB, Gan K, *et al.* Tidal ventilation at low airway pressures can augment lung injury. *Am J Respir Crit Care Med* 1994; 149: 1327–1334.
16 Brower RG, Lanken PN, MacIntyre N, *et al.* Higher *versus* lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; 351: 327–336.
17 Meade MO, Cook DJ, Guyatt GH, *et al.* Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008; 299: 637–645.
18 Mercat A, Richard JC, Vielle B, *et al.* Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008; 299: 646–655.
19 Briel M, Meade M, Mercat A, *et al.* Higher *vs* lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010; 303: 865–873.
20 Broccard A, Shapiro RS, Schmitz LL, *et al.* Prone positioning attenuates and redistributes ventilator-induced lung injury in dogs. *Crit Care Med* 2000; 28: 295–303.
21 Richard JC, Janier M, Lavenne F, *et al.* Effect of position, nitric oxide, and almitrine on lung perfusion in a porcine model of acute lung injury. *J Applied Physiol* 2002; 93: 2181–2191.
22 Richter T, Bellani G, Scott Harris R, *et al.* Effect of prone position on regional shunt, aeration, and perfusion in experimental acute lung injury. *Am J Respir Crit Care Med* 2005; 172: 480–487.
23 Richard JC, Bregeon F, Costes N, *et al.* Effects of prone position and positive end-expiratory pressure on lung perfusion and ventilation. *Crit Care Med* 2008; 36: 2373–2380.
24 Mutoh T, Guest RJ, Lamm WJ, *et al.* Prone position alters the effect of volume overload on regional pleural pressures and improves hypoxemia in pigs *in vivo*. *Am Rev Respir Dis* 1992; 146: 300–306.
25 Chiumello D, Carlesso E, Cadringher P, *et al.* Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2008; 178: 346–355.

DOI: 10.1183/09059180.00001114

26 Mentzelopoulos SD, Roussos C, Zakynthinos SG. Prone position reduces lung stress and strain in severe acute respiratory distress syndrome. *Eur Respir J* 2005; 25: 534–544.
27 Galiatsou E, Kostanti E, Svarna E, *et al.* Prone position augments recruitment and prevents alveolar overinflation in acute lung injury. *Am J Respir Crit Care Med* 2006; 174: 187–197.
28 Cornejo RA, Diaz JC, Tobar EA, *et al.* Effects of prone positioning on lung protection in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2013; 188: 440–448.
29 Papazian L, Gainnier M, Marin V, *et al.* Comparison of prone positioning and high-frequency oscillatory ventilation in patients with acute respiratory distress syndrome. *Crit Care Med* 2005; 33: 2162–2171.
30 Park MS, He Q, Edwards MG, *et al.* Mitogen-activated protein kinase phosphatase-1 modulates regional effects of injurious mechanical ventilation in rodent lungs. *Am J Respir Crit Care Med* 2012; 186: 72–81.
31 Gattinoni L, Tognoni G, Pesenti A, *et al.* Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001; 345: 568–573.
32 Guérin C, Gaillard S, Lemasson S, *et al.* Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. *JAMA* 2004; 292: 2379–2387.
33 Mancebo J, Fernandez R, Blanch L, *et al.* A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006; 173: 1233–1239.
34 Taccone P, Pesenti A, Latini R, *et al.* Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2009; 302: 1977–1984.
35 Ranieri VM, Rubenfeld GD, Thompson BT, *et al.* Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012; 307: 2526–2533.
36 Villar J, Perez-Mendez L, Lopez J, *et al.* An early PEEP/F_{IO_2} trial identifies different degrees of lung injury in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2007; 176: 795–804.
37 Girard R, Baboi L, Ayzac L, *et al.* The impact of patient positioning on pressure ulcers in patients with severe ARDS. Results from a multicentre randomised controlled trial on prone positioning. *Intensive Care Med* 2014; 40: 397–403.
38 Papazian L, Forel JM, Gacouin A, *et al.* Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; 363: 1107–1116.
39 Ferguson ND, Fan E, Camporota L, *et al.* The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med* 2012; 38: 1573–1582.
40 Lee JM, Bae W, Lee YL, *et al.* The efficacy and safety of prone positional ventilation in acute respiratory distress syndrome: updated study-level meta-analysis of 11 randomized controlled trials. *Crit Care Med* 2013 [In press DOI: 10.1097/CCM.0000000000000122].
41 Beitler JR, Shaefi S, Montesi SB, *et al.* Prone positioning reduces mortality from acute respiratory distress syndrome in the low tidal volume era: a meta-analysis. *Intensive Care Med* 2014; 40: 332–341.
42 Hernu R, Wallet F, Thiolliere F, *et al.* An attempt to validate the modification of the American–European consensus definition of acute lung injury/acute respiratory distress syndrome by the Berlin definition in a university hospital. *Intensive Care Med* 2013; 39: 2161–2170.