

Prone positioning acute respiratory distress syndrome patients

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Abstract: Prone position has been used in acute respiratory distress syndrome (ARDS) patients for more than 40 years in ICU. After having demonstrated its capability to significantly improve oxygenation in a large number of patients, sometimes dramatically, this procedure has been found to prevent ventilator-induced lung injury, the primary concern for the intensivists managing ARDS patients. Over the time, several trials have been done, which regularly improved and refined from each other. At the end, significant improvement in survival has been demonstrated in the most severe ARDS patients, at a threshold of 100–150 mmHg PaO₂/FiO₂ ratio. The effect of proning on survival cannot be predicted and seems unrelated with both severity of oxygenation impairment and oxygenation response to proning. The rate of complication is declining with the increase in centers expertise. The pressure sores are more frequent in prone and require a special attention. Prone position is a key component of lung protective mechanical ventilation and should be used as a first line therapy in association with low tidal volume and neuromuscular blocking agents in patients with severe ARDS.

Keywords: Acute respiratory distress syndrome (ARDS); mechanical ventilation; prone position; hypoxemia; ventilator induced lung injury

Submitted Apr 17, 2017. Accepted for publication May 10, 2017.

doi: [10.21037/atm.2017.06.63](https://doi.org/10.21037/atm.2017.06.63)

View this article at: <http://dx.doi.org/10.21037/atm.2017.06.63>

Prone positioning ARDS patients consists in placing the patient face down and continuing mechanical ventilation in this position for a long period of time, like 16 consecutive hours.

This strategy has eventually been found efficient to improve patient outcome in selected ARDS patients.

In this review, we will go over the rationale and then the evidence of using prone position in ARDS patients.

Rationale

The early reason that prompted clinicians to turn ARDS patient to prone was oxygenation improvement. This effect, sometimes dramatic (1), was observed in the large majority of patients. Therefore from the early onset the clinicians used proning to improve oxygenation. This effect resulted from a reduction in intra-pulmonary shunt. For the intra-pulmonary shunt to go down two possibilities

do exist, either more ventilation in well perfused areas or less perfusion in poorly ventilated lung regions. The latter mechanism was considered as true as intuitively it was thought that the change in gravity direction will affect the lung perfusion in the same way, i.e., less perfusion towards dorsal lung regions, now non-dependent, in the prone position. Several experiments found that the dorsal lung regions when in the prone position still had the highest amount of blood flowing through them (2-8). Therefore, this unexpected finding argued against the second mechanism to explain the reduction in intra-pulmonary shunt. Therefore, better ventilation towards well perfused areas accounts for the common scenario to explain better oxygenation in prone (9).

With the recognition of ventilator-induced lung injury (VILI) it turned out that prone position was also able to modulate it. Animal studies, like that of Broccard *et al.* (10), demonstrated that prone position, as compared to supine

position, attenuated and homogenized the distribution of lung injury across the ventral-to-dorsal direction when very high tidal volume were delivered in normal dogs. Lung strain was reduced and homogeneously distributed in prone (11). In humans, several lines of evidence argued in favor of the preventive role of proning against VILI. Papazian *et al.* found a reduction in the lung concentration of pro-inflammatory cytokines after 12 hours in prone as compared to supine position (12). CT studies consistently found that with prone the amount of overinflated lung mass declined and that of non or poorly aerated lung mass increased, indicating lung recruitment (13,14). Cornejo *et al.* (14) extended these findings by showing that this result was present in patients with low or high potential of recruitment in the supine position, whatever they were receiving low or high PEEP. However, tidal recruitment/decreased recruitment, i.e., atelectrauma, was reduced in prone only in those patients with high recruitability and high PEEP in supine position. Finally a rodent study found that prone position was able to modulate the activation and expression of a kinase strongly involved in VILI when rats were subjected to injurious ventilation (15). Furthermore in KO mice for this kinase injurious ventilation was associated with severe lung injury, which was attenuated in prone (15).

Homogenization of lung aeration (16), lung ventilation, lung perfusion, ventilation/perfusion ratio (17), stress and strain is the main effect of prone that accounts for both oxygenation improvement and VILI prevention.

Hemodynamic effect of prone position is an under investigated area and may have importance to explain the effect of prone on patient outcome. From the early use of proning (18) clinicians showed up the hemodynamic stability that contrasted with hemodynamic impairment with high PEEP they were using in case of severe hypoxemia. Circulatory failure in ARDS is frequent and complex (Figure 1). On one side the right ventricle systolic function can be impaired due to pulmonary hypertension resulting from hypoxemia, hypercapnia, vascular injury with thrombosis, overinflation (high PEEP and/or high tidal volume set at the ventilator) with increased resistance of alveolar vessels. Acute cor pulmonale, which occurred in almost 20–25% of ARDS patients (19), may result, at least partly, from pulmonary hypertension. Vieillard-Baron *et al.* (20) found that prone position for long sessions can reverse this phenomenon and, hence either prevent the occurrence or even treat these events. On another hand left ventricle systolic function can be impaired in ARDS patients from lung-heart interaction. Recently, Jozwiak

et al. (21) found that cardiac index increased in prone position in those ARDS patients who were preload dependent (passive leg rising test) while supine and did not in those who were not. This suggests that prone position can shift the blood from unstressed to stressed abdominal vessels and, hence increase venous return.

Evidence

It is worth noting to have in mind that prone position story in ARDS patients was fed by a continuous improvement of pathophysiological knowledge and continuous refinement in the trials that were performed over the years. Given the numerous and impressive physiological benefits observed with prone position, a translation into patient outcome benefit was expected. The first trial by Gattinoni *et al.* (22) in almost 300 patients with acute lung injury and ARDS was disappointing as no effect on survival was found. It was followed by the first trial by Guerin *et al.* (23) on patients with acute hypoxemic respiratory failure. Again no difference in mortality was observed with prone as compared to the control group in supine. Several factors were discussed to explain these negative effects: short (7–8 hours proning sessions), cross over, no lung protective ventilation at this time (Table 1). The third trial by Mancebo *et al.* (24) introduced an important feature with much longer proning sessions (Table 1). The absolute difference in mortality amounted to 15%, which did not reach statistical significance due to lack of power. The authors wrote that the rate of inclusion declined to such a level that they decided to stop the study before end. The second Italian trial (25) brought up new features: patients were stratified according to oxygenation into two groups (above or below 100 mmHg PaO₂/FiO₂ ratio), long proning sessions were employed. Again, no difference statistically significant between prone and supine groups (Table 1). However, these four trials were meta-analyzed at the individual data level (26). This study found no difference in survival in the whole population and in the subgroup of patients with PaO₂/FiO₂ greater than 100 mmHg. However, for the first time, significant better survival was found in patients with PaO₂/FiO₂ <100 mmHg at the time of randomization. This individual meta-analysis confirmed a previous meta-analysis (27) done on grouped-data that included other trials. Finally, we designed a fifth trial with several specific features (28): we enrolled patients qualified as severe ARDS [this was before the Berlin definition (29)] with PaO₂/FiO₂ <150 mmHg and PEEP of at least 5 cmH₂O and FiO₂ of at least 60%, who

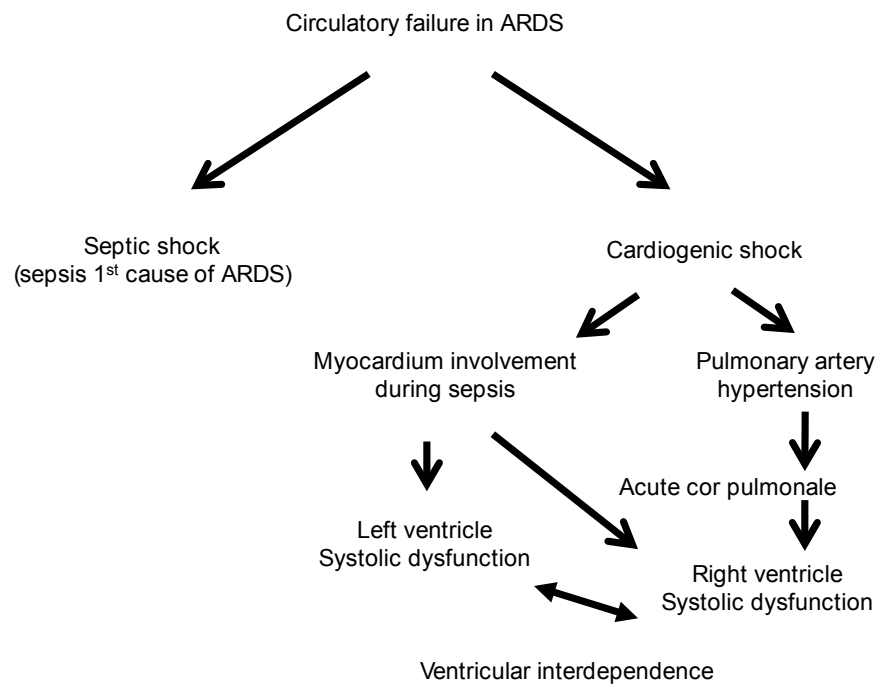


Figure 1 Mechanisms of acute circulatory failure in ARDS. ARDS, acute respiratory distress syndrome.

Table 1 Summary of the five largest trials on prone position

Characteristics	First author				
	Gattinoni (22)	Guerin (23)	Mancebo (24)	Taccone (25)	Sud (28)
No. of 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 MBW	8 MBW	8.4 PBW	8 PBW	6.1 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

SP, supine position; PP, prone position; MBW, measured body weight; PBW, predicted body weight; PEEP, positive end-expiratory pressure.

exhibited these criteria after a 12–24 stabilization period, no cross over was allowed except for life-threatening hypoxemia, strict lung protective ventilation was applied, neuromuscular blockade was used in both groups, the first proning session in the prone group was done within the hour after randomization, the proning sessions lasted at least 16 consecutive hours, predetermined criteria for stopping proning were defined, participating ICU had large

experience with proning for many years. With this protocol, we obtained a significant reduction in mortality from 32.8 in the supine group to 16% in the prone group at day 28 after randomization, which was confirmed at day 90 (41% *vs.* 23.6%, respectively).

Further meta-analyses including the above Proseva trial confirmed the beneficial effect of prone position in ARDS patients (30–33). Clearly prone position benefit to

the most severe ARDS patients (34), even though some meta-analysis suggested the benefit was found regardless the oxygenation level (33). Prone position, lower tidal volume (35) and early use of neuromuscular blocking agents (36) are to date the three only interventions that have proved benefit in ARDS (37). The mechanisms by which ARDS patients survival improved in prone basically stem from the physiological effects reviewed above. Another mechanism was also suggested, namely the prevention of ventilator-associated pneumonia. Indeed, prone is well known to promote respiratory secretions in large amount and this effect could contribute to facilitate drainage and, hence prevent pneumonia. However, in the Proseva trial the rate of ventilator-associated pneumonia was similar in both groups (38). Interestingly, neither the level of hypoxemia at the time of randomization (39) nor the oxygenation or the PaCO₂ response to the first prone position session (40) were associated with patient survival. The role of driving pressure, the current stronger predictor of mortality in ARDS (41), is under investigation. We recently observed that driving pressure share the same information as plateau pressure to predict survival in ARDS patients receiving lung protective mechanical ventilation (42).

However, in routine practice the rate of use of prone position has been found as low as 16% in severe ARDS patients in the recent large prospective epidemiologic Lung safe study (43). Clinicians are reluctant to use this procedure due to its complexity, risk of complications, uncertainty regarding its real effects. The rate of complications affecting airways was, however, not significantly different between the two groups in the Proseva trial. Prone position can also be used in patients under ECMO, indicating that once every effort has been made in the ICU with the caregivers this procedure can be done routinely and safely. It should be mentioned that pressure sores are still an issue. These are more frequent in prone than in supine and preventive means should be done in this area.

Conclusions

Prone position is a key component of lung protective mechanical ventilation and should be used as a first line therapy in association with low tidal volume and neuromuscular blocking agents in patients with severe ARDS.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Cite this article as: Guérin C. Prone positioning acute respiratory distress syndrome patients. *Ann Transl Med* 2017;5(14):289. doi: 10.21037/atm.2017.06.63