Editorial

Prone Positioning for ARDS: still misunderstood and misused

Francesco Pugliese[1], Cristina Babetto[2], Francesco Alessandri[2], Vito Marco Ranieri[2]

[1]Department of General and Specialistic surgery "Paride Stefanini", Sapienza University of Rome, Rome, Italy; [2]Department of Anesthesia and Critical Care Medicine, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy

Correspondence to: Prof. Francesco Pugliese. Associate Professor in Anesthesia and Intensive Care, Department General Surgery and Transplant "Paride Stefanini", University of Rome "La Sapienza", Rome, Italy. Email: f.pugliese@uniroma1.it.

Provenance: This is an invited Editorial commissioned by the Section Editor Dr. Zhiheng Xu (State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, Department of Intensive Care, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China).

Comment on: Guérin C, Beuret P, Constantin JM, *et al.* A prospective international observational prevalence study on prone positioning of ARDS patients: the APRONET (ARDS Prone Position Network) study. Intensive Care Med 2018;44:22-37.

Submitted Mar 10, 2018. Accepted for publication Mar 26, 2018.
doi: 10.21037/jtd.2018.04.157
View this article at: http://dx.doi.org/10.21037/jtd.2018.04.157

Acute respiratory distress syndrome (ARDS) is a clinical syndrome characterized by a non-cardiogenic pulmonary edema with bilateral chest X-ray opacities and hypoxemia refractory to oxygen therapy and low level of positive end-expiratory pressure (1).

Recently, a large observational study reported an ARDS prevalence of 10.4% of all ICU admissions and of 23.4% of all subjects receiving mechanical ventilation (2). Despite these alarming numbers, according to the most recent literature, ARDS is still under-recognized, undertreated, and associated with a mortality rate that in the most severe forms is close to 50% (2).

Among the few therapeutic approaches, Prone Positioning (PP) can be considered one of the oldest attempts, firstly pointed out in the last Seventies as a strategy to improve ventilation in respiratory failure settings (3). Since then, the understanding of the physiology and the effectiveness of PP has been dramatically deepening and at the present time, PP has been recognized as one of three interventions (not considering ECMO) that can actually improve patient survival in ARDS cases, along with lower tidal volume (6 mL/kg of predicted body weight Vt) and continuous intravenous infusion of neuromuscular blocking agent (cisatracurium for 48 hours).

The mechanisms underlying the efficacy of PP to improve outcome include the redistribution of lung densities with a recruitment of dorsal regions, increase of end-expiratory lung volume, an increase in chest-wall elastance, a reduction of alveolar shunts, and the prevention of ventilator-induced lung injury (VILI) by a better distribution of tidal volume (4).

Moreover, lung recruitment may explain the reduction in pulmonary vascular resistance and right heart dimensions observed in PP (5).

However, despite this strong physiological rationale, early randomized clinical trials that tested the efficacy of PP left clinicians with consistent uncertainty on its real benefits on mortality rates. Advocated mechanisms for this low efficacy were lack of inclusion of the most severe forms of hypoxemia, the "low dose" of PP administered (less than 6 h/d), and the lack of use of protective mechanical ventilation (6). Despite these limitations, the survival rate increased among subjects with most severe ARDS treated in prone position (7).

An important breakout on PP can be identified in the PROSEVA trial, that showed a major decrease in mortality rate at 28 and 90 days in subjects treated with PP (The 28-day mortality was 16.0% in the prone group and 32.8% in the supine group; 90-day mortality was 23.6% in the prone group versus 41.0% in the supine group) (8). This was a multi-center randomized controlled trial on early application of prolonged prone position (16 h/d) in subjects with severe ARDS. One of the main features of this trial was the attempt to sharply define ARDS severity and ventilation parameters cutoffs (PaO_2/FIO_2 <150, PEEP >5 cmH_2O, FIO_2 0.6, with an average VT of 6.1 mL/kg of predicted

body weight).

In this perspective, the correct choice of patients and early initiation of prone therapy appear to be key factors for the success of this strategy. Although Munshi *et al.* (9) clearly stated that PP is likely to reduce mortality among patients with severe ARDS if applied for at least 12 hours daily, it was still unclear how this findings modified the actual clinical practice in the ICU settings. The LUNG SAFE study shows that the rate of its application is extremely low (16.3%) (2).

Doubts had arisen that this low rate could be explained on the base that clinicians still perceived the evidence level as weak. Other explanations could be that the process of moving a patient to a prone position is often considered as labor-intensive and, if not correctly performed, it can increase the risk of accidental removal of the endotracheal tube, drains, or catheters, as well as the development of pressure sores.

Under these circumstances, a study specifically designed to enlighten the present situation on prevalence of PP use and the perception of its effectiveness as well as the possible reasons for not using it, is by all means required and welcome.

Recently, Guérin and coworkers reported results of the APRONET study (10). This is a prospective international prevalence study, performed on a single day four times in April, July and October 2016 and January 2017. Over this period, 6,723 patients in 141 ICUs from 20 countries (77% European) were screened. Eventually, 735 patients with ARDS were monitored for use of PP, gas exchange, ventilator settings and plateau pressure. Complications and reasons for not using PP were also recorded. The main finding was that 32.9% of patients with severe ARDS received PP, showing low complication rates and significant improvements in terms of oxygenation and driving pressure.

The APRONET trial is therefore the first work that focuses on the prevalence of the use of PP in a substantial number of ICU centers and countries and that filed a list of the reasons not to use it.

Can we say that the picture substantially changed since the LUNGSAFE trial? According to the Authors, the scenario has significantly progressed in the last two years. The study found that PP was used in 32.9% of severe ARDS patients with a low rate of complications and significant results in terms of oxygenation increase and driving pressure decrease. It is interesting to point out that counting the patients who met the Proseva criteria the rate of pronating rises to 40.2%. However, if we consider the overall population of the study (735 patients that fulfilled the ARDS criteria *vs.* 2,377 in the LUNGSAFE study), the rate of PP goes down to 13.7% (101 patients).

Can we consider this a reliable picture of the present use of PP in the daily practice? The study design may arise some reasonable doubts.

First, the prevalence data collection was based on four days distributed in different seasons of the year between April 2016 and January 2017. This could be a point of strength for the study when looking at the prevalence of ARDS cases on a seasonal base but on the other hand, each center had the freedom to choose to participate how many times as it could, and to join one or more of the predetermined days and it is therefore reasonable to think (and Authors pointed it up) that the prescheduling of the deadlines could have boosted the use of PP in anticipation of the participation to the study. In fact, despite the expected seasonal trends in ARDS prevalence (lower in summer and higher in winter and spring) the prevalence of PP did not differ accordingly.

Second, another possible reason to suspect an overestimation of PP is the choice and the number of the ICUs included in this work. In fact, the APRONET enrolled 141 ICUs from 20 countries (mostly European). Furthermore, most of the ICUs recruited were located in France, Spain and Italy which are the countries that have shown the higher interest in ARDS treatment and have published the larger studies on PP, so far.

Some concerns still arise when it comes to the choice of the patients to pronate and, even most important, the ones not to. Looking at the reasons for not pronating, stands out the clinician misunderstandings about the severity of hypoxemia (accounting for 64.3% of all cases). One of the most challenging issues of PP treatment for ARDS patients has always been the definition of the specific thresholds of PaO_2/FiO_2 that might benefit the most from this strategy.

The Proseva trial represents a cornerstone on this issue and the APRONET study seems to confirm the point. As previously pointed out, the 40% of patients meeting the Proseva criteria in this study had been pronated, reflecting the impact of this trial on the clinicians perception. This same impact may as well be reflected by the overall length of the PP treatment, that is now assessed on 18 (from 16 to 23) hours for the first session, showing a larger consensus on the evidence that duration of positioning consistently affects the efficacy of PP. But more interestingly, how can we explain the choice not to pronate the 60% of patients meeting the Proseva criteria of severe ARDS, and, even

more significant, how can we explain the choice to pronate a number of patients with mild or moderate ARDS?

One possible answer is that a substantial number of patients that showed a PaO_2/FiO_2 ratio <150 were not considered hypoxemic enough to undergo PP. Still, this doesn't match with the 15 patients pronated with a P/F ratio between 295 and 171.

According to this scenario, we have to assume that there is still a deep confusion and a lack of homogeneity when it comes to recognition of the severity of ARDS and progression of treatments.

Consolidated evidence shows that the greatest benefit from each therapeutic strategy can be achieved only if applied to a specific level of ARDS progression (11).

Given that Lung Protective Ventilation should be the base-line of ARDS treatment from the start, patients with a P/F ratio between 200 and 150 should progressively be treated with higher levels of PEEP and neuromuscular blockage. Subsequently, PP represents the third line of treatment after which (in presence of a P/F ratio declining to <100) rescue treatments should be considered (12).

The second most important reason not to pronate (that could partially help to explain the 49 severe ARDS patients that were not pronated), is the hemodynamic instability. This element concurs at the idea that ARDS treatment strategies have not been fully understood and embraced by ICUs physicians, given that pronating have shown to improve hemodynamic rather than worsen it.

Lastly, looking at the possible reasons not to pronate a patient, stands out the undefined voice (others) that accounts for the 6% of the cases (44 patients). It is rational to think that this percentage could be referred to all the logistic and practical reasons that have always played an important role in the low application of PP, so far.

The rates of possible complications have been pointed out, in the past studies, as one of the criticisms in PP practice. The chance of endotracheal tube, drains or catheters removal, and the higher incidence of pressure sores may have accounted for a certain part of not considering PP as a feasible strategy. The Apronet study deviates from this tendency. Complications were reported in 12 of 101 pronated patients. Also in this case, these data can be interpreted as either due to (I) improvement of ICUs standards of practice thanks to a more frequent use of PP; (II) selection of ICUs that have always been more open to the PP practice and therefore have developed the skills to perform it in the most efficient and safe way.

With all these limitations, the APRONET study confirms the efficacy of PP. A significant improvement in oxygenation at the first session of PP was observed, with a reduction of driving pressure (with no variations on Vt). This could represent an interesting finding since driving pressure has been pointed as a strong predictor of mortality in ARDS patients. With all the limitations of the case, the APRONET study gives a first sight on the perception among clinicians of the use of PP.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
2. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA 2016;315:788-800. Erratum in: JAMA 2016;316:350.
3. Piehl MA, Brown RS. Use of extreme position changes in acute respiratory failure. Crit Care Med 1976;4:13-4.
4. Kallet RH. A Comprehensive Review of Prone Position in ARDS. Respir Care 2015;60:1660-87.
5. Jozwiak M, Teboul JL, Anguel N, et al. Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2013;188:1428-33.
6. 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;345:568-73.
7. Guerin C, Gaillard S, Lemasson S, et al. Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. JAMA 2004;292:2379-87.
8. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159-68.
9. Munshi L, Del Sorbo L, Adhikari NKJ, et al. Prone Position for Acute Respiratory Distress Syndrome. A

Systematic Review and Meta-Analysis. Ann Am Thorac Soc 2017;14:S280-8.
10. Guérin C, Beuret P, Constantin JM, et al. A prospective international observational prevalence study on prone positioning of ARDS patients: the APRONET (ARDS Prone Position Network) study. Intensive Care Med 2018;44:22-37.
11. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. N Engl J Med 2005;353:1685-93.
12. Alessandri F, Pugliese F, Ranieri VM. The Role of Rescue Therapies in the Treatment of Severe ARDS. Respir Care 2018;63:92-101.

Cite this article as: Pugliese F, Babetto C, Alessandri F, Ranieri VM. Prone Positioning for ARDS: still misunderstood and misused. J Thorac Dis 2018;10(Suppl 17):S2079-S2082. doi: 10.21037/jtd.2018.04.157

Letter to the Editor

Prone positioning acute respiratory distress syndrome patients

Claude Guérin[1,2,3]

[1]Réanimation médicale, Hôpital de la Croix Rousse, Hospices civils de Lyon, Lyon, France; [2]Université de Lyon, Lyon, France; [3]IMRB, U955 Inserm–Université Paris Est Créteil, Créteil, France

Correspondence to: Claude Guérin. Service de réanimation médicale, Hôpital de la Croix Rousse, 103 Grande Rue de la Croix Rousse, 69004 Lyon, France. Email: claude.guerin@chu-lyon.fr.

Provenance: This is an invited article commissioned by the Section Editor Dr. Zhiheng Xu (State Key Laboratory of Respiratory Disease, Guangzhou Institute of Respiratory Disease, Department of Intensive Care, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China).

Response to: Pugliese F, Babetto C, Alessandri F, *et al.* Prone positioning for ARDS: still misunderstood and misused. J Thorac Dis 2018;10:S2079-82. Hepokoski ML, Odish M, Malhotra A. Prone positioning in acute respiratory distress syndrome: why aren't we using it more? J Thorac Dis 2018;10:S1020-4.

Submitted Apr 19, 2018. Accepted for publication May 10, 2018.
doi: 10.21037/jtd.2018.05.109
View this article at: http://dx.doi.org/10.21037/jtd.2018.05.109

I read with great interest the editorials of my esteemed colleagues regarding the Apronet study (1). This study aimed at making a picture of the use of prone position (PP) in acute respiratory distress syndrome (ARDS) in the current time and to explore the reasons to not proning these patients. I thank *Journal of Thoracic Disease* (*JTD*) for providing me the opportunity to share some comments with them.

Pugliese *et al.* (2) pointed out that the rate of use of PP in the Apronet study may have been overestimated from the design of the study. This argument is very interesting and at the time the Apronet study was designed was not discussed. It is based on the fact that for the purpose of the Apronet study investigators were informed on the dates, had the choice between different times and were prepared to the study. All of this may have forced them to use PP the days of the study something they wouldn't have been doing outside the study context. My problem with this argument is that such design is common in any prospective epidemiological study, like lung safe (3) as an example. If this argument is true prospective epidemiological data does overestimate the true rate of the event under investigation. The only way to avoid this bias would be, therefore, to retrospectively look at the data, which were recorded without the "scrutiny" bias. Another comment pertaining to the argument of overestimation is that the Apronet study mostly involved European ICUs and in particular ICUs from Italy, Spain and France. In these countries intensivists conducted the five largest trials on PP (4-8). Therefore, it is highly likely that PP is used in routine there and, hence it is unlikely, in my opinion, that indication of PP was forced by study design in the Apronet study.

I do agree with Pugliese *et al.* (2) regarding the way the ventilatory and non-ventilatory strategies should be deciphered in relation with the temporal trend of ARDS severity. In the PROSEVA trial (8), a 12-hour stabilization period was mandated before inclusion to confirm the ARDS and assess its severity at standardized settings. However, PP should/must be used more quickly in patients with very severe ARDS once neuromuscular blocking agents, positive end expiratory pressure (PEEP) and nitric oxide have failed to restore a safe oxygenation level. In some ICUs patients like this may not receive PP and are given ECMO straight ahead. The rate of complications due to PP was low in the Apronet study. This may result from a real improvement in practice or an underreporting. Complications attributable to PP have been put forward in the early days of PP and were used for the detractors of the technique to avoid it. It should be mentioned that in none of the trials on PP, the PP group had a significant worst outcome, suggesting that, at the population level, the impact of these complications was less than it was claimed. To date, PP is a safe technique. It is also a simple one and should not be made too complex. As an example, the complications rate was higher in the

Italian PS2 trial (7) in the group of patients in which PP was performed by using a special bed as compared to the own patient bed. Patients under ECMO can be proned safely (9,10). Patients referred to our center for ECMO evaluation are sometimes transported in the PP.

Hepokoski *et al.* (11) emphasized on the prevention of ventilator induced lung injury (VILI) as the main mechanism for the beneficial effect of PP found in trials. This hypothesis is highly likely from the strong pathophysiological background that embedded PP and supports the use of prolonged PP sessions. The longer the application of PP the more efficient the VILI prevention would be. VILI prevention should be disconnected from gas exchange improvement as underlined by Hepoposki *et al.* Even though hypoxemia is not the main reason for death in ARDS patients an acute profound hypoxemia can occur and be life-threatening. Henceforth, PP can be an immediate rescue procedure. In the PROSEVA trial we observed a twice lower rate of cardiac arrest in the PP group than in the control group. Even though the real mechanism subtending cardiac arrest was not investigated in this trial, it could be that PP avoided cardiac arrest from profound hypoxemia. However, the maintenance of prolonged PP sessions, as long as needed, should not be based on oxygenation response. In trials, oxygenation response was not associated with better survival (12,13). Therefore, apart from a deleterious effect of PP on oxygenation, PP should be applied irrespective of the oxygenation response. This contention implies to deal with the issue of PP interruption. Currently the most used criterion is oxygenation-based. In the PROSEVA trial we defined PP weanibility from oxygenation criterion at specific settings in the supine position. May be new tools available at the bedside like electrical impedance tomography that allow measuring regional ventilation and perfusion could be used to define the optimal duration of the PP session. Hepokoski *et al.* (11) also judiciously emphasized on the hemodynamic effect of PP. In the Apronet study (14), the clinicians were reluctant to use PP for the risk of hemodynamic impairment. This was the second reason for not proning ARDS patients, though well after the not severe enough hypoxemia criterion. Worrying the risk of hemodynamic impairment from PP is not supported by the data. Beside the arguments developed by Hepokoski *et al.*, I may add the fact that in the PROSEVA trial there were two days without cardiovascular dysfunction more in the PP group than in the control group (8). The prevention of ventilator associated pneumonia (VAP) could be a mechanism by which PP improved survival. Favoring the clearing of secretions as commonly observed during PP was a relevant rationale for this. However, in the PROSEVA trial the rate of VAP was not reduced in PP (15).

Acknowledgements

None.

Footnote

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

References

1. Guerin C, Beuret P, Constantin JM, et al. A prospective international observational prevalence study on prone positioning of ARDS patients: the APRONET (ARDS Prone Position Network) study. Intensive Care Med 2018;44:22-37.
2. Pugliese F, Babetto C, Alessandri F, et al. Prone Positioning for ARDS: still misunderstood and misused. J Thorac Dis 2018. [Epub ahead of print].
3. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA 2016;315:788-800.
4. Guerin C, Gaillard S, Lemasson S, et al. Effects of systematic prone positioning in hypoxemic acute respiratory failure: a randomized controlled trial. JAMA 2004;292:2379-87.
5. 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;345:568-73.
6. 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;173:1233-9.
7. 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;302:1977-84.
8. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159-68.
9. Kimmoun A, Guerci P, Bridey C, et al. Prone positioning use to hasten veno-venous ECMO weaning in ARDS. Intensive Care Med 2013;39:1877-9.

10. Kimmoun A, Roche S, Bridey C, et al. Prolonged prone positioning under VV-ECMO is safe and improves oxygenation and respiratory compliance. Ann Intensive Care 2015;5:35.
11. Hepokoski ML, Odish M, Malhotra A. Prone positioning in acute respiratory distress syndrome: why aren't we using it more? J Thorac Dis 2018;10:S1020-4.
12. Lemasson S, Ayzac L, Girard R, et al. Does gas exchange response to prone position predict mortality in hypoxemic acute respiratory failure? Intensive Care Med 2006;32:1987-93.
13. Albert RK, Keniston A, Baboi L, et al. Prone position-induced improvement in gas exchange does not predict improved survival in the acute respiratory distress syndrome. Am J Respir Crit Care Med 2014;189:494-6.
14. Guérin C, Beuret P, Constantin JM, et al. A prospective international observational one-day prevalence study on prone positioning in ARDS. The APRONET study. Intensive Care Medicine Experimental 2017;5:44.
15. Ayzac L, Girard R, Baboi L, et al. Ventilator-associated pneumonia in ARDS patients: the impact of prone positioning. A secondary analysis of the PROSEVA trial. Intensive Care Med 2016;42:871-8.

Cite this article as: Guérin C. Prone positioning acute respiratory distress syndrome patients. J Thorac Dis 2018;10(Suppl 17):S2092-S2094. doi: 10.21037/jtd.2018.05.109