Editorial

Prone positioning in acute respiratory distress syndrome: why aren't we using it more?

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Introduction

Acute respiratory distress syndrome (ARDS) is defined by acute onset of bilateral lung infiltrates with impaired gas exchange that is not entirely due to congestive heart failure (1). Strategies to manage ARDS are primarily supportive, with the bulk of the evidence suggesting that improvement in mortality is achieved with optimal setting of mechanical ventilation (2). The mortality rate due to ARDS remains unacceptably high at 30–40%, and a number of recent studies have examined the impact of prone positioning (PP) in ARDS as a life-saving intervention (3,4). The concept of proning patients on mechanical ventilation was proposed in the 1970s and has been used for several decades, although definitive mortality outcome data were only available more recently with the publication of the PROSEVA trial in 2013 and subsequent meta-analyses (3,4).

In the APRONET study by Guerin *et al.*, the authors conducted the first prospective multicenter International prevalence study investigating the use of PP in ARDS patients (5). The authors predicted that PP use would be increasing in patients with ARDS given recent publications demonstrating safety and efficacy (3,4). Overall, 6,723 patients from 141 intensive care units (ICUs) in 20 different countries were screened by the APRONET investigators. The authors observed that PP was generally under-utilized, as only 101 of the 735 patients found to have ARDS received at least one proning session [5.9% of mild ARDS patients, 10.3% of moderate ARDS patients and 32.9% of severe ARDS patients, (P=0.0001)]. These rates are gradually increasing over time compared to prior epidemiological studies, but the numbers remain surprisingly low, especially in severe ARDS where PP has been shown to improve survival. The authors also performed a secondary analysis investigating the reasons for not utilizing PP, and found that the perception that hypoxemia was not severe enough to justify proning and concerns regarding hemodynamic instability were the 2 most common reasons. We applaud the efforts of Guerin *et al.* to identify barriers to implementation of prone ventilation given that it is a safe and inexpensive approach. Their findings suggest that clinicians may have some misconceptions regarding proning, or are unaware of the potential mortality benefits of PP in patients with severe ARDS. In this review, we discuss a few of these issues in more detail with a focus on the mechanical ventilation benefits of PP beyond gas exchange, hemodynamic effects of PP, and alternatives to PP.

Improvements in mechanical ventilation in the prone position beyond gas exchange

PP has teleological appeal given that most quadruped mammals evolve in a primarily prone posture. For decades, studies have suggested that ventilation/perfusion matching and associated gas exchange is markedly improved in the prone position (6,7). Therefore, early clinical utilization of PP was reserved as a rescue therapy for patients with refractory hypoxemia. The more recent findings by Guerin and colleagues, suggest that many clinicians are continuing to use PP only for this indication, even in severe ARDS. In fact, 23% of the patients with severe ARDS evaluated in the APRONET study were still not proned due to the perception that hypoxemia was not severe enough (5).

Multiple organ failure is the leading cause of mortality in ARDS, while refractory hypoxemia less frequently leads to death (8). In fact, the landmark ARMA trial published in 2000 showed that lung protective ventilation with low tidal volumes actually worsened gas exchange while still improving survival by mitigating multiple organ failure due to ventilator induced lung injury (VILI) (9). Interestingly, preclinical and clinical studies have demonstrated that PP leads to alterations in lung mechanics that likely prevent VILI (10,11). In ARDS, the dependent lung units are susceptible to collapse due to surrounding pleural pressures as well as surfactant deficiency/dysfunction. The weight of the heart and abdominal viscera in the supine position further promote collapse of these dorsal lung units. Alternatively, turning a patient prone places the heart in the dependent position supported by the sternum which alleviates the potential compressive effect on the lung. As a result, there are more open lung units to distribute a fixed tidal volume leading to less over-distention (10). Additionally, PP reduces the pleural pressure gradient from nondependent to dependent regions which allows aeration to be delivered more uniformly among these open lung units which reduces regional shear stress (12). Of note, ARDS usually develops off mechanical ventilation whereas PP is exclusively performed while PEEP is applied; thus, there is less lung collapse while prone due to the ability of PEEP to prevent derecruitment. This concept is recognizing that for a given airway pressure, opening collapsed lung units is more challenging than preventing the collapse of open units. Together, these changes reduce the risk of VILI, and VILI has indeed been found to be significantly reduced by PP in animal models (13). Remote organ failures and mortality due to VILI in ARDS are believed to be due to the generation of mediators, e.g., inflammatory cytokines, that enter the circulation and promote organ injury via systemic inflammation in a process referred to as biotrauma (14). The PROSEVA trial did not demonstrate clearly that PP mitigates remote organ dysfunction; however, systemic inflammatory mediators have been found to be significantly reduced by mechanical ventilation in the prone position (15). Further research into the lung protective mechanisms of PP is warranted, but data currently available suggest strongly that the survival benefit observed with proning is likely related to reducing VILI.

Ventilator associated pneumonia is another life-threatening complication of mechanical ventilation that may be mitigated by PP. The drainage of posterior dependent lung units may be improved in the prone position which may explain why some authors observed that PP improves secretion clearance (16). Pulmonary hygiene is an important factor in mitigating VAP, and studies have shown a reduced risk of VAP in subjects treated with PP (17). Additionally, the PROSEVA trial showed more ventilator-free days in proned patients which also further reduces the risk of VAP, and is another likely contributor to improved mortality (4).

Hemodynamic impact of prone

Guerin *et al.* found that the second most common reason not to use PP in ARDS was concerns regarding hemodynamic instability (5). However, PP has not been shown to have deleterious effects on hemodynamics, and the PROSEVA study showed no significant difference in the rate of hypotension in patients who were proned compared to those who were not proned (4,18). Recently, Jozwiak *et al.* measured hemodynamics in proned ARDS patients via pulmonary artery catheter and transesophageal echocardiogram (19). They found that PP in the 18 patients they evaluated actually provided beneficial hemodynamic changes, such as increased right and left cardiac preload and mean arterial pressure (MAP), and decreased pulmonary vascular resistance (PVR). Cardiac output was also increased in the nine patients (50%) who had preload reserve as assessed by passive straight leg raise. Acute cor pulmonale due to the effects of hypoxic vasoconstriction and high airway pressures has been found to occur in 25% of patients with ARDS (20) which may lead to adverse systemic hemodynamic changes. As previously stated, PP may improve gas exchange and lung mechanics in a manner that lowers airway pressures which should lower right ventricular afterload depending on the state of lung inflation. This notion was assessed by Viellard-Baron *et al.* who found that ARDS patients with acute cor pulmonale had a significant improvement in mean right ventricular enlargement and dyskinesia after PP (20). While the sample sizes in these studies are small, it seems that PP improves pulmonary and systemic hemodynamics, and may actually benefit some patients with ARDS and hemodynamic instability.

Remote organ hemodynamics in PP have also been evaluated as PP is known to increase intra-abdominal pressure (IAP) which may compromise blood flow in peripheral organs (19). Despite this concern, PP has not been shown to affect regional hemodynamics adversely. Matojovic *et al.* used hepatic vein catheters to measure hepato-splanchnic flow; hepato-splanchnic oxygen delivery and oxygen consumption, and liver lactate uptake in patients with ARDS in the prone and supine position (21). It is worth noting that the patients they evaluated were hemodynamically stable prior to proning, but they found that systemic hemodynamics and hepato-splanchnic perfusion were unaffected in the prone position compared to supine. Renal hemodynamics have also been evaluated, and renal blood flow, glomerular filtration rate, and urine output have all been found to be unaffected by proning (22).

Alternatives to prone

Despite decades of research dedicated to ARDS, there remains a lack of therapies that are definitively proven to improve mortality beyond lung protective ventilation and PP. Recently, the early use of neuromuscular blockade in patients with severe ARDS was found to improve survival in a randomized controlled trial (23). However, the exact mechanisms of this survival benefit remain unclear, but likely involves alleviating patient/ventilator dyssynchrony. Although additional trials and meta-analyses are needed, neuromuscular blockade is a promising therapeutic strategy that was found to have minimal complications, and may be combined with PP in patients with severe ARDS. In fact, some have argued that the benefits observed by Guerin *et al.* in the PROSEVA study may have been in part due to paralytics given these ARDS patients.

Technological improvements have made extracorporeal membrane oxygenation (ECMO) an attractive therapy in ARDS, as ECMO has long been used as a rescue strategy for refractory hypoxemia. ECMO also offers the ability to utilize ultra-low tidal volume ventilation as a means to prevent VILI while still maintaining adequate gas exchange. However, ECMO remains unproven in ARDS, and it is a costly therapy which has risks, such as bleeding and clotting as well as mechanical complications of instrumentation. These risks need to be weighed *vs.* potential benefits in larger trials before ECMO can be endorsed as a potentially life-saving therapy. Interestingly, recent data have suggested that ECMO use is increasing despite lack of proven efficacy, and Li *et al.* showed that a remarkable majority of patients treated with ECMO in ARDS do not receive a trial of proning prior to ECMO (24). PP is actually being used less in ECMO patients since the publication of the PROSEVA trial. We agree with Li *et al.* that this is an alarming trend given the proven efficacy and cost effectiveness of PP compared to ECMO. Other rescue therapies, such as inhaled nitric oxide, have been found to improve gas exchange, but have not offered survival benefit in ARDS; therefore, they are also poor alternatives to PP (25). Unfortunately, there remains no proven pharmacologic therapy in the treatment of ARDS, but research in this area is ongoing.

Conclusions

Despite the recent advances in our understanding of the risks and benefits of PP in ARDS, a number of questions remain:

- (I) To which patients should PP be applied? For example, could it be used as a preventative strategy to reduce the risk of ARDS or as a rescue strategy when conventional measures have failed?
- (II) What is the optimal approach to lung recruitment and setting of positive end-expiratory pressure (PEEP) on the mechanical ventilator in patients who are undergoing prone ventilation?
- (III) Is the risk and benefit of PP impacted in obesity, as obese patients may convey additional risk, such as, increased IAP or mechanical complications from proning? On the other hand, obese patients may be amenable to recruitment strategies to promote lung homogeneity;
- (IV) Will new technology impact the use of PP? For example, are automated beds helpful for the execution of prone ventilation or an unnecessary expense? Could electrical impedance tomography (EIT) be used to guide prone ventilation?

PP is a low-cost therapeutic strategy, and the findings by Guerin *et al.* in the APRONET trial show that side effects are minimal and decreasing with experience. We believe PP is underutilized and should be considered in all patients with severe ARDS as an adjunctive therapy to lung protective ventilation.

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Footnote

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

References

1. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
2. Hepokoski M, Owens RL, Malhotra A, et al. Mechanical ventilation in acute respiratory distress syndrome at ATS 2016: the search for a patient-specific strategy. J Thorac Dis 2016;8:S550-2.
3. 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;40:332-41.
4. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159-68.
5. 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.
6. Pappert D, Rossaint R, Slama K, et al. Influence of positioning on ventilation-perfusion relationships in severe adult respiratory distress syndrome. Chest 1994;106:1511-6.
7. Douglas WW, Rehder K, Beynen FM, et al. Improved oxygenation in patients with acute respiratory failure: the prone position. Am Rev Respir Dis 1977;115:559-66.
8. Stapleton RD, Wang BM, Hudson LD, et al. Causes and timing of death in patients with ARDS. Chest 2005;128:525-32.
9. Brower RG, Matthay MA, Morris A, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
10. 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;174:187-97.
11. Valenza F, Guglielmi M, Maffioletti M, et al. Prone position delays the progression of ventilator-induced lung injury in rats: does lung strain distribution play a role? Crit Care Med 2005;33:361-7.
12. Lamm WJ, Graham MM, Albert RK. Mechanism by which the prone position improves oxygenation in acute lung injury. Am J Respir Crit Care Med 1994;150:184-93.
13. 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.
14. Hepokoski M, Englert JA, Baron RM, et al. Ventilator-induced lung injury increases expression of endothelial inflammatory mediators in the kidney. Am J Physiol Renal Physiol 2017;312:F654-60.
15. Chan MC, Hsu JY, Liu HH, et al. Effects of prone position on inflammatory markers in patients with ARDS due to community-acquired pneumonia. J Formos Med Assoc 2007;106:708-16.
16. Zanella A, Cressoni M, Epp M, et al. Effects of tracheal orientation on development of ventilator-associated pneumonia: an experimental study. Intensive Care Med 2012;38:677-85.
17. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. Intensive Care Med 2010;36:585-99.
18. Jolliet P, Bulpa P, Chevrolet JC. Effects of the prone position on gas exchange and hemodynamics in severe acute respiratory distress syndrome. Crit Care Med 1998;26:1977-85.
19. 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.
20. Vieillard-Baron A, Schmitt JM, Augarde R, et al. Acute cor pulmonale in acute respiratory distress syndrome submitted to protective ventilation: incidence, clinical implications, and prognosis. Crit Care Med 2001;29:1551-5.
21. Matejovic M, Rokyta R Jr, Radermacher P, et al. Effect of prone position on hepato-splanchnic hemodynamics in acute lung injury. Intensive Care Med 2002;28:1750-5.
22. Hering R, Wrigge H, Vorwerk R, et al. The effects of prone positioning on intraabdominal pressure and

cardiovascular and renal function in patients with acute lung injury. Anesth Analg 2001;92:1226-31.
23. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363:1107-16.
24. Li X, Scales DC, Kavanagh BP. Unproven and Expensive before Proven and Cheap: Extracorporeal Membrane Oxygenation versus Prone Position in Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2018;197:991-3.
25. Gebistorf F, Karam O, Wetterslev J, et al. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. Cochrane Database Syst Rev 2016:CD002787.

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