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EDITORIAL

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Prone position acute respiratory distress syndrome patients: less prone to ventilator associated pneumonia?

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Acute respiratory distress syndrome (ARDS) and pneumonia are tightly entwined as pneumonia is both a frequent cause and a complication of ARDS. Compared to patients without ARDS, the incidence of ventilator associated pneumonia (VAP) appears to be higher in ARDS patients where reported VAP rates may be as high as 60 %, although these estimates vary and may be imprecise as a result of difficulties in diagnosing VAP. As ARDS patients represent a high-risk population for developing VAP, they might benefit the most from preventive measures. Many mechanical interventions have been proposed to prevent VAP. Among these, semirecumbent positioning, subglottic tracheal secretion aspiration, and continuous cuff pressure monitoring of the endotracheal tube have been tested in randomized controlled trials (RCTs). In a small but widely cited study, a dramatic decrease of VAP incidence was observed in patients assigned to 45° semirecumbent as compared to supine position [1]. However, no subsequent study could confirm these findings and maintaining a 45° semirecumbent position may be difficult to comply with in a real-life setting [2, 3]. Stronger evidence exists for subglottic secretion aspiration devices, with three RCTs showing VAP reduction amounting to 50, 42, and 64 %, respectively [4–6]. Finally, continuous control of endotracheal tube cuff pressure is more controversial with two studies showing a decrease in VAP incidence [7, 8] and one study showing no effect [9]. None of these studies have specifically addressed these issues in ARDS patients. Evidence of efficacy of mechanical interventions in VAP prevention is presented in Table 1.

Mechanical ventilation in prone position has established itself as a preferential ventilatory strategy in severe ARDS, since the PROSEVA trial conclusively showed a reduced mortality in patients ventilated in prone as compared to supine position [10]. The mechanisms of the lung protective effect of prone positioning have not been completely unraveled, but seem tightly related to a reduction of ventilator induced injury (VILI) through a reduction of mechanical strain by a more homogeneous distribution of delivered tidal volumes and a decreased collapse of lung due to its own weight and that of the heart. Additionally, prone positioning increases secretion drainage owing to an improvement of the orientation of the endotracheal tube–oropharynx–trachea axis. It also facilitates outwards clearance of fluids both from the mouth and the airway across the endotracheal tube. Prone positioning is also assumed to reduce the risk for aspiration. Thus, it seems reasonable to expect that prone ventilation not only prevents VIVL but also VAP. In this regard, the meta-analysis performed by Sud et al. reported an overall statistically significant reduction in the rate of VAP with prone versus supine positioning in a mixed

Table 1 Evidence of efficacy of mechanical prevention measures for VAP

Intervention	Type of study	*N*	Main findings	References	Evidence
Semirecumbent position					Moderate
Drakulovic et al. (1999)	RCT (supine vs 45°)	86	↘ VAP (16.6 to 2.8 %), $p = 0.01$	[1]	
Keeley (2007)	RCT (25° vs 45°)	56	↘ VAP (54 to 29 %), NS	[2]	
van Nieuwenhoven et al. (2006)	RCT (5° vs 30°)	221	VAP (18.3 vs 14.3 %), NS	[3]	
Subglottic secretion aspiration					Strong
Damas et al. (2015)	RCT	352	↘ VAP (17.6 to 8.8 %), $p = 0.02$	[4]	
Lacherade et al. (2010)	RCT	333	↘ VAP (25.6 to 14.8 %), $p = 0.02$	[5]	
Lorente et al. (2007)	RCT	280	↘ VAP (22.1 to 7.9 %), $p = 0.001$	[6]	
Continuous pressure cuff monitoring					Moderate
Lorente et al. (2014)	Prospective observational	284	↘ VAP (22.0 to 11.2 %), $p = 0.02$	[7]	
Nseir et al. (2011)	RCT	122	↘ VAP (26.2 to 9.8 %), $p = 0.03$	[8]	
Valencia et al. (2007)	RCT	142	VAP (29 vs 22 %), NS	[9]	
Prone position					Weak
Guérin et al. (2004)	RCT (supine vs prone)	791	VAP (24.1 vs 20.6 %), NS	[12]	
Voggenreiter et al. (2005)	RCT	40	↘ VAP (89 to 62 %), $p = 0.048$	[13]	
Fernandez et al. (2008)	RCT	40	VAP (5 vs 14 %), NS	[14]	
Mounier et al. (2010)	Prospective cohort	2409	VAP HR 1.64 [0.7–3.8], NS	[15]	

N number of patients included, *RCT* randomized controlled trial, *VAP* ventilator associated pneumonia, *NS* not significant, *HR* hazard ratio

population of ARDS patients, despite the fact that no single trial was positive in this respect [11]. Indeed, studies that evaluated VAP incidence in prone compared to supine ventilation have provided conflicting results. For example, in their first study on prone ventilation, Guerin et al. observed a non-significant reduction of VAP incidence in the prone versus the supine group (20.6 versus 24.1 %, respectively) [12]. In a study in trauma patients, VAP was diagnosed in 62 % of prone versus 89 % of supine positioned patients ($p =$ NS) [13]. On the other hand, Fernandez et al. found an increased rate of VAP associated with prone positioning [14]. Apart from RCTs, in a propensity score matched case control study derived from the large OUTCOMEREA database, VAP rates were not different between prone and supine positioned patients [15].

In a recent article in *Intensive Care Medicine*, Ayzac et al. report a post hoc analysis of the PROSEVA trial, focusing on the impact of prone positioning on VAP incidence in severe ARDS patients [16]. The working hypothesis that proning would affect VAP incidence was formulated a priori; suspected VAP episodes were recorded prospectively and were systematically reviewed by an independent adjudication committee. The authors found a VAP incidence of 46.6 % in prone and of 33.5 % in supine positioned patients, a difference that was not significant [16]. Importantly, VAP was diagnosed after a median of 12 days after intubation. When considering the Kaplan–Meier curve of the PROSEVA trial, it appears that survival curves diverge from the first days of treatment allocation, are clearly separated at day 12, and run a more or less parallel course from there. As such, it can be observed that prone positioning exerts its protective effects early, well before occurrence of VAP which was essentially late-onset in this study.

A second observation made by the authors is the association between VAP and increased mortality [16]. This must be seen in the context of the ongoing debate about how to measure the impact of VAP on mortality [14, 17, 18], and how to distinguish the label 'VAP' as a diagnosis of a distinct and preventable disease with its own attributable mortality from a simple marker of a severe underlying disease with an inherent unfavorable outcome. This appears to be particularly difficult in ARDS patients, primarily because of the low accuracy of VAP diagnosis tools in this condition. In addition, the complex evolution over time of organ failure in ARDS patients, which may be affected by alternative events and treatments, requires a control for these biases in statistical analysis. While the current analysis used VAP as a time-dependent variable (as recommended in current standards), the association between VAP and mortality was adjusted only for factors present at study inclusion (such as organ failure scores), whereas the large time interval between inclusion and late-onset VAP could have allowed many other intercurrent factors to have contributed.

Taken together, the PROSEVA trial and the current ancillary analysis suggest that the protective effect of prone positioning in severe ARDS seems unrelated to its putative effects on pulmonary infection. Even with a state-of-the-art ventilatory strategy, ARDS patients are still prone to VAP. The search for the ultimate mechanical intervention to prevent VAP is still open.

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