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EDITORIAL

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Prone positioning and neuromuscular blocking agents are part of standard care in severe ARDS patients: we are not sure

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Introduction

Over the last two decades only three interventions have been shown in randomized clinical trials to benefit the ventilatory treatment of acute respiratory distress syndrome (ARDS): lower tidal volume [1], sustained prone positioning [2], and the early use of neuromuscular blocking agents (NMBA) [3]. Acting through different pathways, these techniques decrease the risk inherent to mechanical ventilation.

While selecting low tidal volumes concerns how the ventilator is set, prone positioning focuses on how the lung reacts to those settings. Both in experimental settings and in human ARDS, it has been consistently shown that, beyond the remarkable increase of oxygenation, prone position makes the lungs mechanically more homogeneous, thus preventing/decreasing the uneven distribution of stress and strain that accentuates the risk for ventilation-induced lung injury (VILI) [4]. The biological rationale for using NMBA routinely in therapy for ARDS is grounded in the observations that NMBA often decreases oxygen consumption, improving oxygenation and allowing more "gentle" and coordinated ventilation. NMBA abolish the muscle response to intense respiratory drive and therefore prevent asynchrony and dramatically eliminate negative swings of pleural and transpulmonary pressures. As neither proning nor NMBA are without potentially serious adverse side effects, the indication for their use should be well defined.

Prone position for ARDS

The first recognized benefit from prone position in ARDS was improved oxygenation in association with increased, unmodified, or decreased $PaCO_2$. Improvement of oxygenation during prone position primarily depends on the generation of more recruitment in dorsal zones than derecruitment in ventral ones. If ventilation also improves despite the accompanying decrease of chest wall compliance, prognosis becomes more favorable [5]. The most important rationale for prone positioning, however, is to more homogeneously distribute forces throughout the lung parenchyma, due primarily to more favorable chest wall/lung shape matching. In fact, the greater amount of ventilatable tissue due to recruitment and the more homogeneous distribution of overall inflation dampen the negative effects of mechanical ventilation by distributing stress and strain across a wider and more homogeneous territory [4].

The first randomized trials, however, did not show consistent mortality benefit of prone positioning [6–9]. The largest of these early trials, however, included all

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ARDS patients (from mild to severe) and maintained the prone position for 6 h per day. Despite these limitations, survival rate increased among patients with most severe ARDS treated in prone position [6]. Subsequent studies again clearly suggested better survival among the most severe ARDS patients [10]. The study by Guérin and colleagues, which enrolled only patients with more severe ARDS, persuasively demonstrated this same principle [2].

For proning to benefit, it stands to reason that recruitable tissue and mechanical lung inhomogeneity must be present. Both of these feature characterize severe ARDS [11, 12]. Therefore, the long-term prone position would appear strongly indicated at PaO_2/FiO_2 less than 100, to be considered/tested when less than 150, and without value in most cases of mild-moderate ARDS where the prerequisites for the prone position to work are lacking.

Neuromuscular blocking agents for ARDS

NMBA can improve oxygenation and decrease the ventilatory needs by decreasing the oxygen consumption, improving the mixed venous oxygen content of shunted blood, and/or facilitating recruitment in response to positive end expiratory pressure (PEEP). In the specific setting of ARDS, NMBA may avoid the consequences of the patient's strong drive to breathe, which not only promotes patient–ventilator asynchrony but also violates current principles of VILI avoidance. For the last 25 years, however, the use of NMBA has been discouraged because of their potential to contribute to sustained neuromuscular weakness [13] as well as to predictably impair coughing and secretion clearance. In addition, several reports have indicated the physiological advantages of spontaneous breathing in improving the ventilation of the paradiaphragmatic regions of the lung as well as in avoiding ventilator-associated diaphragmatic dysfunction [14]. Therefore, it was somewhat surprising that Papazian et al. reported a trial on cisatracurium in ARDS that indicates NMBA for 48 h reduces adjusted mortality rate and barotrauma [3].

Subsequent debate has been directed toward certain puzzling aspects of this intriguing trial. Concerns raised have included the following: survival benefit appeared only in those with PaO_2/FiO_2 ratios that indicate very severe disease. Despite high ARDS severity, which tends to benefit from higher PEEP, the range of PEEP applied appears to have been rather modest. Distinct mortality separation between control and intervention groups emerged only late in the disease course, even though cisatracurium was administered for 48 h during the earliest phase. Finally, the study may have been underpowered to show a conclusive mortality difference. Interestingly, group differences in minute ventilation were not significantly different between cohorts, suggesting that effort reduction was not overwhelmingly dominant as the reason for mortality benefit. It should be noted that not all neuromuscular blockers should be considered equivalent; indeed, cisatracurium not only has a somewhat better safety profile than other drugs in common use, but also has been associated with reduction in inflammatory markers by this same investigative group [15]. Is it possible that taking early control of ventilation and imposing a lung protective strategy interrupts the dysfunctional native response which otherwise would have led to intensified inflammation and late mortality?

In the end, we cannot consider NMBA to be standard early phase therapy for all patients with the ARDS. The rationale for their occasional use, however, remains quite strong, especially for patients with severe disease who have chaotic patient–ventilator asynchrony despite optimal sedation, for those with persistent severe hypoxemia, and for those with forceful breathing efforts that jeopardize effective lung protection.

Conclusions

Both prone positioning and neuromuscular blockade appear indicated for selected patients with severe ARDS. Prone positioning has better documented experimental and clinical justifications for adoption as standard practice in such patients than does NMBA use, whose underlying mechanistic rationale, though attractive, is less well supported by clinical data. The available evidence strongly suggests that sustained proning therapy should be considered the standard of care in severe ARDS refractory to usual measures. NMBA should be considered in patients who remain vigorously breathing despite heavy sedation, especially when esophageal pressure measurements reveal dramatically negative pressure swings that provide a strong impetus for their use.

Compliance with ethical standards

Conflicts of interest The authors declare no conflict of interest.

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EDITORIAL

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Prone positioning and neuromuscular blocking agents are part of standard care in severe ARDS patients: no

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The concept of 'standard of care' has different definitions and implications according to its contextual use [1]. In this commentary, we will focus on whether prone positioning and neuromuscular blockade should be considered 'standard of care' in the sense of what is 'best' practice for these patients, as this has relevance for both patient care and future research [1, 2].

Prone ventilation has been studied for over three decades with consistent findings of improved oxygenation and, with one exception, no change in mortality. However, meta-analyses suggest benefit with a longer daily duration of proning when applied to the subset with more severe ARDS [3, 4]. Based on this background, Guerin and colleagues studied longer duration prone ventilation (17 h per day) and limited enrollment to patients with more severe ARDS. They demonstrated improved oxygenation (likely indicating recruitment) and a substantial mortality benefit (likely reflecting lung protection) in comparison to a low tidal volume and lower PEEP approach in the semirecumbent position [5]. Based on this trial and prior work, should prone ventilation now be standard of care for patients with severe ARDS? We think not.

First, consider the results of an individual patient-level meta-analysis of randomized trials of higher PEEP. Higher PEEP approaches improved mortality in the moderate and severe ARDS subsets [PaO2/FiO2 (P/F) $\leq$ 200] in comparison to the lower PEEP approach used by the PROSEVA investigators [6]. Furthermore, a post hoc analysis of the LOV study revealed that, when P/F increases after PEEP is increased, mortality is reduced [adjusted odds ratio 0.80 (95 % confidence interval 0.72–0.89) per 25-mm Hg increase in P/F] [7]. This was particularly evident in patients with more severe disease (P/F $\leq$ 150 mmHg), the threshold for enrollment used by the PROSEVA investigators. Thus, it remains unclear if prone ventilation is superior to higher PEEP strategies particularly in patients with severe ARDS who respond to an increase in PEEP with a substantial increase in P/F (so-called responders). Finally, the safety of prone ventilation in inexperienced centers is also unclear.

Until the results of much-needed studies comparing higher PEEP in responders with prone ventilation are complete, we recommend a lower tidal volume/higher PEEP strategy as the initial approach for patients with

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severe ARDS. Patients with a favorable response to higher PEEP could continue to be treated in the semirecumbent position, though we acknowledge it is unclear whether this approach is superior to going directly to prone ventilation. Patients with severe ARDS who fail to respond to higher PEEP with improved P/F should be managed in the prone position with a return to a lower PEEP strategy, as tested in the PROSEVA study. Inexperienced centers should train their staff on safe prone practices before adopting this approach.

A similar situation exists regarding the use of early routine neuromuscular blockade in patients with ARDS. The potential benefits of neuromuscular blockade may be mediated by improved patient–ventilator interactions. Spontaneously breathing patients with ARDS can have a very high drive to breathe. This can lead to patients drawing larger-than-targeted tidal volumes on each breath with frequent and potentially erratic triggering of the ventilator and ultimately volutrauma and biotrauma. Small RCTs examining mechanistic effects of neuromuscular blockers have shown improved oxygenation along with reductions in inflammatory cytokines in both broncho-alveolar lavage fluid and serum in those patients receiving neuromuscular blockade [8, 9].

In 2010, French investigators reported that the neuromuscular blocker cisatracurium saved lives in patients with moderate–severe ARDS. The ACURASYS trial compared early cisatracurium infusion for 48 h to placebo in 340 patients from 20 French ICUs and showed an improved adjusted survival for patients in the neuromuscular blocker group (hazard ratio 0.68; 95 % CI 0.48–0.98) [10]. However, this approach has not been widely adopted, potentially due to several study limitations. First, the mortality benefit was noted only after statistical adjustment for baseline differences, and the authors themselves acknowledge that the trial was underpowered, a fact which can lead to false positive results [11]. Second, assessment of potential adverse effects of the intervention, including muscle paresis in survivors, lacked sensitivity, potentially leading to their underestimation. Third, both groups in this trial received high doses of sedatives that may impair long-term functional and cognitive outcomes and the control ventilation strategy used a lower PEEP approach that may not have been optimal given the severity of the ARDS, as noted above. Thus, it is possible that ventilation with higher PEEP and less sedation, an approach increasingly used in usual care, could be superior to cisatracurium if adverse effects of sedation and paralysis outweigh the potential benefits of reducing ventilator-induced lung injury through paralysis. As a result of these concerns, the critical care community has collectively recommended a confirmatory clinical trial to definitively test the safety and efficacy of neuromuscular blockade in patients with ARDS [12].

In the past, neuromuscular blockade was commonly used for ventilated patients with acute respiratory failure [13]. However, with its increased utilization, neuromuscular blockade was implicated in the development of ICU-acquired weakness [14], though this association has been recently challenged [15], and we agree that data supporting this link are tenuous at best. If, however, the association does exist, the alleged early benefits of neuromuscular blockade may be offset by ICU-acquired weakness, a syndrome that may limit the ability of patients to be liberated from mechanical ventilation and to recover their autonomy. Neuromuscular blockade is also associated with a risk of paralyzed wakefulness, since paralytics have no intrinsic sedative properties and it is very difficult to assess the depth of sedation in patients who are paralyzed. Thus, neuromuscular blocker use necessitates concomitant deep sedation. In turn, too much sedation can increase the duration of mechanical ventilation.

For all the reasons outlined above, we believe that, while both prone positioning and neuromuscular blockade are promising therapies that may improve mortality for patients with moderate–severe ARDS, their relative place in our treatment armamentarium remains uncertain. In particular, how they compare with a simpler approach of higher PEEP and less sedation is unknown. For these reasons, we believe that their use should be studied further, rather than mandated as standard care.

Compliance with ethical standards

Conflicts of interest Both authors are involved with the design and conduct of an NHLBI-sponsored randomized clinical trial of cisatricurium for patients with ARDS. They do not have any other relevant conflicts of interest to disclose.

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EDITORIAL

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Prone positioning and neuromuscular blocking agents are part of standard care in severe ARDS patients: yes

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The panel of experts who developed the new Berlin definition for acute respiratory distress syndrome (ARDS) recommended customizing ventilator strategies and adjunct therapies according to the level of oxygenation [1, 2]. The definition states that low tidal volumes (V_T) must be applied at all levels of severity. The experts favored the use of positive end-expiratory pressure (PEEP) in all ARDS categories, but at varying levels: low or moderate PEEP in mild ARDS, and high PEEP in severe ARDS.

In severe ARDS, defined as PaO_2/F_IO_2 of less than 100 mmHg under PEEP of at least 5 cmH_2O, the experts also recommended prone position (PP) and use of neuromuscular blocking agents (NMBA). They based their PP recommendation on the results of meta-analyses [1, 2], which were further confirmed by a multicenter trial on severe ARDS, the PROSEVA trial [3]. In this trial, ARDS severity was defined as PaO_2/F_IO_2 no greater than 150 mmHg with PEEP of at least 5 cmH_2O, F_IO_2 of at least 0.6 with an average V_T of 6.1 ml/kg predicted body weight. The PROSEVA trial showed a major decrease in mortality rate at 28 and 90 days after randomization in patients treated with PP. The experts recommendation of using NMBA was based on a randomized placebo-controlled trial, the ACURASYS trial [4]. In this trial, ARDS severity was defined as PaO_2/F_IO_2 no greater than 150 mmHg with PEEP of at least 5 cmH_2O and with an average V_T of 6.5 ml/kg predicted body weight. The ACURASYS trial showed a significant reduction in the hazard ratio for death at 90 days in the NMBA group as compared to the placebo group, after adjusting for confounding variables (PaO_2/F_IO_2 ratio, SAPS II, and end-inspiratory plateau airway pressure levels). Patients with the lowest PaO_2/F_IO_2 (defined as a threshold of 120 mmHg in the Cox model) made up two-thirds of the population and showed the highest reduction in mortality rate when NMBA were administered.

There are three main reasons for PP and NMBA forming part of standard care in severe ARDS patients: pathophysiological rationale, clinical benefit, and safety. Regarding the pathophysiological background, PP and NMBA achieve the two main goals of invasive mechanical ventilation in ARDS, namely to maintain safe gas exchange (which very often markedly improves in PP) and to prevent ventilator-induced lung injury [5]. In PP, as compared with supine position, transpulmonary pressure and ventilation are more homogeneously distributed throughout the lung [6]. Overall lung stress and overdistension are minimized [7, 8], lung volumes increase, and biotrauma and ventilator-induced lung injury are decreased [9, 10]. By resting the respiratory muscles, NMBA can avoid high regional transpulmonary pressures, and hence induce less regional volutrauma or biotrauma [11]. In the ACURASYS trial, the rate of pneumothorax [4] was significantly lower in the NMBA group than in the placebo group. In addition, the amount of lung inflammation was significantly lower in the NMBA group than in the placebo group in a previous

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randomized trial involving 36 patients [12]. The use of NMBA can also avoid dangerous respiratory entrainment ("reverse-triggered" breaths) [13] and pendelluft phenomena [14]. Reverse-triggered breaths may increase end-inspiratory lung volume and hence overinflation. Pendelluft phenomena occur in spontaneously triggered breaths: at the very beginning of inspiration, the non-dependent regions deflate while the dependent regions are overstretched. Pendelluft magnifies cyclic recruitment–derecruitment of unstable, dependent alveoli. Finally, the use of NMBA avoids a number of asynchronies such as double-triggering and double inspirations, and also wasted inspiratory efforts during the expiratory phase. When double-triggering and double inspirations are abolished by NMBA, breath-stacking phenomena and excessive end-inspiratory lung volume will, most likely, disappear. The absence of wasted inspiratory efforts avoids pliometric or eccentric contractions of the respiratory muscles that may generate ventilator-induced diaphragmatic injury.

Among the numerous interventions that have been tested in ARDS over the years, only three have proven beneficial to patient survival: low V_T, PP, and NMBA. These interventions, however, do not change the clinical course of the underlying disease leading to ARDS. Hence, the most likely interpretation for the success of these three interventions is that the overall supportive strategy in ARDS is useful to prevent the harmful effects of mechanical ventilation: high tidal volumes generating overdistension, suboptimal recruitment of collapsed units generating cyclic opening and closing of alveoli, and abnormal patient–ventilator interactions impeding the delivery of "protective" ventilator breaths.

How patients were selected and treated in the ACURASYS and the PROSEVA trials is a highly relevant aspect in relation to the beneficial effects of NMBA and PP. These two trials showed almost identical 28-day mortality rates in the control groups, 33.3 % in the former and 32.8 % in the latter [5, 6]. Both trials enrolled patients with confirmed ARDS: the median time from ARDS diagnosis to inclusion was 16 h in the ACURASYS trial, and the mean time from intubation to randomization was close to 32 h in the PROSEVA trial. The way the interventions were applied should also be considered. NMBA and PP were both applied early, with a specific strategy, at adequate doses, and for a sufficient duration. NMBA were administered for 48 h, and PP was administered for sessions over 17 consecutive hours. In the case of PP, sessions were continued until predetermined criteria of oxygenation improvement were met.

Additional pathophysiological benefits may operate in PP. Since oxygenation is markedly improved, this may help to reduce PEEP. If high PEEP levels are decreased, then the right ventricle will be unloaded, thus helping to prevent acute cor pulmonale, which has been shown to occur in up to 50 % of ARDS patients [15, 16]. Furthermore, in ARDS patients who have a preload reserve while in the supine position, the change to PP has been shown to increase cardiac output [17].

But can we balance all these benefits with risk and safety issues? The safety of proning has long been a concern for caregivers because of the risk of serious complications such as intravascular line dislodgment or endotracheal tube removal during the procedure. However, the PROSEVA trial was conducted in experienced centers and the rate of airway-related complications did not differ significantly between the supine and the prone position groups. In a previous randomized trial, also conducted in experienced centers, more than 700 proning procedures were performed and only 28 complications were observed [18]. These data indicate that the maneuver is safe and has a minimal risk profile when performed by skilled personnel and in well-selected patients. Intensivists have long been reluctant to use NMBA because these molecules were implicated in ICU-acquired neuromuscular weakness. This was the case particularly when NMBA had been used in conjunction with glucocorticoids in patients with status asthmaticus. Data to support such claims however, is, at best, poor [19, 20]. Importantly, in the ACURASYS trial, 16 % of patients in the NMBA

Table 1 Risk–benefit balance of using neuromuscular blocking agents (NMBA) and prone position (PP) in severe ARDS

	NMBA	PP
Improvement in oxygenation	Yes	Yes
Prevention of ventilator-induced lung injury	Not proven	Yes
Pneumothorax rate reduction	Yes	No
Biotrauma modulation	Yes	Yes
Patient–ventilator asynchrony reduction	Yes	No
More homogeneous strain/stress distribution	Not proven	Yes
Hemodynamic preservation/improvement	No	Yes
Muscle weakness	No	No
Endotracheal tube dislodgement/kinking	No	Yes, but risk minimized in trained teams
Withdrawal of indwelling catheters and pressure sores	No	Yes, but risk minimized in trained teams
Mortality reduction	Yes	Yes
Price	Expensive	Cheap, but requires motivated and skilled caregivers

group and 23 % in the control group received corticosteroids for ARDS, and 39 % of patients in the NMBA group and 45 % of patients in the control group also received corticosteroids for septic shock. In spite of the simultaneous use of corticosteroids and NMBA, the British Medical Research Council score for muscle strength assessed at 3 months after enrollment was remarkably similar in both groups. Table 1 summarizes the benefit–risk profile of PP and NMBA administration.

In summary, there is currently sufficient, consistent, and reproducible data to confirm the overall usefulness of early prone positioning in severe ARDS and to consider it as part of routine care in these patients. Data on NMBA are perhaps less impressive. However, their use in conjunction with PP is justified in view of the strong pathophysiological rationale, the remarkably low rate of side effects, and the potential risks of not using them, especially when facing abnormal patient–ventilator interactions.

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