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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

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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