Neuromuscular Blockade Applicability in Early Acute Respiratory Distress Syndrome

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Papazian *et al.*[1] reported in 2010 that use of neuromuscular blocking agents within 48 h of development of acute respiratory distress syndrome (ARDS) had a positive effect on survival in patients with severe disease (Pao_2/Fio_2 less than 120 mmHg) compared with management with deep sedation alone. Supporting this survival benefit, a retrospective study by Steingrub *et al.*[2] reported lower in-hospital mortality when mechanically ventilated patients with severe sepsis and a respiratory source of infection received neuromuscular blocking agents within the first two hospital days (treated: 31.9%, untreated: 39.3% in-hospital mortality; $P < 0.001$). Possible mechanisms by which this benefit might occur include decreasing oxygen consumption and improving oxygenation, decreasing the systemic inflammatory response associated with ARDS, and improving patient–ventilator synchrony. The general use of neuromuscular blocking agents in early ARDS, however, is not without consequence. Risks associated with this intervention include prolonged mechanical ventilation owing to excessive sedation, prolonged paralysis after discontinuation of neuromuscular blocking agents, development of critical illness myopathy and polyneuropathy, development of corneal abrasions and ulcerations, and risk of apnea with unrecognized ventilator disconnections.[3] A decade later, The National Heart, Lung, and Blood Institute (Bethesda, Maryland) Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network published a multicenter trial comparing a 48-h infusion of cisatracurium accompanied by deep sedation with usual-care and lighter sedation targets in patients with moderate to severe ARDS (a Pao_2/Fio_2 less than 150 mmHg with a positive end-expiratory pressure (PEEP) greater than or equal to 8 cm H_2O.[4] The trial was stopped early for futility to detect a difference in the primary outcome variable of in-hospital death at 90 days.

How shall we use these studies to guide our clinical practice? In patients who can be managed with light sedation, neuromuscular blockade plus deep sedation appears to offer no advantage. In those patients requiring deep sedation, the addition of neuromuscular blockade may be beneficial.

Potential Benefits of Neuromuscular Blockade

Improved Oxygenation

Neuromuscular blockade appears to improve oxygenation in some studies of ARDS patients. In a randomized, controlled trial of 56 patients with ARDS performed by Gannier *et al.*,[5] patients who received neuromuscular blocking agents for 48 h early in the course of ARDS had significantly improved Pao_2/Fio_2 ratios after 48 h compared with a placebo group. Both groups received deep sedation. A separate randomized trial by Forel *et al.*[6,7] reported similar improvements in oxygenation with the use of neuromuscular blocking agents in early ARDS. The mechanism for improved oxygenation is likely multifactorial. Muscle paralysis, or even deep sedation, may reduce oxygen consumption by ventilatory muscles, which can be considerable during ARDS, and improve oxygenation of mixed venous blood.[8,9] Muscle paralysis may also improve thoracopulmonary compliance and permit more precise control of driving pressure and PEEP. Lung inflation and ventilation–perfusion relationships might be more uniform throughout all lung fields.[10] In both the Gannier and Forel trials, as well as Papazian *et al.*, the improvement in oxygenation persisted beyond the 48 h of muscle paralysis and deep sedation,[5,6] which suggests that the reduction in oxygen consumption cannot be the primary mechanism of improved oxygenation. One mechanism that could induce a prolonged increase in oxygenation is a cistracurium-induced reduction in lung inflammation and pulmonary edema (see following section).[11] But because few ARDS patients die exclusively of refractory hypoxemia, and other interventions that improve oxygenation, such as inhaled nitric oxide, have not been demonstrated to improve outcomes, it is unlikely that the changes in arterial oxygenation demonstrated with neuromuscular blocking agent use alone would improve mortality.

Anti-inflammatory Effects

It is possible that muscle paralysis may improve thoracopulmonary compliance and permit greater homogeneity of the distribution of PEEP and tidal volume, thus reducing

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secondary ventilator-induced lung injury.[6,12] Repetitive opening and closing of atelectatic lung units have been associated with inflammatory mediator release. Forel's trial of cisatracurium in ARDS provides supporting evidence for this hypothesis in that patients randomized to a 48-h cisatracurium infusion *versus* placebo had reduced levels of the inflammatory mediators interleukin-6 and interleukin-1β in serum and interleukins-6, -8, and -1β in bronchoalveolar lavage fluid.[6]

Cisatracurium and other neuromuscular blocking agents may have direct receptor-mediated anti-inflammatory effects, which are mediated through blockade of the nicotinic acetylcholine receptor α1.[10,11] In addition to its presence at the neuromuscular junction, this nicotinic acetylcholine receptor is expressed on endothelial and epithelial cells, macrophages, mesangial cells, and fibroblasts and exerts proinflammatory properties.[11,13,14] Although clinical data are extremely limited, Fanelli *et al.*[11] investigated the anti-inflammatory role of nicotinic acetylcholine receptor α1 blockade in an elegant series of studies of *in vivo* and *ex vivo* rodent models of lung injury as well as *in vitro* cell models. In a rat model of lung injury, both cisatracurium and pancuronium improved oxygenation and thoracopulmonary compliance, reduced indices of pulmonary edema, and decreased levels of tumor necrosis factor-α in plasma and bronchoalveolar lavage fluid and the level of interleukin-6 in plasma. Cisatracurium also attenuated cytokine responses in human epithelial cells subjected to mechanical stretch, in endothelial and $CD14^+$ cells stimulated by lipopolysaccharide, and in $CD14^+$ cells exposed to bronchoalveolar lavage fluid or plasma from patients with ARDS. When nicotinic acetylcholine receptor α1 expression was knocked down in human endothelial cells exposed to lipopolysaccharide or plasma from patients with ARDS, the attenuation of interleukin-6 production by cisatracurium was reduced, providing further evidence that the anti-inflammatory effects of cisatracurium are mediated, at least in part, through blockade of the nicotinic acetylcholine receptor α1.

Improved Synchrony

Asynchrony between the patient's spontaneous respiratory pattern and the pattern set by the mechanical ventilator can contribute to patient discomfort and dyspnea,[15] increase work of breathing, increase respiratory muscle fatigue, and complicate assessment of respiratory rate and readiness to wean. Difficulties with weaning translate into worse outcomes, increased length of stay in the intensive care unit (ICU), and increased mortality.[10,16–20] Clinicians may use deeper levels of sedation or neuromuscular block in an attempt to minimize or eliminate asynchrony, but this practice is inconsistent with our current goals of minimizing sedation and mobilizing patients early in their clinical course.[21,22] Only 11% of the Prevention and Early Treatment of Acute Lung Injury investigators surveyed stated that continuous infusions of neuromuscular blocking agents were commonly used for ARDS patients with a Pao_2/Fio_2 less than 150 mmHg in their hospitals.[4]

Respiratory drive can be increased in ARDS, which increases tidal volumes, active exhalation, and patient–ventilator asynchrony.[20,23] Breath stacking can occur when a ventilator-delivered breath triggers a second spontaneous patient-initiated breath.[20] This produces a tidal volume that is larger than anticipated. The high tidal volumes might then induce further lung injury, increased work of breathing, and injurious patterns of lung inflation.[20,23] One might assume that deep sedation would improve patient–ventilator synchrony. The incidence of double-triggering, breath stacking, and injurious inflation patterns, however, appears to be high with deeper sedation levels.[20,24,25] Unless esophageal pressure or electrical activity of the diaphragm are measured, which is uncommon in clinical practice, these effects can go unnoticed. Neuromuscular blockade, of course, can entirely eliminate potentially injurious diaphragmatic activity and asynchrony. A note of caution, however, is necessary. Although synchronous ventilation was associated with improved oxygenation compared with asynchronous ventilation in the rat lung injury model of Fanelli *et al.*,[11] this effect was not associated with a significant change in cytokine levels. Hence, the lung protective effects of nondepolarizing muscle relaxants appear multifactorial, and the impact of improved oxygenation, reduced inflammation, and improved synchrony in clinical situations requires further study.

The 2010 Papazian *et al.* Trial

Papazian *et al.* published a large randomized, controlled study to address the question of whether neuromuscular blockade improves outcome in patients with early ARDS.[1] This was a multicenter, placebo-controlled, double-blind study of 340 patients with ARDS (defined as a Pao_2/Fio_2 ratio less than 150 mmHg with a PEEP greater than or equal to 5 cm H_20 and a tidal volume of 6 to 8 ml/kg predicted body weight) conducted in France. Major exclusion criteria included age less than 18 yr, continuous infusion of neuromuscular blocking agent at time of enrollment, expected duration of mechanical ventilation of less than 48 h, lack of consent, severe chronic respiratory disease requiring home oxygen or mechanical ventilation, or severe chronic liver disease. The specific aim of the study was to determine whether a 48-h infusion of cisatracurium accompanied by deep sedation early in the course of severe ARDS would improve clinical outcomes compared with a strategy of deep sedation alone. The primary endpoint was 90-day mortality, which was 31% (95% CI, 25% to 38%) in the cisatracurium group compared to 40% in the placebo group (95% CI, 33% to 48%; $P = 0.08$). After performing preplanned adjustments for baseline Pao_2/Fio_2, plateau pressure, and Simplified Acute Physiology Score, they reported that the hazard ratio for death at 90 days in the cisatracurium group, as compared with placebo, was 0.68 (95% CI, 0.48–0.98, $P = 0.04$). The

improved survival in the cisatracurium group was limited to the two-thirds of patients presenting with a Pao_2/Fio_2 less than 120 mmHg. The cisatracurium group had more ventilator-free days than the placebo group during the first 28 and 90 days (10.6 *vs.* 8.5, $P = 0.04$ and 53.1 *vs.* 44.6, $P = 0.03$), and more days spent outside of the ICU within the first 90 days compared with placebo (47.7 *vs.* 39.5, $P = 0.03$). The incidence of ICU-acquired paresis as evaluated by the Medical Research Council scale on day 28 or at time of ICU discharge did not differ between the two groups.

This trial had important limitations. The study was statistically underpowered because mortality was lower than anticipated. The trial included 340 patients. For the actual mortality rates reported in the study, 885 patients, rather than the 339 subjects enrolled in the trial, would be required to achieve 80% statistical power.[1] Hence, it is plausible that the study may have rejected its null hypothesis prematurely (type I error). In addition, the survival benefit was limited to those patients with a Pao_2/Fio_2 less than 120 mmHg, further limiting statistical strength. Finally, the mortality difference between the cisatracurium and placebo groups was not statistically significant until day 18 of the study. The delay in the mortality benefit after the initial 48-h infusion raises concern that the mortality difference might be due, at least in part, to factors other than the direct effects of neuromuscular blockade.

The 2019 Reevaluation of Systemic Early Neuromuscular Blockade Study

Because of the limitations of the trial conducted by Papazian *et al.* and changes in critical care practices over the intervening decade, a new trial of neuromuscular blockade was conducted by the National Institutes of Health Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network. The Reevaluation of Systemic Early Neuromuscular Blockade study was a multicenter, open-label, randomized trial of 1,008 ARDS patients admitted to the emergency department or ICU in 48 U.S. hospitals.[4] Eligibility criteria for the trial included the presence of ARDS for less than 48 h and a Pao_2/Fio_2 less than 150 mmHg with a PEEP at or above 8 cm H_2O. Exclusion criteria included a Pao_2/Fio_2 greater than 200 mmHg at time of randomization, current administration of continuous neuromuscular blockade at enrollment, use of extracorporeal membrane oxygenation, obesity, severe chronic liver disease, or mechanical ventilation for longer than 120 h. The goal of this trial was to assess the effects of a 48-h continuous infusion of cisatracurium (dosed identically to the trial of Papazian *et al.*) accompanied by deep sedation to a usual-care approach with light sedation targets and without neuromuscular blockade. The trial was stopped for futility at a planned interim analysis. Mortality at 90 days was 42.5% in the cisatracurium group and 42.8% in the control group (between group absolute difference of −0.3%; 95% CI, −6.4 to 5.9%; $P = 0.93$). At 28 days, no between-group differences were noted in hospital mortality, days free of mechanical ventilation, days out of the ICU, days out of the hospital, Sequential Organ Failure Assessment scores, or assessment of muscle strength or ICU-acquired weakness. Serious cardiac adverse events were more slightly frequent in the intervention group, but occurred in only a small proportion of patients (2.8% in the intervention group and 0.8% in the control group; $P = 0.02$). Patient-reported outcomes assessed at 3, 6, and 12 months after enrollment, which included reports of disability, cognitive function, symptoms of posttraumatic stress, and pain, were not different between the groups. In-hospital recall of paralysis was low (1.8% of patients in the intervention group) and, interestingly, not different from patients in the control group.

Comparison of the Two Trials

Why were the findings of the two trials seemingly different? Both trials were well-designed and conducted. Each had carefully designed protocols and statistical plans, complete follow-up, and used an intention-to-treat analysis. In both studies, subjects were recruited from multiple centers with high standards of care and extensive experience with critical care trials. The doses and duration of the cisatracurium infusions were identical. Both studies similarly permitted neuromuscular blocking agent use for high plateau pressures in control patients.

However, the 2019 Reevaluation of Systemic Early Neuromuscular Blockade study is not a duplication of the 2010 trial by Papazian *et al.* (table 1). The trials were designed to address different research questions. Papazian *et al.* compared the addition of neuromuscular blockade with a strategy of deep sedation. The Reevaluation of Systemic Early Neuromuscular Blockade study compared a strategy of deep sedation plus neuromuscular blockade with one that emphasized light sedation and spontaneous breathing. The study designs differed. The study by Papazian *et al.* was a double-blind, placebo-controlled trial that progressed to completion without interim analyses. The Reevaluation of Systemic Early Neuromuscular Blockade trial was open-label and was stopped for futility after an interim analysis. The characteristics of the enrolled patients were different. In Papazian *et al.*, patients were enrolled after a median of 16 h after diagnosis. The subjects in the Reevaluation of Systemic Early Neuromuscular Blockade trial were enrolled earlier (median of 7.6 h) and ventilated with higher PEEP levels (12.5 *vs.* 9.2 cm H_2O). Also, more subjects were excluded for receiving continuous neuromuscular blocking agents on enrollment in the Reevaluation of Systemic Early Neuromuscular Blockade study (Papazian *et al.*: 42 of 1,326 [3.2% of assessed pts]; Reevaluation of Systemic Early Neuromuscular Blockade study: 655 of 4,848 [13.5%]). It is possible that earlier enrollment of patients in the Reevaluation of Systemic Early Neuromuscular Blockade study might have produced a more heterogeneous subject sample—including some who might not have survived and

Table 1. Comparison of the Papazian *et al.* (2010) and Reevaluation of Systemic Early Neuromuscular Blockade (2019) Clinical Trials[1,4]

Comparison	Papazian *et al.* (2010)	Reevaluation of Systemic Early Neuromuscular Blockade (2019)
Study considerations		
Study design	Multicenter randomized double-blind	Multicenter randomized open label
Intervention before randomization	Sedation/mechanical ventilator adjustments	Tidal volume adjusted
Randomization	Placebo/cisatracurium	Usual Care/cisatracurium
Study conducted	March 2006 through March 2008	January 2016 to April 2018
No. of centers	20 multidisciplinary ICUs in France	48 hospitals (emergency departments and ICUs) in United States
No. of patients analyzed/screened, n/total screened (%)	339/1,326 (26%)	1,006/4,848 (21%)
No. of patients per study group	Cisatracurium: 177 Control: 162	Cisatracurium: 501 Control: 505
Study stopping considerations	Enrollment completed; no interim analysis	Stopped for futility for primary outcome at 2nd interim analysis
Criteria for moderate-to-severe ARDS	Pa_{O_2}/Fi_{O_2} < 150 mmHg with a PEEP of ≥ 8 cm H_2O	Pa_{O_2}/Fi_{O_2} < 150 mmHg with a PEEP of ≥ 8 cm H_2O on assessment; Pa_{O_2}/Fi_{O_2} < 200 mmHg at randomization
Ventilator mode	Volume assist-control for first 48 h, moderate PEEP	Controlled mode during paralysis, otherwise not specified except for target tidal volume, high PEEP
Sedation targets	Target Ramsey score of 6 in both groups for first 48 h	Target Ramsey score of 2 to 3 in controls; deeper sedation permitted per clinician discretion
Drug	Cisatracurium: 15 mg, then 37.5 mg/h × 48 h;	Cisatracurium: 15 mg, then 37.5 mg/h × 48 h
Primary outcome	90-day in-hospital mortality rate	90-day in-hospital mortality rate
Adjustments for mortality	Baseline Pa_{O_2}/Fi_{O_2}, Simplified Acute Physiology Score II, plateau pressure	None
Patient characteristics		
PEEP on entry, cm H_2O, mean ± SD	Cisatracurium: 9.2 ± 3.2 Control: 9.2 ± 3.5	Cisatracurium: 12.6 ± 3.6 Control: 12.5 ± 3.6
Time from diagnosis to enrollment, h, median (interquartile range)	16 (6 – 29)	7.6 (3.7 to 15.6)
Prone position use, n/total (%)	Overall: 97/339 (29) Cisatracurium: 50/177 (28) Control: 47 /162 (29)	Overall: 159/1,006 (16) Cisatracurium: 84/501 (17) Control: 75/505 (15)
Steroids for ARDS, n/total (%)	Overall: 65/339 (19) Cisatracurium: 28/177 (16) Control: 37/162 (23)	Overall: 244/970 (25) Cisatracurium: 109/482 (23) Control: 135/488 (28)
Pulmonary vasodilators, inhaled nitric oxide, or epoprostenol, n/total (%)	Overall: 103/339 (30) Cisatracurium: 50/177 (28) Control: 53/162 (33)	Overall: 77/1,006 (8) Cisatracurium: 33/501 (7) Control: 44/505 (9)
Outcomes		
Mortality before discharge before day 90, %	Cisatracurium: 31.6 Control: 40.7	Cisatracurium: 42.5 Control: 42.8
Mortality before discharge before day 90 in patients with Pa_{O_2}/Fi_{O_2} < 120 mmHg, %	Cisatracurium: 30.8 Control: 44.6	Cisatracurium: 42.5 Control: 42.2

ARDS, acute respiratory distress syndrome; ICU, intensive care unit; PEEP, positive end-expiratory pressure.

some who may have improved if enrolled later. Exclusion of patients already receiving neuromuscular blocking agents might have eliminated patients who clinicians thought were more likely to benefit from paralysis from the study sample.

Clinical care differed somewhat between the two studies. Papazian *et al.* used a ventilation strategy tested by the Acute Respiratory Distress Syndrome Network in 2000.[26] The Reevaluation of Systemic Early Neuromuscular Blockade study used a higher PEEP strategy that was based on more recent clinical trials.[27–29] As already mentioned, lighter sedation was targeted in the control group of the Reevaluation of Systemic Early Neuromuscular Blockade trial. Papazian *et al.* used deep sedation in both the neuromuscular blocking agent and control groups. Papazian *et al.* also used prone ventilation (Papazian *et al.*: 97 of 339 [29%] of subjects; Reevaluation of Systemic Early Neuromuscular Blockade: 159 of 1,006 [16%]) and inhaled pulmonary vasodilators (Papazian *et al.*: 103 of 339 [30%] of subjects; Reevaluation of Systemic Early Neuromuscular Blockade: 77 of 1,006 [8%]) more frequently than the Reevaluation of Systemic Early Neuromuscular Blockade study.

Both studies have limitations. Cisatracurium was the only neuromuscular blocker investigated, and it was studied only at a single high dose and for a limited infusion period.

Evaluation of neuromuscular recovery was somewhat limited in both studies. Importantly, transpulmonary pressures and patient–ventilator synchrony were not examined, so the potential influence of adverse patient-ventilator interactions remains speculative. In the trial by Papazian *et al.*, all patients were mechanically ventilated for the first 48 h in a volume assist–control mode, and this mode was not changed.[1] Although the Reevaluation of Systemic Early Neuromuscular Blockade study required a controlled mode of ventilation during the period of neuromuscular blockade, any mode of ventilation that delivered a prescribed tidal volume of 6 mg/kg predicted body weight was permitted in the control group and after 48 h in subjects receiving cisatracurium. It is conceivable that the differences in ventilator modes and settings might have produced differences in the frequency and severity of asynchrony in the control groups of both studies.

How should we interpret the two trials, given their different study designs and outcomes? One may hypothesize that one or both studies may have produced a type I (reject the null hypothesis inappropriately) or type II (inappropriately failing to reject a null hypothesis) error. Such possibilities can only be tested by further clinical studies. On the other hand, one can also reasonably conclude that both studies were appropriately designed, conducted, and analyzed and are likely valid. The study by Papazian *et al.* compared the addition of neuromuscular blockade with a strategy of deep sedation. If deeper sedation levels are associated with more frequent, or more damaging, patient-ventilator interactions, then eliminating these adverse interactions with neuromuscular blockade should improve patient outcome compared with deep sedation alone. The Reevaluation of Systemic Early Neuromuscular Blockade study compared a strategy of light sedation with a deep sedation strategy and neuromuscular blockade. If light sedation was associated with fewer adverse patient–ventilator interactions and avoided the adverse effects of deep sedation and neuromuscular blockade (increased cardiac adverse effects, decreased mobility, *etc.*), then a difference between the two strategies might not be detectable, as reported in the Reevaluation of Systemic Early Neuromuscular Blockade trial.

Application to Clinical Practice

The question remains: How does the use of neuromuscular blocking agents fit into the early treatment of ARDS? There are risks to the use of neuromuscular blocking agents (fig. 1). Unrecognized ventilator disconnections can quickly lead to hypoxemia and hypercarbia and cause cardiopulmonary collapse. Indeed, the Reevaluation of Systemic Early Neuromuscular Blockade study reported a greater number of adverse cardiac events, compared with usual care, in patients receiving cisatracurium.[4] Inadequate sedation and analgesia in a paralyzed patient might cause psychologic distress. Few patients in the Reevaluation of Systemic Early Neuromuscular Blockade study, however, recalled being paralyzed, and the proportion was no different than those patients who did not receive neuromuscular blockade. The inhibition of a cough reflex can lead to poor secretion clearance and mucus plugging. Paralyzed patients are at risk for corneal abrasions and ulcerations, cannot be mobilized easily, and are difficult to evaluate neurologically, but patients receiving deep sedation are likely to have similar adverse events.

Whether neuromuscular blocking agents contribute to ICU-acquired weakness remains unclear. We know that critical illness polyneuropathy and myopathy is common and associated with significant morbidity in critically ill patients.[30] Whereas some reports have noted a positive association between neuromuscular blocking agent use and critical illness polyneuropathy,[31] others have not been able to support an independent relationship between neuromuscular blocking agent use and the development of critical illness polyneuropathy and myopathy.[1,32–35] In addition, neither the study by Papazian *et al.* nor the Reevaluation of Systemic Early Neuromuscular Blockade study identified differences ICU-acquired weakness, recovery of muscle strength, or health-related disabilities between subjects receiving cisatracurium or usual care.[1,4]

In analyzing these two studies together, a reasonable conclusion is that mortality and clinical outcomes are either no different (Reevaluation of Systemic Early Neuromuscular Blockade) or improved (Papazian *et al.*) with early cisatracurium use in patients with ARDS. Neither study suggested that cisatracurium use produced significantly worse outcomes. To explain the differences between the studies, we can speculate that deep sedation alone is not superior to either light sedation or deep sedation with neuromuscular blockade. A reasonable hypothesis for further clinical testing is that deep sedation may be associated with adverse patient–ventilator interactions, which are less likely to occur in the setting of light sedation or neuromuscular blockade.

Although not examined in either study, it may be reasonable to use lower neuromuscular blocking agent doses and assess the depth of blockade with peripheral neuromuscular monitoring. In a prospective, randomized, single-blind trial of critically ill patients receiving continuous neuromuscular blocking agent, dosing guided by clinical response *versus* peripheral neuromuscular monitoring resulted in less drug per hour and total drug used. Patients who underwent peripheral neuromuscular monitoring recovered neuromuscular function and spontaneous ventilation faster than control patients.[36]

Suggestions for current management of early ARDS, which appear consistent with other recent reviews of this topic, include the following.[20,37,38] First, patients successfully managed with low plateau or transpulmonary pressures should not routinely receive continuous neuromuscular blockade. Second, patients with persistently increased airway pressures or with evident adverse patient–ventilator interactions should receive a trial period of ventilator adjustments and/or changes in sedation level.[39] Neuromuscular blockade may be considered in patients requiring deep sedation

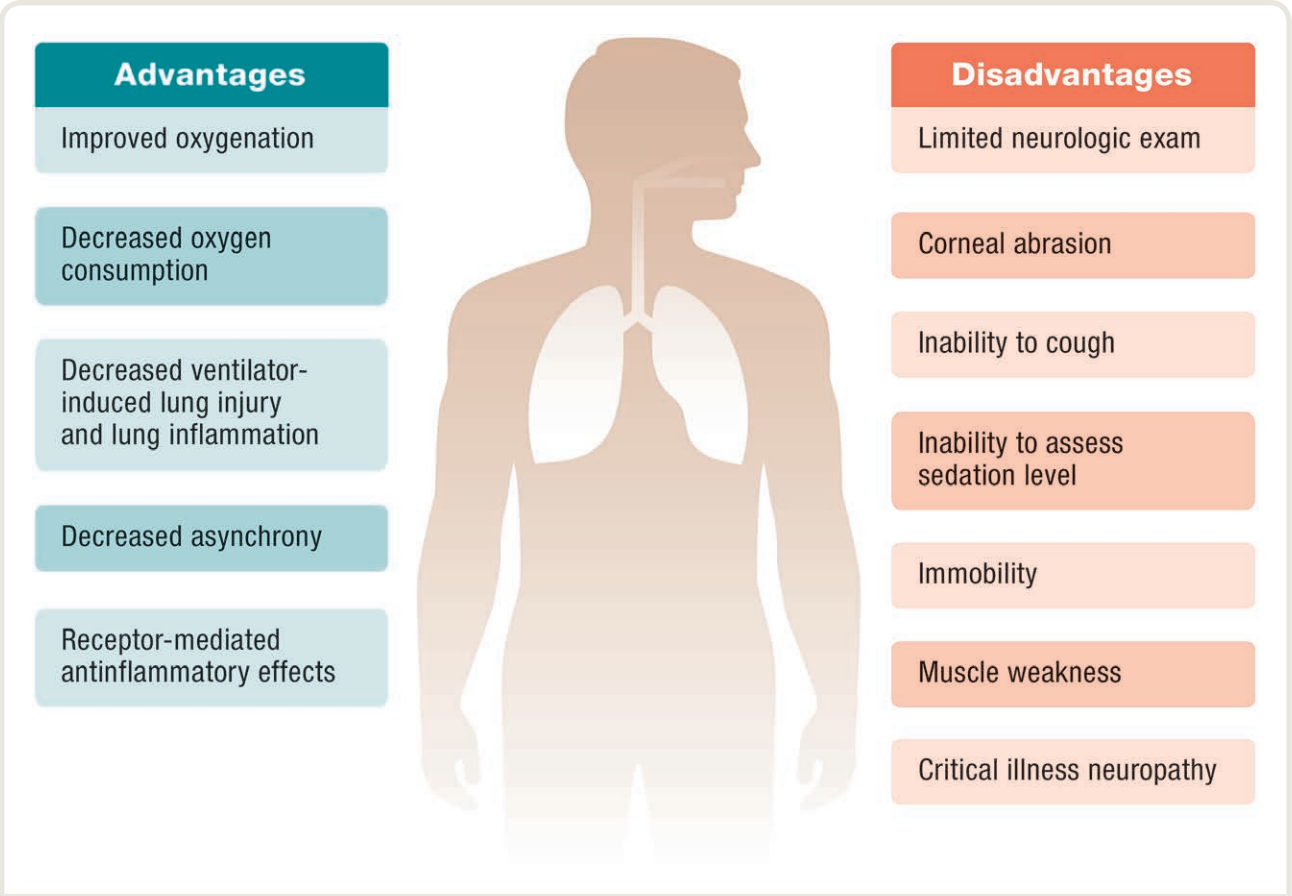

Fig. 1. Potential advantages and disadvantages of neuromuscular blockade in early acute respiratory distress syndrome (ARDS).

to reduce vigorous spontaneous respiratory efforts, reduce asynchrony, or permit adjunctive therapies such as prone positioning.[20,38] Third, partial neuromuscular blockade and higher levels of PEEP may be useful to decrease the magnitude of spontaneous efforts.[40,41] Both neuromuscular block and deep sedation should be tapered as soon as clinically feasible. Lastly, cisatracurium remains a reasonable choice if neuromuscular blockade is needed because it is free of active metabolites and significant side effects.

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Competing Interests

The author declares no competing interests.

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