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Counterpoint: Should Paralytic Agents Be Routinely Used in Severe ARDS? No

The cornerstone of ARDS management is the delivery of positive pressure ventilation with sufficient inflation pressure to recruit and maintain alveoli in an inflated state while avoiding alveolar overdistension and associated pulmonary and systemic inflammation and barotrauma. Severe ARDS is characterized by profound hypoxemia that often is refractory to traditional management and, along with multiple organ failure, is a frequent cause of death.[1] A variety of ventilatory and nonventilatory interventions have been used to improve oxygenation in severe ARDS, including the use of neuromuscular blocking agents (NMBAs).[2,3] Such measures are typically applied on the basis of the patient's severity of gas exchange derangement and other individualized factors rather than routinely administered. However, results from a placebo-controlled trial in which patients with severe ARDS randomized to receive the NMBA cisatracurium had superior outcomes have prompted this debate.[4]

To consider this question of clinical decision-making, it is important to weigh the strength of the evidence, the risk and benefit of the intervention, and the reproducibility and generalizability of the supporting results. Furthermore, the key components of the question should be carefully examined, including paralytic agents, whether they should be routinely used, and severe ARDS.

NMBAs have been used for decades in the management of patients in the ICU with respiratory failure primarily due to ARDS or status asthmaticus to permit passive ventilation by eliminating active inspiratory and expiratory efforts that can impair gas exchange and increase the risk for barotrauma.[5-7] Guidelines published in 2001 support the use of NMBAs to facilitate mechanical ventilation when sedation alone is inadequate, particularly in patients with severe gas exchange impairments.[5] In fact, NMBAs were administered to 25% to 55% of patients enrolled in modern ARDS clinical trials.[8-11] A key question is whether all patients with severe ARDS should be treated with NMBAs or whether this treatment should be individualized.

Nondepolarizing NMBAs act by competing with acetylcholine for binding at the nicotinic receptor of the motor end plate, producing paralysis of skeletal muscles. Potential consequences of widespread muscular paralysis include VTE, compromised skin integrity, corneal ulcers, nerve compression, impaired communication, patient awareness and pain while paralyzed, impaired cough, and elimination of protective reflexes.[5-7] Additionally, protracted weakness is described following NMBA administration as a result of either prolonged receptor blockade due to reduced elimination of parent drug and active metabolites or acute quadriplegic myopathy (AQM).[5] One of a number of forms of ICU-acquired paresis,[12] AQM is believed to arise from the loss of myosin and myosin-associated proteins, and perhaps from myonecrosis, typically following the concomitant use of an NMBA and

corticosteroid.[5,13] The clinical picture includes paretic spinal nerve-innervated muscles with sparing of cranial nerve-innervated muscles and intact sensory function and cognition, often producing profound weakness that lasts weeks to months. Safe practice emphasizes avoiding unnecessary use of NMBAs and limiting the duration of therapy to avoid these complications.[5]

In their multicenter, placebo-controlled, randomized controlled trial (RCT) conducted in 340 French patients with severe ARDS, Papazian et al[4] reported provocative results after the administration of cisatracurium for 48 h, including a lower 90-day mortality rate after adjustment for selected baseline variables (but not crude mortality [$P = .08$]), more ventilator- and organ failure-free days, and less barotrauma. Furthermore, they found no difference in rates of ICU-acquired paresis between groups by Medical Research Council score for muscle strength. Although the primary results are indeed noteworthy, it is important to examine details of the study design and conduct as one considers the strength of evidence as well as generalizability. Eligibility criteria were traditional ARDS criteria but required a PaO_2/FIO_2 ratio < 150 mm Hg while mechanically ventilated with a positive end-expiratory pressure (PEEP) > 5 cm H_2O and tidal volume of 6 to 8 mL/kg predicted body weight. Similar to many RCTs, only 25% of eligible patients were enrolled, limiting generalizability related to the numerous exclusions. Data from the post hoc analysis revealed that the survival benefit was limited to the two-thirds of enrolled patients who had a $PaO_2/FIO_2 < 120$ mm Hg. Survival was virtually identical for the cisatracurium and placebo groups for $PaO_2/FIO_2 \geq 120$ mm Hg. Unfortunately, other outcome data and safety data for these subpopulations were not reported. This threshold for severe ARDS is more consistent with the recent Berlin ARDS criteria that classify severe ARDS as $PaO_2/FIO_2 < 100$ mm Hg.[14]

Papazian et al[4] used a very conservative approach to PEEP, both regarding selecting their patient population and during management. Villar et al[15] demonstrated that $> 40\%$ of patients with ARDS are reclassified as having a $PaO_2/FIO_2 > 200$ mm Hg (and, thus, no longer meeting ARDS criteria) by applying 10 cm H_2O PEEP at 24 h and rechecking the PaO_2/FIO_2. This was not done by Papazian et al[4] but could have influenced patient selection. More importantly, the PEEP strategy that Papazian et al[4] used was conservative, resulting in lower average PEEP values than the low-PEEP arm of all of the RCTs that compared low-PEEP and high-PEEP strategies,[9-11] except the French study by Mercat et al[8] (Fig 1). The average PEEP used was far lower than that used in high-PEEP strategies that are associated with lower mortality and shorter length of stay by meta-analysis.[16] Furthermore, the barotrauma rate of nearly 12% in the placebo arm of

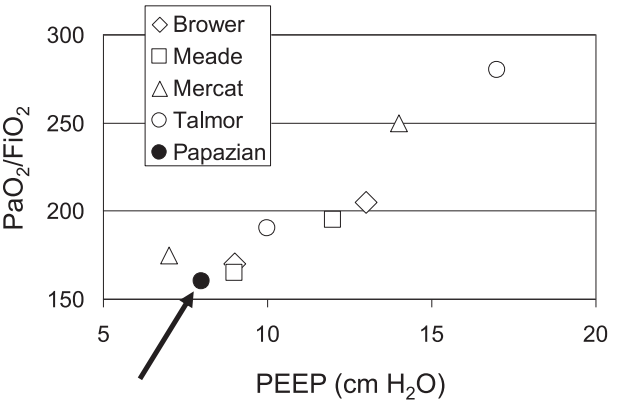

FIGURE 1. Average PaO_2/FIO_2 vs average PEEP on day 3 for subjects from Papazian et al[4] and from subjects randomized to the low-PEEP and high-PEEP groups in Mercat et al,[8] Meade et al,[9] Brower et al,[10] and Talmor et al.[11] PEEP = positive end-expiratory pressure.

the Papazian et al study was higher than in any of the high-PEEP RCTs.[8-11] One wonders whether the same benefits found with cisatracurium by Papazian and colleagues would have been observed if a higher PEEP strategy had been used.

There are additional aspects of patient management in the Papazian et al[4] study that may limit generalizability. Twenty percent of patients received continuous IV infusion ketamine in their sedation regimen, and 5% received the respiratory stimulant almitrine; neither intervention is used in most ICUs.[4] Cisatracurium was administered at a set dose (37.5 mg/h) for 48 h without titrating to clinical measures of safety or efficacy. The technique of periodically measuring response to peripheral nerve stimulation, which is widely used to test for depth of paralysis and to avoid overdosing with NMBAs,[5] was not used. Both fixed cisatracurium dosing and lack of monitoring were departures from conventional practice.[5] Also of note, at least 50% of patients in each study arm received as-needed doses of cisatracurium, potentially clouding the results.[4] Finally, although the median Medical Research Council muscle strength score and the proportion of patients without ICU-acquired paresis at day 28 and at ICU discharge were similar between the cisatracurium and placebo groups, one wonders whether the infrequent case of AQM that can produce prolonged disability and ventilator support was adequately captured with these authors' approach.

Papazian et al[4] selected cisatracurium as the NMBA to test, but it is possible that their results are not reproducible with other NMBAs. Important differences exist among nondepolarizing NMBAs, particularly when comparing aminosteroidal agents like pancuronium and vecuronium to benzylisoquinolinium drugs like atracurium and cisatracurium. Key differences include the process of drug elimination and the presence of active metabolites.[6] Aminosteroids are eliminated by