Reversing Neuromuscular Blockade: Not Just the Diaphragm, but Carotid Body Function Too

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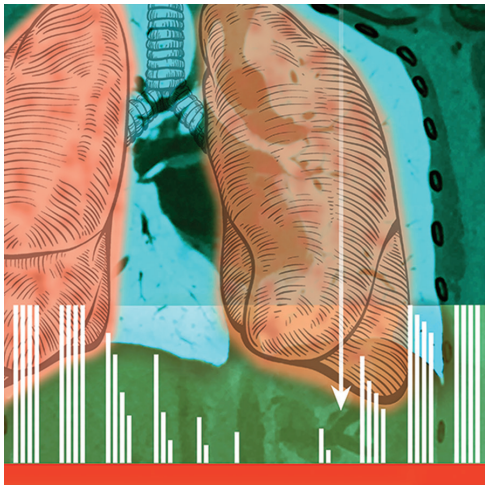
Neuromuscular blocking drugs have—for years—enabled anesthesiologists beneficially to relax skeletal muscles to improve anesthetic management, increase safety and quality of tracheal intubation, and to provide favorable intraoperative conditions for complex surgical procedures. While achieving these goals, a growing body of evidence has uncovered a price to pay in potential side effects, most frequently associated with the respiratory system having an increased risk of adverse pulmonary outcomes[1] or, more rarely, "accidental intraoperative awareness," which occurs almost exclusively in cases where neuromuscular blockade has been used.[2]



"[After] neuromuscular block reversal…even when the train-of-four ratio [has] recovered to 1.0, the acute [ventilatory response to hypoxia can remain] significantly depressed."

In the late 1990s, it was shown that subparalyzing concentrations of neuromuscular blocking drugs markedly impaired the acute ventilatory response to hypoxia[3] in volunteers. Later animal studies located this effect to the carotid body, where these drugs blocked acetylcholine-dependent oxygen signaling pathways.[4] In this issue of Anesthesiology, Broens *et al.* show that partial rocuronium block in volunteers depresses the acute ventilatory response to hypoxia—and also to hypercapnia.[5] This confirms and extends earlier work,[3,4] and also explores the effect of neuromuscular block reversal with neostigmine or sugammadex. A key finding is that even when the adductor pollicis train-of-four ratio had recovered to 1.0, the acute hypoxic response remained significantly depressed in several subjects. In this Editorial View, we will discuss the clinical implications of these results, and touch upon some relevant physiology.

Importantly, resting minute ventilation in the study of Broens *et al.*, and in the earlier works,[3] was unaffected by partial paralysis, reflecting a maintained central respiratory drive. This drive originates from the background phasic activity of brainstem respiratory circuits. On the other hand, abrupt changes in arterial oxygen or carbon dioxide tensions trigger ventilatory responses *via* the carotid body chemoreflex which, in contrast to the phasic activity, reflects the system's "responsiveness." Thus, normal resting minute ventilation (phasic activity) does not necessarily mean that the patient will respond with hyperventilation to hypoxemia (responsiveness). Perioperative hypoxemia can arise for several reasons, and a weak reflex response can lead to adverse outcomes.

Broens *et al.* found that reversal to a train-of-four ratio of 1.0 was still associated with depressed acute hypoxic response in some subjects. The human carotid body express nicotinic subunits α3, α7, and β2 of the pentameric neuronal subtype acetylcholine receptor, whereas muscle type receptors are pentamers of α1, β1, γ, δ, or ε subunits typically expressed in striated muscles.[6,7] Importantly, neuromuscular blocking drugs have distinct affinity for both classes of acetylcholine receptors in clinically relevant dose ranges.[7] In the neuromuscular junction, up to 75% of muscle type receptors must be occupied before there is detectable reduction in twitch tension; in contrast, neuronal cholinergic signaling is blocked in a dose-dependent manner. This could explain why hypoxic ventilatory control remains impaired even when neuromuscular function has recovered.[7] Moreover, Broens *et al.* studied rocuronium as the sole drug administered. In clinical practice, there may be synergism with residual concentrations of

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This editorial accompanies the article on p. 467. For a downloadable PPT slide containing this article's citation information, please visit https://anesthesiology.pubs.asahq.org/ss/downloadable_slide.aspx.

Accepted for publication April 19, 2019. From the Nuffield Department of Anaesthetics, Oxford University Hospitals, Oxford, United Kingdom (J.J.P.), and the Department of Physiology and Pharmacology, Section for Anaesthesiology and Intensive Care Medicine, Karolinska Institute, and Function Perioperative Medicine and Intensive Care, Karolinska University Hospital, Stockholm, Sweden (L.I.E.).

 Anesthesiology 2019; 131:453–5. DOI: 10.1097/ALN.0000000000002814

<zdoi;. DOI: 10.1097/ALN.0000000000002814>

other agents used during anesthesia such as inhalational or intravenous anesthetics, benzodiazepines and opioids, all of which have been shown to impair chemoreflex control.[8,9] The findings by Broens *et al.* therefore emphasize the importance of ensuring neuromuscular recovery to minimize the risk of impaired postoperative regulation of breathing.[5]

This raises the question of which reversal agent to use, and how (when) to use it. Broens *et al.* found no statistical difference between neostigmine and sugammadex, but appear to prefer the latter. Sugammadex should theoretically have advantages over neostigmine because recovery of neuromuscular function appears more rapidly and reliably achieved by sugammadex with fewer adverse outcomes.[10] The importance of neuromuscular monitoring for dosing of neuromuscular blocking drugs, and the correct administration of reversal agents to allow return of neuromuscular function, are now established in series of national and international guidelines.[11,12] The findings by Broens *et al.* further underscore the importance of neuromuscular recovery as a *sine qua non*—an absolutely necessary, but not of itself sufficient criterion—for minimizing the risk for impaired regulation of breathing with hypoxia in the postoperative period. If neuromuscular recovery is not achieved, then we can be confident that the ventilatory response to hypoxia has also not recovered.

A better understanding of the cellular pharmacology of how neuromuscular blockade inhibits carotid body function would enable insights into prevention or drug development, and this in turn requires better understanding of how hypoxia is sensed at the carotid body and the relevant drug interactions. Volatile and intravenous anesthetic agents are well established to depress whole-body acute hypoxic response and the isolated carotid body response to hypoxia.[8,9,13,14] The carotid body is rich in neurotransmitters and their receptors, including acetylcholine. Neuromuscular blocking drugs do not prevent isolated glomus cells from responding to hypoxia,[9] so the results of Broens *et al.*,[5] Eriksson *et al.*,[3] and Wyon *et al.*[4] imply that neuromuscular blocking drugs block the nicotinic postsynaptic acetylcholine receptors at the afferent nerve terminal. Because residual anesthetics and neuromuscular blocking drugs depress chemoreflex function by actions at multiple sites in these established ways, single interventions like carotid body–stimulating drugs (*e.g.*, doxapram) may have limited utility alone in antagonizing all these actions postoperatively.[14]

The work of Broens *et al.* emphasizes that carotid bodies are inhibited by residual concentrations of neuromuscular blocking drugs, which may expose patients with residual neuromuscular block to an increased risk for serious respiratory adverse events. This underscores the need for complete return of neuromuscular function to limit this risk. In addition, we must recognize that there is a subset of patients in whom, despite objective reversal of neuromuscular block, there may be a remaining impact of neuromuscular blockade on ventilatory regulation; understanding this important observation requires further research.

Research Support

Support was provided solely from institutional and/or departmental sources. Dr. Eriksson has received lecture fees from Merck, Sharp & Dohme (Stockholm, Sweden).

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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