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Quantitative Neuromuscular Monitoring and Postoperative Outcomes: A Narrative Review

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ABSTRACT

Over the past five decades, quantitative neuromuscular monitoring devices have been used to examine the incidence of postoperative residual neuromuscular block in international clinical practices, and to determine their role in reducing the risk of residual neuromuscular block and associated adverse clinical outcomes. Several clinical trials and a recent meta-analysis have documented that the intraoperative application of quantitative monitoring significantly reduces the risk of residual neuromuscular blockade in the operating room and postanesthesia care unit. In addition, emerging data show that quantitative monitoring minimizes the risk of adverse clinical events, such as unplanned postoperative reintubations, hypoxemia, and postoperative episodes of airway obstruction associated with incomplete neuromuscular recovery, and may improve postoperative respiratory outcomes. Several international anesthesia societies have recommended that quantitative monitoring be performed whenever a neuromuscular blocking agent is administered. Therefore, a comprehensive review of the literature was performed to determine the potential benefits of quantitative monitoring in the perioperative setting.

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"*It cannot be emphasized too strongly that merely observing the movements of the rebreathing bag is not an adequate assessment of ventilation… [A] patient can have a normal tidal volume when 90% of his respiratory muscle-fibers are still paralyzed.*

"*The only satisfactory method of determining the degree of neuromuscular block is to stimulate a motor nerve with an electric current and observe the contraction of the muscles innervated by that nerve." —H. C. Churchill-Davidson, 1965*[1]

None of the myriad neuromuscular blocking drugs, their antagonists, and the entire industry of medical neuromuscular monitoring devices might be available today, were it not for the experiments by Sir Henry Hallett Dale in 1913 and Otto Loewi in 1921.[2] These two pioneers were awarded the 1936 Nobel Prize for "the discovery of chemical synaptic transmission."[3] In 1941, Eccles, Katz, and Kuffler demonstrated that in the presence of curare, there was a decrease in the end-plate potential at the postsynaptic muscle membrane such that the action potential could no longer be propagated in response to motor nerve stimulation.[4] These findings elucidated the function of acetylcholine and the electrical events at the neuromuscular junction and opened the research gates into the physiology and pharmacology of the neuromuscular junction.[5]

The aim of this narrative review is to examine the published evidence supporting the use of quantitative monitoring in the perioperative setting. A brief review of the basics of neuromuscular monitoring will follow, which includes the various patterns of stimulation, the stages of neuromuscular block, and the definition of residual neuromuscular block and its perioperative incidence. The various monitoring technologies, including mechanomyography, acceleromyography, electromyography, and kinemyography, are described. Studies that have assessed the effectiveness of objective monitoring in reducing the incidence of postoperative residual neuromuscular blockade are reviewed. Additionally, clinical trials evaluating the impact of intraoperative quantitative monitoring on postoperative outcomes will be examined. For this review, we searched the National Library of Medicine's PubMed for the terms "quantitative neuromuscular monitoring" and "objective neuromuscular monitoring" in all available years. The search terms were purposefully broad in order to retrieve all pertinent data. Applicable articles were selected by the authors for inclusion.

Basics of Neuromuscular Monitoring

Science progressed not only in physiology and pharmacology of the neuromuscular junction; understanding of physiology was facilitated by advances in technology. One hundred years ago, Gasser and Erlanger (recipients of the Nobel Prize for Physiology or Medicine in 1944) explored the action currents of nerves using the first low-voltage cathode ray oscillograph and were the first to describe that action potentials are biphasic.[6] By the mid-1960s, force displacement transducers, which were initially developed to record muscle responses in experimental animals, were later adapted to measure the responses to nerve stimulation in

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man—usually the adductor pollicis muscle of the thumb in response to ulnar nerve stimulation.[7]

In the intact neuromuscular junction, neurostimulation will result in contraction of the innervated muscle. Assessment of such evoked responses involved the use of a nerve stimulator that was "designed and built for the author [RL Katz] by Burroughs Wellcome and Co. (U.S.A.) Inc."[8] The development of peripheral nerve stimulators was followed by medical devices (monitors) that not only delivered an electrical stimulus to the nerve but also could display, record, and analyze the evoked muscle responses.

Patterns of Stimulation and Depth of Neuromuscular Block

The first "new device for monitoring force of thumb adduction" was reported by Hassan Ali in 1970 (fig. 1).[9] This device incorporated a new *pattern of neurostimulation*, the train-of-four.[10] Assessment of the degree of neuromuscular block involved the delivery of a sequence of four stimuli (train-of-four) at a frequency of 2 Hz and the comparison of the amplitude of the last evoked train-of-four response (T4) to the amplitude of the first response (T1); this comparison resulted in a train-of-four ratio (T4/T1 ratio) that was indicative of the *depth of nondepolarizing neuromuscular block*. At the intact neuromuscular junction, a train-of-four stimulation will result in muscle responses of equal force (amplitude), such that the baseline train-of-four ratio will be 100% (1.0). When approximately 70 to 80% of postsynaptic receptors are inactivated by the nondepolarizing neuromuscular blocking agent, the amplitude of the repetitive muscle contractions starts to decrease, and the train-of-four ratio starts to "fade" (train-of-four ratio less than 1.0), until T4 = 0, and only the first, second, and third train-of-four responses (T1, T2, and T3, respectively) are present. This degree of block is assessed based on the number of train-of-four responses elicited; when T1, T2, and T3 are present, for instance, the train-of-four count is 3; when only T1 is still present, the train-of-four count is 1, and the depth of block is greater. Once train-of-four count is 0, a 5-s, 50-Hz tetanic stimulus will transiently increase the amount of acetylcholine at the neuromuscular junction, allowing for a short-lived amplification of muscle responses termed posttetanic potentiation, and resulting in transient,

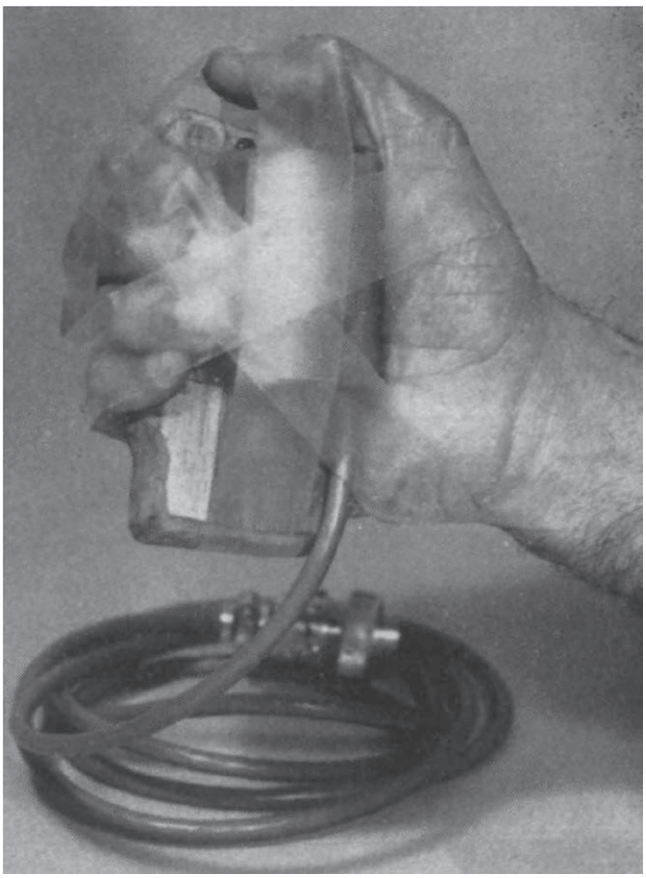

Fig. 1. Photograph of the apparatus designed to in response to ulnar nerve stimulation.[9] Republished with permission of Elsevier Science & Technology Journals. From Ali HH: A new device for monitoring force of thumb adduction. Br J Anaesth 1970; 42:83–5; permission conveyed through Copyright Clearance Center, Inc..

progressively decreasing posttetanic muscle contractions (posttetanic count). The train-of-four ratio, train-of-four count, and posttetanic count are *patterns of neuromuscular responses* that allow clinicians to determine the time course and depth of neuromuscular block (table 1) and adjust the timing and dosing of neuromuscular blocking agents and their antagonists.

Stages of Neuromuscular Block

While the posttetanic count is indicative of a *deep neuromuscular block*, the presence of a train-of-four count represents *moderate block*, and fade in train-of-four ratio (*i.e.*, train-of-four ratio less than 1.0) is indicative of *residual effects* of neuromuscular blocking agents. It should be emphasized that there is a significant and clinically relevant difference between qualitative (subjective) *evaluation* of responses to neurostimulation and quantitative (objective) *monitoring* of neuromuscular function. The subjective evaluation of deep and intermediate levels of block using posttetanic count or train-of-four count, respectively, can be helpful if only a peripheral nerve stimulator is available to the clinician. However, adequate recovery from neuromuscular block as evidenced by a train-of-four ratio greater than 0.90 cannot be determined qualitatively with a peripheral nerve stimulator.[11] Despite the common use of clinical signs of neuromuscular recovery such as presence of normal tidal volume, response to verbal commands, gagging on the tracheal tube, *etc.*, subjective assessment of neuromuscular recovery using peripheral nerve stimulation and/or clinical testing are inadequate to ensure normal neuromuscular function recovery.[12–14] The failure of clinical signs to indicate adequate neuromuscular recovery was underscored almost 20 yr ago: "It was not possible within 30 min to achieve a train-of-four ratio of 0.9 in all patients, regardless of the number of tactile responses present at neostigmine administration."[15]

Residual neuromuscular block was defined in early studies using quantitative devices as a train-of-four ratio less than 0.7.[16] This accepted threshold was based upon data from conscious volunteers who received tubocurarine; these data demonstrated that vital capacity and inspiratory force measured by pulmonary function tests were significantly reduced at a train-of-four ratio less than 0.7.[17] However, subsequent studies reported that clinically meaningful muscle weakness was present at train-of-four ratios up to 0.9.[18] At train-of-four ratios below this threshold, subjects exhibited an impairment of the hypoxic ventilatory response,[19] experienced airway obstruction[20] and impairment of airway protective reflexes,[21] were at increased risk of aspiration,[21] had an inability to breathe deeply,[22] experienced unpleasant symptoms of muscle weakness,[23] and had prolonged postanesthesia care unit (PACU) stays.[24] Therefore, the accepted threshold for defining postoperative residual neuromuscular blockade used in the majority of studies since 1997 has been a train-of-four ratio less than 0.9.[12,18,21] Recent studies have, however, documented that even return of the acceleromyographic train-of-four ratio to the baseline value of 1.00 (100%) is associated with a recovery of postoperative forced vital capacity to only 84 ± 0.11% of baseline in surgical patients,[25] and a return of the acute hypoxic ventilatory response to only 86 ± 25% of baseline values in healthy volunteers.[19] Therefore, despite apparent full reversal of neuromuscular block, pulmonary function and the hypoxic chemoreflex are not fully restored. These findings are not surprising, since it has been known since 1967 that 75 to 80% of the nicotinic acetylcholine receptors can be blocked while the muscle response to neurostimulation will still be normal.[26]

Table 1. Depth of Neuromuscular Block

Depth of Neuromuscular Block	Quantitative Measurement
Complete (total)	Posttetanic count = 0
Deep (profound)	Posttetanic count ≥ 1; train-of-four count = 0
Moderate	Train-of-four count = 1–3
Shallow	Train-of-four ratio < 0.4 (train-of-four count = 4)
Minimal	Train-of-four ratio 0.4–0.9
Acceptable recovery	Train-of-four ratio ≥ 0.9*

*Measurement obtained by mechanomyography, electromyography, or calibrated and normalized acceleromyography.

Incidence of Residual Neuromuscular Block

The development of simple and reliable patterns of neurostimulation such as the train-of-four ratio and the ability to correlate specific quantitative, repeatable recovery milestones (such as the train-of-four ratio greater than 0.90) with clinical outcomes have facilitated the introduction of perioperative neuromuscular monitoring.[10,16,27,28] However, since 1979, when Viby-Mogensen first reported an incidence of residual block (defined at that time as train-of-four ratio less than 0.70),[29] more than 50 studies have confirmed the high incidence (approximately 30 to 65%) of this complication.[30]

Neuromuscular Monitoring Technologies

Since the 1970s, a variety of *quantitative devices and technologies* have been utilized in clinical trials (table 2). The investigators used quantitative monitors to examine the incidence of postoperative residual neuromuscular block; to assess the effect of anesthetic interventions (type of muscle relaxant, mode of administration—bolus *vs.* continuous infusion, interaction with volatile and intravenous anesthetics, type of reversal agents, *etc.*) on the risk of incomplete neuromuscular recovery; and to determine the role of quantitative monitoring in reducing the risk of residual neuromuscular block and associated adverse clinical outcomes.[30] In the initial volunteers and

Table 2. Quantitative Monitoring Technologies Used in Research and Clinical Care

Modality	Principle	Advantages	Disadvantages	Monitoring Site	Clinical Availability
Mechanomyography	Directly measures isometric muscle contraction force.	- Measures muscle force directly. - The "reference" modality.	Cumbersome and time-consuming setup. Not suitable for clinical practice.	- Ulnar nerve - adductor pollicis muscle; - posterior tibial nerve - flexor hallucis brevis muscle	Commercially not available
EMG	Measures compound muscle action potentials evoked by neurostimulation.	- Many different muscles can be examined. - Does not require freely moving limbs. - Easy and fast set up and short calibration.	Possible interference from other electrical equipment (electrocautery).	- Ulnar nerve - adductor pollicis, abductor digiti minimi and first dorsal interosseous muscles; - posterior tibial nerve - flexor hallucis brevis muscle; - phrenic nerve - diaphragm	-E-NMT (GE DATEX-Ohmeda NMT; USA); https://www.gehealthcare.com -TetraGraph (Senzime Inc.; USA); https://www.senzime.com -TwitchView (Blink Device Company; USA); https://www.blinkdc.com -StimPod (Xavant Technology; South Africa; awaiting Food and Drug Administration clearance as of September 1, 2021); https://www.xavant.com
Acceleromyography	Measures the acceleration of the thumb or any freely moving muscle. The acceleration is directly proportional to the force according to Newton's second law.	- Current neuromuscular blockade management guidelines are based on acceleromyography measurements. - Most widely used technique.	Requires use of hand adapter (increases precision), fixation of arm and fingers, free movement of thumb, normalization of recovery train-of-four ratios.	- Ulnar nerve - adductor pollicis muscle; - facial nerve - orbicularis oculi, corrugator supercilii muscles; - posterior tibial nerve - flexor hallucis brevis muscle	-Infinity Trident NMT SmartPod (Dräger; Germany); https://www.draeger.com -IntelliVue NMT (Philips; The Netherlands); https://www.usa.philips.com -TOF-Scan (IDMed; France); https://www.idmed.fr -StimPod (Xavant Technology; South Africa); https://www.xavant.com
Kinemyography	Measures the distortion of a piezoelectric film sensor. The level of distortion is proportional to the force of thumb contraction.	- Easy to apply.	Available only in modular form. Validation *vs.* mechanomyography and electromyography questionable.	- Ulnar nerve - adductor pollicis muscle	M-NMT (GE DATEX-Ohmeda NMT; USA); https://www.gehealthcare.com
Cuff pressure modality	Measures the pressure change in a modified non-invasive blood pressure cuff due to upper arm muscles' contraction in response to brachial plexus neurostimulation.	- Easy to apply.	Needs further validation, overestimates the train-of-four ratio at the adductor pollicis by mechanomyography and acceleromyography.	- Brachial plexus - muscles of upper arm	TOF-Cuff (RGB Medical Devices; Spain); https://www.rgb-medical.com

EMG, electromyography.

patient studies, both electromyography and mechanomyography were used to determine the train-of-four ratio as a "more sensitive index to the degree of curarization."[27] *Mechanomyography* measures the isometric force of contraction of the thumb's adductor pollicis muscle in response to electrical ulnar nerve stimulation and was considered the accepted standard technology for decades. In a small number of later studies, electromyography was used to assess neuromuscular recovery.[31] *Electromyography* measures the muscle action potentials after nerve stimulation, and responses recorded with this technology compare favorably with responses obtained with mechanomyography.[31] In contrast to early mechanomyography and electromyography devices, acceleromyographic monitors—primarily the TOF-Watch (Schering-Plough Corp.; USA), which is no longer commercially available—were utilized intraoperatively in the majority of published investigations.[30]

Acceleromyography estimates the force of muscle contraction from Newton's second law of motion, which states that force is proportional to the product of an object's mass and its acceleration; since the mass (thumb) is constant, force and acceleration are proportional. Acceleromyographic devices measure the acceleration of a stimulated muscle using a piezoelectric transducer attached to the thumb. When a force is applied to the piezoelectric crystal, an electrical impulse is generated, which can then be analyzed and measured. The use of a hand adapter to apply a preload increases the precision of measurements.[32] An important limitation of acceleromyography is that baseline train-of-four ratio measurements (*i.e.*, those obtained before neuromuscular blocking agent administration) often exceed 1.0 (100%).[33] To address this problem and prevent overestimation of neuromuscular recovery, the process of normalization has been advocated: any train-of-four ratio before tracheal extubation should be compared (normalized) to the baseline

(pre–muscle relaxant administration) train-of-four ratio. Since normalization is not commonly performed in clinical practice, it is recommended that the threshold for adequate neuromuscular recovery be raised from the generally accepted threshold train-of-four ratio of 0.9 to 1.0 when using this technology.[34] Despite the significant limitations of acceleromyography-based monitors, they became the predominant technology in routine clinical use and research from the 1990s until recently. Some of the explanations for the adoption of acceleromyography include the facts that mechanomyography-based monitors were cumbersome to set up, calibrate, and use, and commercially unavailable; until very recently, free-standing, portable electromyography monitors were also not commercially available; and small, battery-operated acceleromyographic devices came into use when there were few attractive alternatives.

Kinemyography utilizes a piezoelectric sensor to quantify neuromuscular function by measuring the degree of bending or deformation of the piezoelectric sensor during thumb contraction in response to ulnar nerve stimulation; the bending of the transducer between the thumb and index fingers generates an electrical signal that is converted to a train-of-four ratio. Although kinemyography has been used in clinical studies, its ability to accurately quantify the degree of neuromuscular blockade (correlation with mechanomyography) has been questioned.[35–37] Other limitations include the availability of only one sensor size for all adults, and one sensor size for all pediatric patients.

Cuff pressure modality (TOFcuff; RGB Medical Devices; Spain) measures the pressure changes in a partially inflated modified noninvasive blood pressure cuff in response to stimulation of the upper arm, but no additional information is found on the company website. It is now clear that this device overestimates the train-of-four ratio obtained at the adductor pollicis in the critical range of train-of-four values greater than 0.60.[38]

Effect of Quantitative Monitoring on the Incidence of Postoperative Residual Neuromuscular Block

In 1979, Viby-Mogensen *et al.* documented with mechanomyography that 42% of patients who received long-acting muscle relaxants were admitted to the PACU with train-of-four ratio less than 0.7 (the threshold for neuromuscular recovery at that time).[29] Since this initial clinical investigation, several studies have been published specifically examining the impact of objective monitoring on the incidence of residual neuromuscular block in the PACU.

Comparative Studies Examining the Effect of Quantitative Monitoring *versus* No Monitoring *versus* Peripheral Nerve Stimulator Assessment on the Incidence of Postoperative Residual Neuromuscular Block

In a 1995 study published by Mortensen *et al.*, 40 patients given pancuronium were randomized to no intraoperative monitoring ("according to the routine of the department") or to an acceleromyography monitoring group (table 3).[39] Patients' tracheas were extubated based on clinical criteria in the no monitoring group and when achieving a train-of-four ratio greater than 0.7 in the acceleromyography group. Postoperative train-of-four ratios less than 0.7 (the threshold that defined residual neuromuscular weakness at the time the study was performed) measured with mechanomyography were observed in 50% of the patients in the no monitoring group *versus* only 5.3% of those in the acceleromyography group ($P = 0.03$). Using a similar study design, Gätke *et al.* randomized 120 patients given rocuronium and neostigmine reversal to no intraoperative monitoring or to acceleromyography monitoring groups.[40] Extubation was performed when clinical criteria were met, but patients in the acceleromyography group had to additionally achieve a train-of-four ratio greater than 0.8. Train-of-four ratios less than 0.8 were found in 10 patients in the no monitoring group (16.7%) compared to 2 patients in the acceleromyography group (3%; $P = 0.029$). However, the reduction in risk of residual neuromuscular block was achieved in the acceleromyography group at the expense of an extended time from end of surgery to tracheal extubation (12.5 min longer).

Wardhana *et al.*[41] assessed whether an "optimal" neostigmine dosing regimen (no rocuronium dosing within 30 min of reversal, dosing based on clinical signs and using a peripheral nerve stimulator) was equivalent to a neostigmine dosing regimen based on acceleromyography monitoring. The primary outcome measure was the incidence of postoperative residual neuromuscular blockade. Of the 72 patients randomized, 6 patients (16.7%) monitored with a peripheral nerve stimulator had postoperative train-of-four ratios less than 0.9 *versus* 1 patient (2.8%) monitored with acceleromyography. The equivalence test showed that the 95% CI value of this study was outside the range of equivalence margins.[41]

In the largest to date prospective investigation examining the effect of quantitative monitoring on the incidence of postoperative residual neuromuscular blockade as a primary outcome, Murphy *et al.* randomized 185 patients to acceleromyography monitoring or to peripheral nerve stimulator monitoring.[42] In both groups, patients' tracheas were extubated when standard clinical criteria (sustained head lift or hand grip for more than 5 s, the ability to follow simple commands, a stable ventilatory pattern with acceptable arterial oxygen saturation, and no observation of fade during train-of-four stimulation) were met; additionally, those in the acceleromyography group had to achieve a train-of-four ratio greater than 0.8 before extubation (this threshold was selected to allow tracheal extubation of patients who were unable to tolerate the tracheal tube until a train-of-four greater than 0.9 was reached). Train-of-four ratios less than 0.9 in the PACU were observed in 30% of patients in the peripheral nerve stimulator group *versus* only 4.5% in the acceleromyography group ($P < 0.0001$).[42] Another trial

Table 3. Comparative Studies Assessing the Effect of Quantitative Monitoring on the Incidence of Postoperative Residual Neuromuscular Block

	Year	Trial Design	Threshold of Recovery	Number of Subjects	Quantitative Monitor	Control Group	Muscle Relaxant	Criteria for Extubation	Incidence of Residual Block (percentage of patients)
Mortensen[39]	1995	Randomized	Train-of-four < 0.7	40	Acceleromyography	No monitor	Pancuronium	Control group: clinical criteria Study group: clinical + train-of-four > 0.7	50% in control group 5.3% in acceleromyography group
Gätke[40]	2002	Randomized	Train-of-four < 0.8	120	Acceleromyography	No monitor	Rocuronium	Control group: clinical criteria Study group: clinical + train-of-four > 0.8	16.7% in control group 3% in acceleromyography group
Wardhana[41]	2019	Randomized	Train-of-four < 0.9	72	Acceleromyography	Peripheral nerve stimulator	Rocuronium	Control group: > 15 min after reversal; Study group: train-of-four ≥ 0.9	16.7% in control group 2.8% in acceleromyography group
Murphy[42]	2008	Randomized	Train-of-four < 0.9	185	Acceleromyography	Peripheral nerve stimulator	Rocuronium	Control group: clinical criteria Study group: clinical + train-of-four > 0.8	30% in control group 4.5% in acceleromyography group
Murphy[43]	2011	Randomized	Train-of-four < 0.9	155	Acceleromyography	Peripheral nerve stimulator	Rocuronium	Control group: clinical criteria Study group: clinical + train-of-four > 0.8	50% in control group 14.5% in acceleromyography group
Domenech[44]	2019	Retrospective cohort	Train-of-four < 0.9	240	Kinemyography	No monitor	Rocuronium Vecuronium Atracurium	Not stated	32% in control group 1.6% in kinemyography group

by the same investigators randomized 155 patients to acceleromyography or peripheral nerve stimulator monitoring, with postoperative residual neuromuscular block as a secondary measure.[43] The authors observed train-of-four ratios less than 0.9 in 50% of patients monitored with peripheral nerve stimulators compared to 14.5% of those assessed with acceleromyography ($P < 0.0001$).[43] Finally, a retrospective cohort study from Argentina examined the effect of the type of neuromuscular monitor or reversal agent on the incidence of incomplete neuromuscular recovery in 240 consecutive surgical patients.[44] Train-of-four ratios less than 0.9 were present in 1.6% of patients who received quantitative monitoring *versus* 32% of patients who were not monitored ($P < 0.01$).

In a recent performance improvement initiative, 100 patients who received neuromuscular blocking agents intraoperatively and who were managed according to the local qualitative assessment practice were also tested quantitatively with an electromyography-based monitor immediately before tracheal extubation.[45] The quantitative measurement was always obtained *after* the clinical care team declared that the block was fully antagonized, and the patient was ready for emergence and spontaneous respiration. The incidence of residual neuromuscular block was 60%. Using the local hospital's National Surgical Quality Improvement Program database, the authors calculated that the proportion of patients *with* residual neuromuscular block who suffered a postoperative complication was 5.4%; the proportion of patients *without* residual block who suffered a postoperative complication was 1.8%. Thus, if the residual neuromuscular block were eliminated, the rate of postoperative complications would be reduced from 5.4% to 1.8%—a 66% reduction. The authors also calculated the average variable cost of care for patients without complications ($14,522) and the cost of care for patients with pneumonia and/or unplanned reintubation ($50,895). A 66% reduction in postoperative complications and associated costs would translate into a net savings to the institution of $4.6 million annually; this figure includes the cost of implementing universal quantitative monitoring.[45]

In summary, seven clinical trials (five randomized, one retrospective, and one observational)[39–45] evaluated the incidence of postoperative residual neuromuscular block in patients monitored with a quantitative device and those who either were assessed with a peripheral nerve stimulator or received no monitoring. In each of these trials, a statistically significant reduction in the incidence of postoperative residual neuromuscular block was observed when quantitative devices were used. Although the studies were appropriately designed to examine a quantifiable outcome of interest (train-of-four ratio), limitations of the investigations were that two of the five randomized studies were relatively small (fewer than 80 patients),[38,40] none of the trials were blinded, and the time of measurement of the postoperative train-of-four ratios varied.

Meta-analyses Analyzing the Effect of Quantitative Monitoring on Incidence of Postoperative Residual Neuromuscular Block

Intraoperative quantitative monitoring has been utilized in several clinical investigations in which the primary outcome was not postoperative residual neuromuscular blockade, yet postsurgical train-of-four ratios were recorded. These noncomparative studies provide further data on the efficacy of objective monitoring. Naguib *et al.* performed a meta-analysis of data from 24 trials involving 3,375 patients (1979 to 2005) to determine the effect of monitoring (quantitative and qualitative) on the percentage of patients with postoperative train-of-four ratios less than 0.9 and less than 0.7.[46] Neuromuscular function was monitored in 823 patients, and quantitative devices were used in 280 patients. The analysis did not demonstrate that the use of "monitoring" significantly reduced the risk of postoperative residual neuromuscular block. As noted in a subsequent letter to the editor, the meta-analysis used pooled data on both qualitative and quantitative devices, making conclusions about the effectiveness of objective monitoring unclear.[47] In response, Naguib *et al.* performed additional analyses to examine data only on quantitative monitoring, and concluded that there was no evidence that quantitative monitors were superior to peripheral nerve stimulators in reducing the incidence of incomplete neuromuscular recovery.[48]

A more comprehensive meta-analysis was published in 2020.[30] Carvalho *et al.* analyzed data from 53 trials (109 study arms; 12,664 patients) published between 1979 and 2019. No monitoring was used in 4,416 patients, peripheral nerve stimulators were applied in 1,528 patients, and quantitative monitoring was used in 6,181 patients. The primary endpoint was the incidence of postoperative residual neuromuscular block, defined as train-of-four ratios less than 0.7, 0.9, and 1.0. In addition to train-of-four thresholds, models accounting for monitoring type, muscle relaxant duration, type of anesthesia, reversal agent use, and publication year were used. The investigators identified 18 studies using quantitative devices, 11 studies using peripheral nerve stimulators, and 20 studies using no monitoring when the search criteria were limited to patients who received intermediate-acting muscle relaxants and when the threshold for residual neuromuscular block was a train-of-four ratio less than 0.9. This analysis revealed the absolute risk (95% CI) for a train-of-four less than 0.9 with quantitative monitoring was 0.119 (0.061 to 0.191), which was significantly lower than that for peripheral nerve stimulator monitoring (0.311 [0.216 to 0.415]), and no monitoring (0.338 [0.243 to 0.440]). However, the authors reported that the Grading of Recommendations Assessment, Development and Evaluation global level of evidence was very low (on a "high," "moderate," "low," and "very low" scale), and the refined assessment of confidence in network meta-analysis raised concerns of within- and across-study bias.[30] However, the analysis did not raise significant concerns on the likelihood of the conclusions of this meta-analysis of being modified by upcoming trials. Despite these limitations, the meta-analysis by Carvalho *et al.*[30] represented a significantly more comprehensive examination of the published data (109 study arms and 12,664 patients) than that of Naguib *et al.*,[46] it included more recent trials (up to 2019 rather than up to 2005), and study data were subjected to a more rigorous analysis than the previous meta-analysis.[46] Additionally, only eight studies using intermediate-acting muscle relaxants were included in the meta-analysis by Naguib *et al.*, and the threshold defining residual neuromuscular block used was a train-of-four ratio of 0.7, not the currently accepted threshold of 0.9.[46]

In summary, data from comparative and noncomparative investigations demonstrate that the use of intraoperative quantitative monitoring results in a significant reduction in the incidence of postoperative residual neuromuscular block.

Effect of Quantitative Monitoring on Clinical Outcomes

As described in the previous section, evidence supports the use of intraoperative quantitative monitoring as a method of assuring full recovery of neuromuscular strength at the end of surgery. Additionally, several clinical investigations have documented an association between residual neuromuscular blockade in the PACU and adverse outcomes after tracheal extubation. Therefore, the application of intraoperative quantitative monitoring, by attenuating the risk of residual neuromuscular blockade, has the potential to enhance recovery from anesthesia and decrease postoperative morbidity.

During early recovery from surgery in the PACU, patients with train-of-four ratios less than 0.9 are at increased risk for adverse events. The incidences of hypoxemic events and episodes of airway obstruction are more common in patients with residual neuromuscular blockade.[42,49] A multicenter study from Spain documented that patients with train-of-four ratios less than 0.9 were not only at increased risk for adverse respiratory events (odds ratio, 2.57; 95% CI, 1.23 to 5.36; $P = 0.009$) but also at a higher risk for unplanned reintubation.[50] A similar study investigating predictors of postoperative adverse respiratory events observed that the strongest independent risk factor for these events in the PACU was residual neuromuscular block (odds ratio, 6.4; 95% CI, 3.0 to 13.4; $P < 0.001$).[51] A systematic review of 58 studies reported that patients with residual neuromuscular block had higher rates of acute respiratory events compared to those with more complete recovery.[52] Additionally, PACU length of stay was increased by 80 min in patients admitted to the PACU with train-of-four ratios less than 0.9, with only age and residual neuromuscular block independently associated with this adverse outcome.[24]

Residual neuromuscular blockade may also impact clinical outcomes after PACU discharge. Patrocínio *et al.* retrospectively analyzed data of 6,224 patients who were monitored quantitatively for postoperative respiratory complications (defined as need for invasive mechanical ventilation within 7 days or postextubation desaturation).[53] The investigators observed that a low train-of-four ratio (less than 0.9) was associated with postoperative pulmonary complications (adjusted odds ratio, 1.43 [95% CI, 1.11 to 1.85]; $P = 0.006$). In a randomized trial enrolling 691 patients, those who received pancuronium and had residual block in the PACU had a 3.5-fold higher risk of a postoperative pulmonary complication (defined as a pneumonic infiltrate or atelectasis on a chest radiograph).[54] Similarly, an observational study enrolling 558 patients reported that major critical respiratory events, defined as pneumonia or atelectasis on a chest radiograph, were significantly associated with residual neuromuscular block; 93% of patients with evidence of a major critical respiratory event had train-of-four ratios less than 0.9 in the PACU.[49] In a study by Grabitz *et al.* that examined data from 2,233 patients, those admitted to the PACU with train-of-four ratios less than 0.9 had a threefold higher incidence of unplanned intensive care unit admission than those with train-of-four ratios 0.9 or greater.[55]

Quantitative Monitoring and Adverse Respiratory Events

There are fewer studies examining the effect of quantitative monitoring on respiratory outcomes than its impact on the incidence of residual neuromuscular block. However, emerging data from recent clinical trials have documented that the use of intraoperative quantitative monitoring can reduce the risk of adverse respiratory events associated with residual neuromuscular block. The following section summarizes the findings of these investigations.

Postoperative hypoxemia and airway obstruction are not uncommon events and are frequently associated with residual neuromuscular blockade.[49–51,56] Three randomized clinical trials have examined the effect of quantitative monitoring on these outcome measures. In a double-blinded study, Adembesa *et al.* randomized 168 patients undergoing general anesthesia and neuromuscular block with cisatracurium to be extubated either when train-of-four ratios 0.9 or greater were achieved with quantitative monitoring (acceleromyography) or when standard clinical criteria (*i.e.*, 5-s head-lift) were met.[57] The primary outcome measure was the incidence of adverse respiratory events in the PACU. During the first 30 min of PACU admission, significantly fewer patients who were monitored quantitatively experienced mild hypoxia (oxygen saturation measured by pulse oximetry [Spo_2] of 90 to 93%; 1% *vs.* 12% in clinical assessment group; $P = 0.005$). In addition, the incidence of upper airway obstruction was significantly lower in the patients monitored quantitatively (14%) than in patients assessed clinically (45%; $P < 0.0001$); fewer patients monitored quantitatively required tactile stimulation (2% *vs.* 21% in the clinical assessment group; $P < 0.0001$), and significantly fewer experienced snoring in the PACU (12% *vs.* 31%; $P = 0.003$). The two groups did not differ in the incidence of severe hypoxemic events (Spo_2 less than 90%).[57] Sauer *et al.* randomized 114 orthopedic patients to either a study group (who received neostigmine 20 μg/kg and were extubated at a train-of-four ratio of 1.0 measured with an acceleromyography quantitative monitor) or a control group (who received saline and had no fade with train-of-four or double-burst stimulation assessed with a peripheral nerve stimulator).[58] The primary outcome was the incidence of critical respiratory events, defined as hypoxemia (Spo_2 less than 93%), airway obstruction, tachypnea, or respiratory insufficiency. Hypoxemia developed in 40% of patients in the PACU, with significantly fewer patients in the study group having this event (28%) compared to the control group (50.9%; $P = 0.021$). No differences were observed between groups in other respiratory events. Although this investigation was designed to assess the effect of residual neuromuscular block on postoperative airway events, the findings illustrate that achieving a train-of-four ratio of 1.0 with acceleromyography can attenuate the risk of postoperative hypoxemia when compared to monitoring with a peripheral nerve stimulator.[58]

Murphy *et al.* randomized 185 patients to intraoperative quantitative (acceleromyographic) monitoring or a standard peripheral nerve stimulator.[42] The incidence of adverse respiratory events (mild hypoxemia = Spo_2 93 to 90%; severe hypoxemia = Spo_2 less than 90%; airway obstruction) was one of two primary endpoints. The investigators observed that during transport from the operating room to the PACU, the percentage of patients with severe hypoxemia was lower in the group monitored with acceleromyography (0% *vs.* 21.1% in peripheral nerve stimulator group; $P < 0.0001$) and fewer patients in this monitored group required an intervention to maintain airway patency (0% *vs.* 11.1% in peripheral nerve stimulator group; $P = 0.002$). In addition, the incidence, severity, and duration of hypoxemic events during the first 30 min of PACU admission were less in the acceleromyography group (all $P < 0.001$; table 4).[42]

Patrocínio *et al.* analyzed 101,510 patient charts for the primary outcome of postoperative respiratory complications, defined as a composite of postoperative desaturation less than 90% within 10 min of extubation, or invasive mechanical ventilation requirement within 7 days after surgery.[53] Their primary objective was to analyze the association between a recently developed prediction score (Residual Neuromuscular Block Prediction Score) and respiratory complications, while the secondary aim was to compare Residual Neuromuscular Block Prediction Score to train-of-four ratio less than 0.90 as an indicator of postoperative pulmonary complications. Of the 6,224 patients who had train-of-four ratio data available, 3,733 (60%) had a train-of-four ratio less than 0.90 before extubation; of these

Table 4. Effect of Intraoperative Neuromuscular Monitoring on Postoperative Adverse Airway Events

	Acceleromyography Group	Conventional Peripheral Nerve Stimulator Group	Difference (99% CI)	*P* Value
Number (n)	89	90	—	—
Spo_2 on PACU arrival, %	97 (90 to 100)	95 (72 to 100)	2 (1 to 3)	< 0.0001
No. with Spo_2 90–93% on arrival in PACU	5 (5.6%)	22 (24.4%)	–18.8% (–32.9 to –5.5%)	< 0.001
No. with Spo_2 < 90% on arrival in PACU	0 (0%)	9 (10.0%)	–10.0% (–21.1 to –2.7%)	0.003
No. with episodes of Spo_2 90–93% in PACU	6 (6.7%)	39 (43.3%)	–36.6% (–51.2 to –21.1%)	< 0.0001
No. of Spo_2 90–93% episodes in PACU	0 (0 to 4)	0 (0 to 12)	0 (–1 to 0)	< 0.0001
No. with episodes of Spo_2 < 90% in PACU	0 (0%)	19 (21.1%)	–21.1% (–34.0 to –12.2%)	< 0.0001
No. of Spo_2 < 90% episodes in PACU	0 (0 to 0)	0 (0 to 6)	0 (0 to 0)	< 0.0001
Lowest Spo_2 in PACU, %	96 (90 to 100)	93.5 (80 to 100)	3 (2 to 4)	< 0.0001
No. requiring airway maneuver in PACU	0 (0%)	4 (4.4%)	–4.4% (–13.8 to 2.7%)	0.12
No. requiring stimulation to maintain Spo_2 in PACU	0 (0%)	7 (7.8%)	–7.8% (–18.3 to –0.5%)	0.014

Data are mean ± SD, median (range), or number of patients (%).

PACU, postanesthesia care unit; Spo_2, oxygen saturation measured by pulse oximetry.

From Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS, Nisman M: Intraoperative acceleromyographic monitoring reduces the risk of residual neuromuscular blockade and adverse respiratory events in the postanesthesia care unit. ANESTHESIOLOGY 2008; 109:389–98. Reprinted with permission.

patients, 302 (4.9%) developed postoperative respiratory complications. Of note, only 6.1% of the 101,510 patients had undergone intraoperative quantitative monitoring. The authors concluded that quantitative monitoring to ensure a train-of-four ratio less than 0.90 was superior to Residual Neuromuscular Block Prediction Score as a predictor of postoperative respiratory complications and recommended that "clinicians use quantitative neuromuscular monitoring in patients at risk for residual neuromuscular blockade."[53]

Todd *et al.* reported on the implementation of an electromyographic quantitative monitoring system at an academic medical center after a review of an adverse events database that revealed that two to four reintubations occurred in the PACU per year that were likely related to residual neuromuscular block.[59] The investigators conducted five sampling surveys, involving 409 patients, over a 2-yr period after the electromyographic system was installed in all operating rooms. In the initial survey, quantitative monitoring was used in 51% of patients, and 31% of patients had train-of-four ratios less than 0.9 in the PACU. A fifth survey 2 yr later revealed that 93% of patients were monitored quantitatively, and only 17% of patients had train-of-four ratios less than 0.9. Most importantly, no patients required reintubation in the PACU due to residual neuromuscular weakness during the 2-yr study period.[59]

Surgical patients with incomplete neuromuscular recovery may also be at risk for more significant pulmonary complications, such as atelectasis and pneumonia, which are diagnosed after the patient is discharged from the PACU. An association between residual neuromuscular block in the PACU and these postoperative pulmonary complications has been documented.[49,54] Furthermore, the use of sugammadex, which significantly decreases the risk of incomplete neuromuscular recovery after surgery, has been associated with a lower incidence of these postoperative pulmonary complications when compared to neostigmine.[60,61] It is possible, therefore, that intraoperative strategies such as quantitative monitoring that facilitate recovery of neuromuscular function have the potential to further attenuate the risk of postoperative pulmonary complications. Currently, however, few reports (a prospective observational study[62] and a subsequent reanalysis of the data from that investigation[63]) have examined this topic.

The Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR) study was a prospective observational cohort study that enrolled 22,803 noncardiac surgical patients from 211 European hospitals.[62] The primary endpoint was the incidence of postoperative pulmonary complications (defined as at least one postoperative pulmonary event), observed on a postoperative visit or review of the patient's chart, that occurred from the time of PACU admission until postoperative day 28. The analysis examined the effect of muscle relaxants, neuromuscular monitoring, and reversal agents on the primary outcome measure. The investigators reported that the use of quantitative neuromuscular monitoring (used in 4,182 patients *vs.* 2,686 who were assessed with a peripheral nerve stimulator and 10,282 patients with no monitoring) was not associated with a decreased risk of postoperative pulmonary complications, and that extubation at a train-of-four ratio 0.9 or greater was not associated with better pulmonary outcomes.[62]

A significant limitation of the POPULAR study was that the train-of-four ratio threshold for acceptable neuromuscular recovery was defined in the analysis as a train-of-four ratio of 0.9. However, acceleromyography technology was used by the majority (87%) of clinicians who used quantitative monitors.[62] It is well known that baseline train-of-four ratios measured with acceleromyography before muscle relaxant administration (baseline) usually exceed 1.0 (up to

1.47),[64] and that train-of-four ratio measurements should be corrected or "normalized" to this baseline value in order to accurately assess the threshold of neuromuscular recovery. If baseline values are not recorded and normalization is not performed, in order to detect a train-of-four ratio 0.9 or greater with a 95% probability, train-of-four recovery to 1.0 is recommended.[34] To address this important limitation, Blobner *et al.* re-analyzed their original POPULAR data to determine if a higher train-of-four threshold impacted the incidence of postoperative pulmonary complications.[63] Data from 3,150 patients with complete quantitative neuromuscular monitoring data were split into subcohorts of train-of-four ratios from 0.86 to 0.96 to identify an optimal train-of-four value to signify recovery (fig. 2). The investigators observed that extubating patients' trachea when train-of-four ratio was greater than 0.95 rather than greater than 0.9 decreased the adjusted risk of postoperative pulmonary complications by 3.5% (95% CI, 0.7 to 6.0%) from the reported incidence in the POPULAR study (11.3%). Increasing the recommended train-of-four ratio threshold from 0.9 to 0.95 reduced the adjusted risk by 4.9% (95% CI, 1.2 to 8.5%).[63] These findings suggest that when quantitative monitoring is used as recommended, a beneficial effect of quantitative monitoring on postoperative pulmonary complications may be observed.

In summary, several recent investigations have assessed the effect of quantitative monitoring on adverse respiratory outcomes. These studies have documented that the use of quantitative monitoring may reduce the risk of hypoxemic events and episodes of airway obstruction in the PACU, decrease the need for postoperative reintubation, and attenuate the incidence of postoperative pulmonary complications. Currently, the data are strongest for early adverse respiratory events in the PACU, with only few studies that have examined pulmonary events beyond PACU discharge. An important limitation is that there is currently no standardized definition of a "postoperative pulmonary complication." Such a standardized definition will aid in the design of future clinical trials and allow pooling of data for meta-analyses. Additional larger investigations are also needed to assess the effect of quantitative monitoring on the more significant respiratory events such as postoperative pneumonia and other postoperative pulmonary complications that may persist beyond PACU discharge and impact patient safety and return to preoperative status.

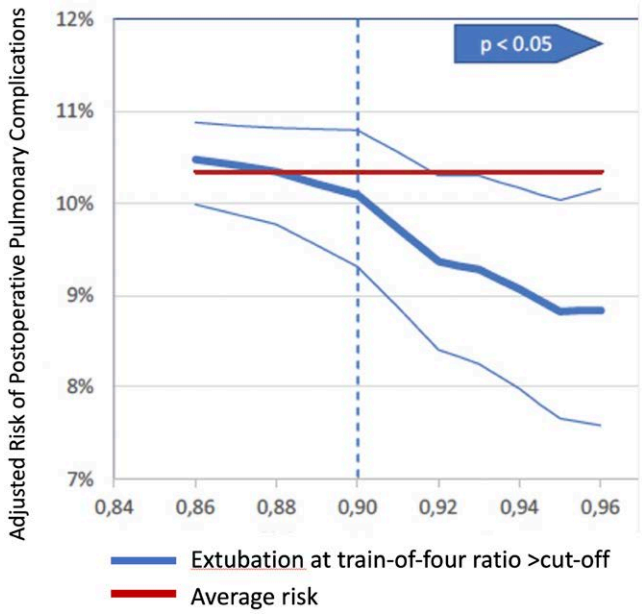

Fig. 2. Train-of-four ratio cutoff optimization. The cohort of patients with quantitative neuromuscular monitoring (n = 3,510) was split into two varying subcohorts using the train-of-four ratio before extubation as the cutoff. Several splits with train-of-four ratio cutoffs starting from 0.86 to 0.96 were created. The adjusted risk of postoperative pulmonary complications and its 95% CI (*thin blue lines*) is calculated for each split and plotted against the respective train-of-four ratio cutoff. The adjusted risk of postoperative pulmonary complications at the cutoff of train-of-four ratio greater than 0.90, which is the currently recommended recovery level (*blue dotted vertical line*), does not significantly differ from the cohort's average risk (*red horizontal line*). Significantly lower risks are achieved at train-of-four ratio cutoffs greater than 0.92.[63] Reprinted from Blobner M, Hunter JM, Meistelman C, Hoeft A, Hollmann MW, Kirmeier E, Lewald H, Ulm K: Use of a train-of-four ratio of 0.95 *versus* 0.9 for tracheal extubation: An exploratory analysis of POPULAR data. Br J Anaesth 2020; 124:63–72, with permission from Elsevier.

Effect of Quantitative Monitoring on Postoperative Symptoms of Muscle Weakness

Patients admitted to the PACU are at increased risk for unpleasant symptoms of muscle weakness, which may persist for several hours. Patients commonly remember and may characterize these symptoms as "taking a long time to wake up."[23] A randomized clinical trial by Murphy *et al.* assessed the effect of quantitative neuromuscular monitoring on postoperative symptoms of residual paresis.[43] One hundred fifty-five patients were randomized to monitoring with acceleromyography or assessment with a peripheral nerve stimulator. The primary outcome variable was the total number of symptoms of muscle weakness at four predetermined times in the PACU. The investigators reported that patients in the acceleromyography group had less overall weakness (graded on a 0 to 10 scale) and reported significantly fewer symptoms of muscle weakness during the first 60 min of PACU admission ($P < 0.0001$) compared to patients assessed qualitatively with a peripheral nerve stimulator.[43] Additionally, overall quality of recovery in the PACU was improved in patients in the acceleromyography group. These data suggest that patient-centered outcome measures can be enhanced when quantitative neuromuscular monitoring is used intraoperatively.

While there were no differences in the number of signs of muscle weakness between the quantitative and qualitative monitoring groups in the study by Murphy *et al.*,[43] in an investigation by Mortensen *et al.*, 35% of patients who were not monitored intraoperatively were unable to sustain a 5-s head-lift and 25% of patients were unable to lift an arm, as compared to one and zero patients, respectively, in the acceleromyography group ($P < 0.05$).[39]

Limitations of the Studies Assessing the Effect of Quantitative Monitoring on the Incidence of Residual Neuromuscular Block and Clinical Outcomes

There are limitations to the available evidence supporting the use of quantitative monitoring in the operating room. First, apart from the POPULAR trial,[62] most of the published investigations enrolled a relatively small number of subjects. When assessing the effect of monitoring on the incidence of residual neuromuscular block, the largest comparative and noncomparative studies included 240 patients[44] and 602 patients,[65] respectively. Similarly, the largest clinical outcome study enrolled only 185 patients.[42] Future studies should be powered to assess outcomes of interest to clinicians, such as postoperative pulmonary complications. However, calculation of appropriate enrollment in these investigations is complicated by the fact that there is no standard definition of "postoperative pulmonary complication"; most studies have used a composite outcome measure that combined several adverse respiratory events. Designing trials to assess the effect of quantitative (objective) monitoring on the incidence of more specific, yet uncommon, pulmonary outcomes such pneumonia would likely necessitate study enrollment that would be large or larger than that of the POPULAR study.[62] Second, there is no standardization of the time point at which postoperative residual neuromuscular block is measured. Some trials have assessed final train-of-four ratios after tracheal extubation or even immediately before extubation; at PACU admission; or 5, 10, or 15 min after PACU arrival. Others have documented that train-of-four ratio values recorded before or after extubation were significantly lower than those recorded 15 min after PACU admission.[30] Third, the majority of clinical trials used acceleromyography technology, and many investigators did not calibrate the monitors, obtain baseline values, or normalize the final train-of-four ratios.[30] Normalization of acceleromyographic train-of-four ratios is critical, because at a mechanomyographic train-of-four ratio of 0.9, the corresponding acceleromyographic train-of-four ratio is 0.95, with a range of 0.86 to 1.0.[34] After normalization, the train-of-four ratios of mechanomyography and acceleromyography are equivalent (train-of-four ratios of 0.90 and 0.89, respectively).[34] It is likely, therefore, that these acceleromyographic studies underestimated the true incidence of residual neuromuscular block. Furthermore, many researchers using acceleromyography did not calibrate the monitors, did not use a thumb preload, and did not allow for a period of signal stabilization, which are procedures needed to obtain accurate results.[30,64,66] Additionally, different acceleromyographic monitors (such as the ToFscan; IDMED; France) use a modified algorithm: when the train-of-four ratio exceeds 1.0 and T2 is greater than T1, the train-of-four ratio is calculated as T4/T2; all train-of-four ratio values greater than 1.0 (100%) are truncated and displayed as 100%. This modification of the displayed raw data further increases the variability of measured responses among different manufacturers.[67] Fourth, a variety of different quantitative monitors were used in various trials. Since each technology (based on measurement of force, acceleration, or electrical activity) measures a different physiologic event after neurostimulation, results obtained with different monitors may vary slightly, complicating interpretations of findings and interfering with comparisons of study data. Alternatively, the vast majority of neuromuscular monitoring studies since 2005 have used acceleromyography, but "the more practical and user-friendly nature of acceleromyography comes at a known practicality/accuracy trade-off because of its susceptibility to well-described overestimation artefacts. These could potentially overestimate the reduction of [postoperative residual neuromuscular block] over time."[30] The trade-off may well explain the reported pooled incidence of residual weakness after quantitative monitoring of 0.115 (95% CI, 0.057 to 0.188) in the meta-analysis of Carvalho *et al.*[30] While these limitations of acceleromyography are well described and may

partly explain the failure of acceleromyographic monitors to completely avoid the occurrence of residual neuromuscular block, there are no studies to indicate that the use of quantitative monitors may actually *increase* the incidence of residual block; this suggests that the effect of quantitative monitoring on residual neuromuscular block is not random. Finally, the great majority of the studies comparing quantitative monitoring to either no monitoring or qualitative monitoring with peripheral nerve stimulators used neostigmine as a reversal agent.[30] The effect of quantitative monitoring on the incidence of residual neuromuscular block when using sugammadex is less significant, yet still poorly defined. However, although sugammadex reduces the incidence of residual neuromuscular block, the meta-analysis of Carvalho *et al*. concluded that "sugammadex does not eliminate postoperative residual curarization and its use and monitoring should be guided by appropriate quantitative neuromuscular monitoring."[30]

Conclusions and a (Hopeful) Look to the Future

In conclusion, clinical trials have shown that the intraoperative use of quantitative monitoring significantly decreases the incidence of postoperative residual neuromuscular blockade in the operating room and PACU. Similarly, recent studies have documented that quantitative monitoring can decrease the risk of adverse postoperative events associated with incomplete neuromuscular recovery, which include hypoxemic events, episodes of airway obstruction, postoperative reintubations, and other postoperative pulmonary complications, as well as unpleasant symptoms of muscle weakness.

The authors also wish to point out several topics that are not mentioned in the literature regarding the availability and effectiveness of quantitative monitoring; the first is the "signal" that is generated by using quantitative monitoring, which either shows "no effect" on the incidence of residual neuromuscular block (and associated complications), or a "decrease" in these outcomes. To date, there are no reports of the use of quantitative monitoring being associated with an *increase* in the incidence of residual block and its complications. The second topic deals with the timing of the measurement of the train-of-four ratio in relation to tracheal extubation; some studies report the train-of-four ratio immediately before extubation, while others report it immediately after. If the train-of-four ratio immediately before extubation is less than 0.9, then quantitative monitoring is reported to have "failed" to prevent residual neuromuscular block. Ultimately, the monitor can only provide the quantitative information—it is the clinician who makes decisions based on these data. Third, it should be acknowledged that most peripheral neve stimulators in clinical use today are decades old and in need of replacement. However, even the newest and most feature-laden peripheral nerve stimulators are not "monitors," since they do not measure responses—they only provide neurostimulation, and those units without a built-in digital ammeter are to be avoided. While the cost per patient of disposable electrodes associated with the use of electromyography-based quantitative monitors may be $15 to $30, the savings from more judicious use of neuromuscular blocking drugs and their antagonists may offset such costs.[45,68] This topic is particularly important, because there have not been any prospective economic studies of the impact of quantitative neuromuscular monitors on the cost of care. However, we do know that the highest independent adjusted costs per adverse event derived from the American College of Surgeons National Surgical Quality Improvement Program (Chicago, Illinois) were $48,168 (for prolonged ventilation) and $26,718 (for unplanned intubation).[69] These costs are comparable to those reported recently.[45] If quantitative neuromuscular monitoring can help avoid such pulmonary complications, the cost of monitors and disposables is trivial.[45]

There is increased recognition of the adverse effects of impaired neuromuscular recovery on clinical outcomes, with the expression of expert opinion, *via* editorials[70–72] and review articles,[73,74] that quantitative monitoring should be used whenever a muscle relaxant is administered. Furthermore, national guidelines from anesthesiology societies, including the Association of Anaesthetists of Great Britain and Ireland (London, United Kingdom)[75]; the Canadian Anesthesiologists' Society (Toronto, Ontario, Canada)[76]; the French Society of Anesthesiology and Intensive Care (Paris, France)[77]; and the Spanish Society of Anesthesiology, Intensive Care, and Pain Therapy (Madrid, Spain),[78] have all recommended the use of intraoperative quantitative monitoring. Other societies' guidelines have appeared in nonindexed, peer-reviewed publications: the Australian and New Zealand College of Anaesthetists (Melbourne, Australia); the Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care (Rome, Italy); the Czech Society of Anesthesiology (Prague, Czech Republic); and the Portuguese Society of Anesthesiology (Lisbon, Portugal).

Additional support for the use of objective monitoring was provided in a consensus statement produced by a panel of clinical scientists with expertise in neuromuscular monitoring[79] (table 5) concluding that "…whenever a neuromuscular blocker is administered, neuromuscular function must be monitored by observing the evoked muscular response to peripheral nerve stimulation. Objective monitoring (documentation of train-of-four ratio ≥0.90) is the only method of assuring that satisfactory recovery of neuromuscular function has taken place."[79] Although recommendations on management of neuromuscular blockade have not been provided by the American Society of Anesthesiologists (Schaumburg, Illinois), the development of guidelines is reportedly underway.

The reasons for clinicians' reluctance to adopt routine use of quantitative monitoring are varied. There are several possible explanations. Surveys of anesthesiologists suggest

Table 5. Recommendations from the Consensus Panel on the Perioperative Use of Neuromuscular Monitoring

1. Quantitative (objective) monitoring should be used whenever a nondepolarizing neuromuscular blocking drug is administered:
   a) Quantitative monitoring is defined as an objective real-time measurement of the train-of-four ratio. The difference between quantitative and qualitative assessments of neuromuscular block is in their ability to objectively measure the train-of-four ratio. Qualitative (subjective) assessments using peripheral nerve stimulator devices depend on the anesthesia practitioner estimating the strength of muscle contractions in response to train-of-four stimulation by visual or tactile means only, and thus are prone to error.
   b) The panel recognizes that replacing conventional peripheral nerve stimulator devices with quantitative monitoring equipment will take time and education. During this interim period, the use of a peripheral nerve stimulator in any patient receiving a neuromuscular blocking drug is mandatory.
2. Subjective or clinical tests of are not predictive of adequate neuromuscular recovery and are not sensitive to the presence of residual neuromuscular weakness; their use should be abandoned in favor of objective monitoring:
   a) After the train-of-four ratio recovers to > 0.40, clinicians can no longer detect the presence of fade by tactile or visual observation (subjectively). Therefore, clinicians may assume complete recovery from neuromuscular block (*i.e.*, train-of-four ratio ≥ 0.9) despite the actual presence of minimal or shallow degrees of neuromuscular block.
   b) After emergence from anesthesia and tracheal extubation, undetected minimal or shallow levels of neuromuscular block can lead to adverse airway or pulmonary complications.
   c) Clinical signs (such as the 5-s head-lift or sustained handgrip) and clinical tests (such as presence of spontaneous respiration) do not guarantee complete resolution of neuromuscular block and no longer have a place as the sole determinant of adequate recovery of neuromuscular function.
3. Professional organizations should develop practice standards and guidelines detailing how best to monitor and manage perioperative administration of neuromuscular blocking drugs.
4. Terms that describe the levels of neuromuscular block should be standardized (complete, deep, moderate, shallow).

From Naguib M, Brull SJ, Kopman AF, Hunter JM, Fulesdi B, Arkes HR, Elstein A, Todd MM, Johnson KB: Consensus statement on perioperative use of neuromuscular monitoring. Anesth Analg 2018; 127:71–80. Reprinted with permission.

that many practitioners believe that residual neuromuscular block is a rare event that occurs infrequently in their clinical practice.[80,81] There is also poor awareness of the limited ability of clinical tests of muscle strength (*i.e.*, 5-s head-lift, grip strength, vital capacity) and qualitative (visual, tactile) monitoring to detect full recovery of neuromuscular function. Furthermore, first-generation quantitative monitors required a relatively long time to place and calibrate before administration of muscle relaxants, and experience with use of the devices was needed to obtain accurate and reliable results.[82] These time and experience requirements in the setting of the busy operating room environment likely limited the widespread adoption of first-generation monitors. There is also a significant degree of overconfidence in the clinicians' own assessment of their knowledge and quality of care they provide, which is common among all physicians.[83]

It is likely that simply placing quantitative monitors in each anesthetizing location will not solve the problem of clinician avoidance of using them, or of postoperative residual neuromuscular block. Acquisition of these devices needs to be accompanied by comprehensive educational efforts that are sustained over time. Clinicians should recognize the incidence and clinical implications of incomplete neuromuscular recovery, the limitations of clinical signs of neuromuscular recovery and of peripheral nerve stimulator monitoring, and the limitations of the pharmacology of reversal agents.[79] Additionally, appropriate training is required to obtain reliable results from quantitative monitoring.[82,84] Successful implementation of a quantitative monitoring program into an anesthesia department requires dedicated local champions and persistence, and such efforts will increase patient safety and enhance postoperative quality of recovery of our surgical patients.

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Competing Interests

Dr. Murphy is a consultant for Merck & Co. (Kenilworth, New Jersey) and has served on the Scientific Advisory Board for Senzime AB (Uppsala, Sweden). Dr. Brull has intellectual property assigned to Mayo Clinic (Rochester, Minnesota); has received research support (funds to Mayo Clinic) from Merck & Co., Inc.; was a consultant for Merck & Co., Inc.; is a principal shareholder and Chief Medical Officer in Senzime AB; and is a member of the Scientific/Clinical Advisory Boards for The Doctors Company (Napa, California), Coala Life Inc. (Irvine, California), NMD Pharma (Aarhus, Denmark), and Takeda Pharmaceuticals (Cambridge, Massachusetts).

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References

1. Churchill-Davidson HC: The D-tubocurarine dilemma. Anesthesiology 1965; 26:132–3
2. Ewins AJ: Acetylcholine, a new active principle of ergot. Biochem J 1914; 8:44–9

3. Todman D: Henry Dale and the discovery of chemical synaptic transmission. Eur Neurol 2008; 60:162–4
4. Eccles JC, Katz B, Kuffler SW: Nature of the "end-plate potential" in curarized muscle. J Neurophys 1941; 4:362–87
5. Loewi O: "The Ferrier lecture: On problems connected with the principle of humoral transmission of nervous impulses." Proc R Soc Lond B Biol Sci 1935; 118:299–316
6. Gasser HS, Erlanger J: A study of the action currents of nerve with the cathode ray oscillograph. Am J Physiol 1922; 62:496–524
7. Katz RL, Gissen AJ, Karis JH: The effects of hexafluorenium and edrophonium on the neuromuscular blocking actions of succinylcholine, decamethonium, imbretil and D-tubocurarine. Anesthesiology 1965; 26:154–61
8. Katz RL: Comparison of electrical and mechanical recording of spontaneous and evoked muscle activity. The clinical value of continuous recording as an aid to the rational use of muscle relaxants during anesthesia. Anesthesiology 1965; 26:204–11
9. Ali HH: A new device for monitoring force of thumb adduction. Br J Anaesth 1970; 42:83–5
10. Ali HH, Utting JE, Gray C: Stimulus frequency in the detection of neuromuscular block in humans. Br J Anaesth 1970; 42:967–78
11. Viby-Mogensen J, Jensen NH, Engbaek J, Ording H, Skovgaard LT, Chraemmer-Jørgensen B: Tactile and visual evaluation of the response to train-of-four nerve stimulation. Anesthesiology 1985; 63:440–3
12. Kopman AF, Yee PS, Neuman GG: Correlation of the train-of-four fade ratio with clinical signs and symptoms of residual curarization in awake volunteers. Anesthesiology 1997; 86:765–71.
13. Pedersen T, Viby-Mogensen J, Bang U, Olsen NV, Jensen E, Engboek J: Does perioperative tactile evaluation of the train-of-four response influence the frequency of postoperative residual neuromuscular blockade? Anesthesiology 1990; 73:835–9
14. Cammu G, De Witte J, De Veylder J, Byttebier G, Vandeput D, Foubert L, Vandenbroucke G, Deloof T: Postoperative residual paralysis in outpatients *versus* inpatients. Anesth Analg 2006; 102:426–9
15. Kirkegaard H, Heier T, Caldwell JE: Efficacy of tactile-guided reversal from cisatracurium-induced neuromuscular block. Anesthesiology 2002; 96:45–50
16. Ali HH, Utting JE, Gray TC: Quantitative assessment of residual antidepolarizing block. II. Br J Anaesth 1971; 43:478–85
17. Ali HH, Wilson RS, Savarese JJ, Kitz RJ: The effect of tubocurarine on indirectly elicited train-of-four muscle response and respiratory measurements in humans. Br J Anaesth 1975; 47:570–4
18. Heier T, Caldwell JE, Feiner JR, Liu L, Ward T, Wright PM: Relationship between normalized adductor pollicis train-of-four ratio and manifestations of residual neuromuscular block: A study using acceleromyography during near steady-state concentrations of mivacurium. Anesthesiology 2010; 113:825–32
19. Broens SJL, Boon M, Martini CH, Niesters M, van Velzen M, Aarts LPHJ, Dahan A: Reversal of partial neuromuscular block and the ventilatory response to hypoxia: A randomized controlled trial in healthy volunteers. Anesthesiology 2019; 131:467–76
20. Eikermann M, Groeben H, Hüsing J, Peters J: Accelerometry of adductor pollicis muscle predicts recovery of respiratory function from neuromuscular blockade. Anesthesiology 2003; 98:1333–7
21. Eriksson LI, Sundman E, Olsson R, Nilsson L, Witt H, Ekberg O, Kuylenstierna R: Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: Simultaneous videomanometry and mechanomyography of awake human volunteers. Anesthesiology 1997; 87:1035–43
22. Kumar GV, Nair AP, Murthy HS, Jalaja KR, Ramachandra K, Parameshwara G: Residual neuromuscular blockade affects postoperative pulmonary function. Anesthesiology 2012; 117:1234–44
23. Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Shear T, Vender JS, Gray J, Landry E: Postoperative residual neuromuscular blockade is associated with impaired clinical recovery. Anesth Analg 2013; 117:133–41
24. Butterly A, Bittner EA, George E, Sandberg WS, Eikermann M, Schmidt U: Postoperative residual curarization from intermediate-acting neuromuscular blocking agents delays recovery room discharge. Br J Anaesth 2010; 105:304–9
25. Fu S, Lin W, Zhao X, Ge S, Xue Z: Quantitative relationships between pulmonary function and residual neuromuscular blockade. Biomed Res Int 2018; 2018:9491750
26. Paton WD, Waud DR: The margin of safety of neuromuscular transmission. J Physiol 1967; 191:59–90
27. Ali HH, Utting JE, Nightingale DA, Gray C: Quantitative assessment of residual curarization in humans. Br J Anaesth 1970; 42:802–3
28. Ali HH, Utting JE, Gray TC: Quantitative assessment of residual antidepolarizing block. I. Br J Anaesth 1971; 43:473–7
29. Viby-Mogensen J, Jørgensen BC, Ording H: Residual curarization in the recovery room. Anesthesiology 1979; 50:539–41
30. Carvalho H, Verdonck M, Cools W, Geerts L, Forget P, Poelaert J: Forty years of neuromuscular monitoring and postoperative residual curarisation: A meta-analysis and evaluation of confidence in network meta-analysis. Br J Anaesth 2020; 125:466–82
31. Engbaek J, Ostergaard D, Viby-Mogensen J, Skovgaard LT: Clinical recovery and train-of-four ratio measured mechanically and electromyographically following atracurium. Anesthesiology 1989; 71:391–5

32. Claudius C, Skovgaard LT, Viby-Mogensen J: Is the performance of acceleromyography improved with preload and normalization? A comparison with mechanomyography. Anesthesiology 2009; 110:1261–70
33. Kopman AF, Chin W, Cyriac J: Acceleromyography vs. electromyography: An ipsilateral comparison of the indirectly evoked neuromuscular response to train-of-four stimulation. Acta Anaesthesiol Scand 2005; 49:316–22
34. Capron F, Alla F, Hottier C, Meistelman C, Fuchs-Buder T: Can acceleromyography detect low levels of residual paralysis? A probability approach to detect a mechanomyographic train-of-four ratio of 0.9. Anesthesiology 2004; 100:1119–24
35. Kern SE, Johnson JO, Westenskow DR, Orr JA: An effectiveness study of a new piezoelectric sensor for train-of-four measurement. Anesth Analg 1994; 78:978–82
36. Dahaba AA, von Klobucar F, Rehak PH, List WF: The neuromuscular transmission module *versus* the relaxometer mechanomyograph for neuromuscular block monitoring. Anesth Analg 2002; 94:591–6; table of contents
37. Khandkar C, Liang S, Phillips S, Lee CY, Stewart PA: Comparison of kinemyography and electromyography during spontaneous recovery from non-depolarising neuromuscular blockade. Anaesth Intensive Care 2016; 44:745–51
38. Veiga Ruiz G, García Cayuela J, Orozco Montes J, Parreño Caparrós M, García Rojo B, Aguayo Albasini JL: Monitoring intraoperative neuromuscular blockade and blood pressure with one device (TOF-Cuff): A comparative study with mechanomyography and invasive blood pressure. Rev Esp Anestesiol Reanim 2017; 64:560–7
39. Mortensen CR, Berg H, el-Mahdy A, Viby-Mogensen J: Perioperative monitoring of neuromuscular transmission using acceleromyography prevents residual neuromuscular block following pancuronium. Acta Anaesthesiol Scand 1995; 39:797–801
40. Gätke MR, Viby-Mogensen J, Rosenstock C, Jensen FS, Skovgaard LT: Postoperative muscle paralysis after rocuronium: Less residual block when acceleromyography is used. Acta Anaesthesiol Scand 2002; 46:207–13
41. Wardhana A, Kurniawaty J, Uyun Y: Optimised reversal without train-of-four monitoring *versus* reversal using quantitative train-of-four monitoring: An equivalence study. Indian J Anaesth 2019; 63:361–7
42. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS, Nisman M: Intraoperative acceleromyographic monitoring reduces the risk of residual neuromuscular blockade and adverse respiratory events in the postanesthesia care unit. Anesthesiology 2008; 109:389–98
43. Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Marymont JH, Vender JS, Gray J, Landry E, Gupta DK: Intraoperative acceleromyography monitoring reduces symptoms of muscle weakness and improves quality of recovery in the early postoperative period. Anesthesiology 2011; 115:946–54
44. Domenech G, Kampel MA, García Guzzo ME, Novas DS, Terrasa SA, Fornari GG: Usefulness of intra-operative neuromuscular blockade monitoring and reversal agents for postoperative residual neuromuscular blockade: A retrospective observational study. BMC Anesthesiol 2019; 19:143
45. Edwards L-A, Ly N, Shinefeld J, Morewood G: Universal quantitative neuromuscular blockade monitoring at an academic medical center – A multimodal analysis of the potential impact on clinical outcomes and total cost of care. Perioper Care Oper Room Manag 2021; 24:100184
46. Naguib M, Kopman AF, Ensor JE: Neuromuscular monitoring and postoperative residual curarisation: A meta-analysis. Br J Anaesth 2007; 98:302–16
47. Viby-Mogensen J, Claudius C, Eriksson LI: Neuromuscular monitoring and postoperative residual curarization. Br J Anaesth 2007; 99:297; author reply 297–9
48. Naguib M, Kopman AF, Ensor JE: Neuromuscular monitoring and postoperative residual curarization. Br J Anaesth 2007; 99:297–9
49. Martinez-Ubieto J, Ortega-Lucea S, Pascual-Bellosta A, Arazo-Iglesias I, Gil-Bona J, Jimenez-Bernardó T, Muñoz-Rodriguez L: Prospective study of residual neuromuscular block and postoperative respiratory complications in patients reversed with neostigmine *versus* sugammadex. Minerva Anestesiol 2016; 82:735–42
50. Errando CL, Garutti I, Mazzinari G, Díaz-Cambronero Ó, Bebawy JF; Grupo Español De Estudio Del Bloqueo Neuromuscular: Residual neuromuscular blockade in the postanesthesia care unit: Observational cross-sectional study of a multicenter cohort. Minerva Anestesiol 2016; 82:1267–77
51. Xará D, Santos A, Abelha F: Adverse respiratory events in a post-anesthesia care unit. Arch Bronconeumol 2015; 51:69–75
52. Raval AD, Anupindi VR, Ferrufino CP, Arper DL, Bash LD, Brull SJ: Epidemiology and outcomes of residual neuromuscular blockade: A systematic review of observational studies. J Clin Anesth 2020; 66:109962
53. Patrocínio MD, Shay D, Rudolph MI, Santer P, Grabitz SD, Xu X, Nabel S, Bose S, Eikermann M: REsidual neuromuscular block Prediction Score *versus* train-of-four ratio and respiratory outcomes: A retrospective cohort study. Anesth Analg 2021; 133:610–9
54. Berg H, Roed J, Viby-Mogensen J, Mortensen CR, Engbaek J, Skovgaard LT, Krintel JJ: Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised, and blinded study of postoperative pulmonary

complications after atracurium, vecuronium and pancuronium. Acta Anaesthesiol Scand 1997; 41:1095–103
55. Grabitz SD, Rajaratnam N, Chhagani K, Thevathasan T, Teja BJ, Deng H, Eikermann M, Kelly BJ: The effects of postoperative residual neuromuscular blockade on hospital costs and intensive care unit admission: A population-based cohort study. Anesth Analg 2019; 128:1129–36
56. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS: Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. Anesth Analg 2008; 107:130–7
57. Adembesa I, Mung'ayi V, Premji Z, Kamya D: A randomized control trial comparing train of four ratio > 0.9 to clinical assessment of return of neuromuscular function before endotracheal extubation on critical respiratory events in adult patients undergoing elective surgery at a tertiary hospital in Nairobi. Afr Health Sci 2018; 18:807–16
58. Sauer M, Stahn A, Soltesz S, Noeldge-Schomburg G, Mencke T: The influence of residual neuromuscular block on the incidence of critical respiratory events. A randomised, prospective, placebo-controlled trial. Eur J Anaesthesiol 2011; 28:842–8
59. Todd MM, Hindman BJ, King BJ: The implementation of quantitative electromyographic neuromuscular monitoring in an academic anesthesia department. Anesth Analg 2014; 119:323–31
60. Kheterpal S, Vaughn MT, Dubovoy TZ, Shah NJ, Bash LD, Colquhoun DA, Shanks AM, Mathis MR, Soto RG, Bardia A, Bartels K, McCormick PJ, Schonberger RB, Saager L: Sugammadex *versus* Neostigmine for Reversal of Neuromuscular Blockade and Postoperative Pulmonary Complications (STRONGER): A multicenter matched cohort analysis. Anesthesiology 2020; 132:1371–81
61. Krause M, McWilliams SK, Bullard KJ, Mayes LM, Jameson LC, Mikulich-Gilbertson SK, Fernandez-Bustamante A, Bartels K: Neostigmine *versus* sugammadex for reversal of neuromuscular blockade and effects on reintubation for respiratory failure or newly initiated noninvasive ventilation: An interrupted time series design. Anesth Analg 2020; 131:141–51
62. Kirmeier E, Eriksson LI, Lewald H, Jonsson Fagerlund M, Hoeft A, Hollmann M, Meistelman C, Hunter JM, Ulm K, Blobner M; POPULAR Contributors: Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): A multicentre, prospective observational study. Lancet Respir Med 2019; 7:129–40
63. Blobner M, Hunter JM, Meistelman C, Hoeft A, Hollmann MW, Kirmeier E, Lewald H, Ulm K: Use of a train-of-four ratio of 0.95 *versus* 0.9 for tracheal extubation: An exploratory analysis of POPULAR data. Br J Anaesth 2020; 124:63–72
64. Claudius C, Viby-Mogensen J: Acceleromyography for use in scientific and clinical practice: A systematic review of the evidence. Anesthesiology 2008; 108:1117–40
65. Kim KS, Lew SH, Cho HY, Cheong MA: Residual paralysis induced by either vecuronium or rocuronium after reversal with pyridostigmine. Anesth Analg 2002; 95:1656–60, table of contents
66. Fuchs-Buder T, Claudius C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogensen J: 8th International Neuromuscular Meeting: Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: The Stockholm revision. Acta Anaesthesiol Scand 1996; 40:59–74
67. Kopman AF, Kopman DJ: An analysis of the TOFwatch algorithm for modifying the displayed train-of-four ratio. Acta Anaesthesiol Scand 2006; 50:1313–4
68. Iwasaki H, Kurosawa A, Iida T, Sasakawa T, Kanda H: Use of intraoperative neuromuscular monitor reduces the reversal dose of sugammadex: A single-center retrospective study. J Anesth 2020; 34:276–80
69. Merkow RP, Shan Y, Gupta AR, Yang AD, Sama P, Schumacher M, Cooke D, Barnard C, Bilimoria KY: A comprehensive estimation of the costs of 30-day postoperative complications using actual costs from multiple, diverse hospitals. Jt Comm J Qual Patient Saf 2020; 46:558–64
70. Viby-Mogensen J, Claudius C: Evidence-based management of neuromuscular block. Anesth Analg 2010; 111:1–2
71. Eriksson LI: Evidence-based practice and neuromuscular monitoring: It's time for routine quantitative assessment. Anesthesiology 2003; 98:1037–9
72. Donati F: Neuromuscular monitoring: What evidence do we need to be convinced? Anesth Analg 2010; 111:6–8
73. Lien CA, Kopman AF: Current recommendations for monitoring depth of neuromuscular blockade. Curr Opin Anaesthesiol 2014; 27:616–22
74. Hemmerling TM, Le N: Brief review: Neuromuscular monitoring: An update for the clinician. Can J Anaesth 2007; 54:58–72
75. Klein AA, Meek T, Allcock E, Cook TM, Mincher N, Morris C, Nimmo AF, Pandit JJ, Pawa A, Rodney G, Sheraton T, Young P: Recommendations for standards of monitoring during anaesthesia and recovery 2021: Guideline from the Association of Anaesthetists. Anaesthesia 2021; 76:1212–23
76. Dobson G, Chow L, Filteau L, Hurdle H, McIntyre I, Milne A, Milkovich R, Perrault MA, Sparrow K, Swart PA, Wang Y: Guidelines to the practice of anesthesia - Revised edition 2021. Can J Anaesth 2021; 68:92–129
77. Plaud B, Baillard C, Bourgain JL, Bouroche G, Desplanque L, Devys JM, Fletcher D, Fuchs-Buder T, Lebuffe G, Meistelman C, Motamed C, Raft J, Servin

F, Sirieix D, Slim K, Velly L, Verdonk F, Debaene B: Guidelines on muscle relaxants and reversal in anaesthesia. Anaesth Crit Care Pain Med 2020; 39:125–42

78. Alvarez Gómez JA, Ariño Irujo JJ, Errando Oyonarte CL, Matínez Torrente F, Roigé i Solé J, Gilsanz Rodríguez F; Sociedad Española de Anestesiología, Reanimación y Terapéutica del Dolor: Empleo clínico de bloqueantes neuromusculares y su reversión. Recomendaciones del grupo de expertos de la Sociedad Española de Anestesiología, Reanimación y Terapéutica del Dolor [Use of neuromuscular blocking agents and reversal of blockade: Guidelines from Sociedad Española de Anestesiología, Reanimación y Terapéutica del Dolor]. Rev Esp Anestesiol Reanim 2009; 56:616–27
79. Naguib M, Brull SJ, Kopman AF, Hunter JM, Fülesdi B, Arkes HR, Elstein A, Todd MM, Johnson KB: Consensus statement on perioperative use of neuromuscular monitoring. Anesth Analg 2018; 127:71–80
80. Naguib M, Kopman AF, Lien CA, Hunter JM, Lopez A, Brull SJ: A survey of current management of neuromuscular block in the United States and Europe. Anesth Analg 2010; 111:110–9
81. Phillips S, Stewart PA, Bilgin AB: A survey of the management of neuromuscular blockade monitoring in Australia and New Zealand. Anaesth Intensive Care 2013; 41:374–9
82. Söderström CM, Eskildsen KZ, Gätke MR, Staehr-Rye AK: Objective neuromuscular monitoring of neuromuscular blockade in Denmark: An online-based survey of current practice. Acta Anaesthesiol Scand 2017; 61:619–26
83. Naguib M, Brull SJ, Hunter JM, Kopman AF, Fülesdi B, Johnson KB, Arkes HR: Anesthesiologists' overconfidence in their perceived knowledge of neuromuscular monitoring and its relevance to all aspects of medical practice: An international survey. Anesth Analg 2019; 128:1118–26
84. Todd MM, Hindman BJ: The implementation of quantitative electromyographic neuromuscular monitoring in an academic anesthesia department: Follow-up observations. Anesth Analg 2015; 121:836–8