

Residual Paralysis after Emergence from Anesthesia

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SEVERAL studies have documented that neuromuscular block often persists in the postanesthesia care unit (PACU), even with the administration of acetylcholinesterase inhibitors. The frequency of this phenomenon, which has been called “residual curarization,” “residual neuromuscular block,” “postoperative residual curarization,” or “residual paralysis,” ranges between 4 and 50% depending on the diagnostic criteria, the type of nondepolarizing neuromuscular blocking drug (NMBD), the administration of a reversal agent, and, to a lesser extent, the use of neuromuscular monitoring. The problem is obviously clinically relevant, because residual paralysis after emergence from anesthesia (henceforth referred to as residual paralysis) is associated with muscle weakness, oxygen desaturation, pulmonary collapse, and acute respiratory failure that could lead to severe permanent brain damage or death. Despite extensive documentation of such residual paralysis in the literature, awareness of its clinical consequences remains surprisingly limited, and the use of NMBDs, neuromuscular monitoring, and reversal agents are dictated more by tradition and local practices than by evidence-based medicine.

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Residual paralysis is associated with postoperative complications such as hypoxia, weakness, and respiratory failure. However, these complications may have many other causes so that the role of neuromuscular block is often unrecognized. Thus, it is important to manage neuromuscular block rationally and have a sound strategy to prevent, diagnose, and treat residual paralysis. This can be accomplished by adhering to simple and consistent guidelines not only before tracheal extubation but also throughout the surgical procedure. The data in the current literature on residual paralysis were obtained with acetylcholinesterase inhibitors as the only agents available to accelerate neuromuscular recovery. Reassessment of practice in this regard is relevant now that sugammadex, a selective binding agent, has become available in certain parts of the world.

Evolving Definitions of Residual Paralysis

Absence of residual paralysis means that neuromuscular transmission has recovered sufficiently, and so the unaided patient can breathe normally, clear secretions, cough, prevent aspiration of gastric contents, and maintain a patent upper airway. Because this return to complete recovery cannot be assessed easily before emergence from anesthesia and even during the early postanesthesia recovery phase, anesthesiologists have to rely on surrogate measurements. With the introduction, in the early 1970s, of the train-of-four (TOF) stimulation applied to the ulnar nerve, it became necessary to correlate adductor pollicis response to indices of respiratory function (fig. 1). In a study conducted by Ali *et al.*¹ on six healthy awake volunteers, vital capacity, inspiratory force, and expiratory force were found to be normal when TOF ratio (TOFR; the ratio of the fourth to the first twitch height) was more than or equal to 0.70.

Based on that evidence, the 0.7-TOFR threshold was considered to indicate adequate neuromuscular recovery for nearly two decades. However, in the 1990s, several lines of evidence indicated that clinically relevant neuromuscular block still persists at TOFR = 0.7. In human volunteers, hypoxic ventilatory drive was shown to be decreased by vecuronium up to a TOFR more than or equal to 0.9.² In another study, the ability to swallow was also found to be impaired when the TOFR was less than 0.9.³ Masseter muscle function, assessed by the ability to hold a tongue depressor between one's teeth against resistance, did not return to

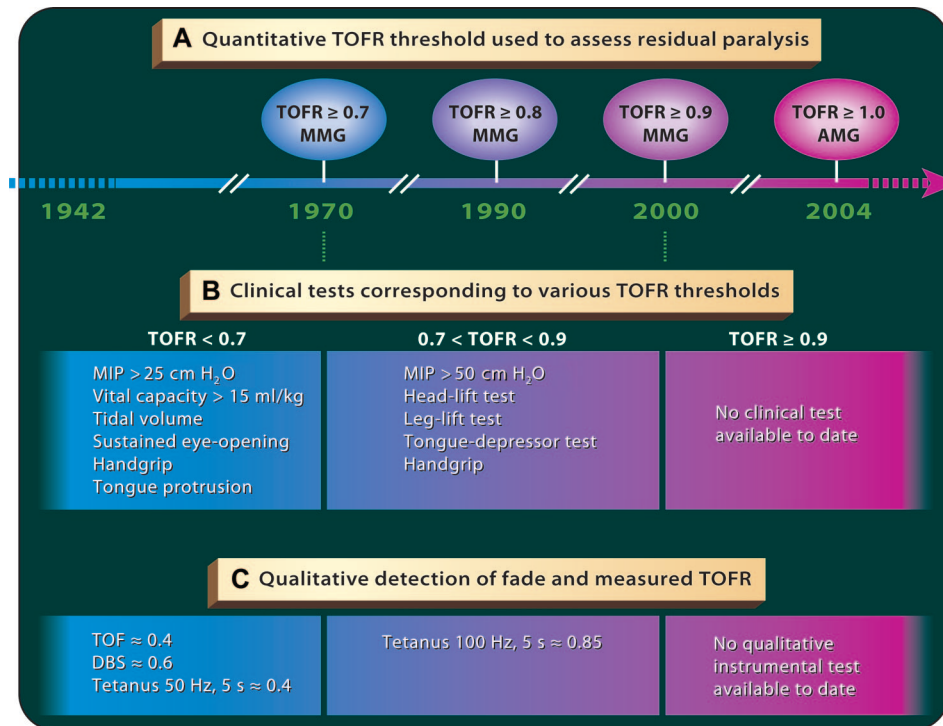


Fig. 1. (A) The evolution, since 1970, of the train-of-four ratio (TOFR) threshold used to define the absence of residual paralysis during emergence. (B) The different clinical tests usually recommended as a function of the TOFR threshold used to define residual paralysis. At present, the TOFR threshold is 0.9–1.0, and no clinical test is able to detect such low-level paralysis. (C) Qualitative instrumental measurements of TOFR at which tests are no longer associated with fade. AMG = acceleromyography; DBS = double-burst stimulation; MIP = maximum inspiratory pressure; MMG = mechanomyography; TOF = train-of-four.

normal unless TOFR equaled 0.8–0.9.⁴ Therefore, a revisited TOFR threshold more than or equal to 0.90, obtained by force measurement or mechanomyography, was proposed in the late 1990s. With the advent of techniques measuring acceleration, or acceleromyography, a TOFR more than or equal to 1.0 was recommended.⁵

Tests to Detect Residual Paralysis

The degree of residual paralysis can be evaluated in different ways: (1) clinical tests requiring the patient's cooperation, which normally can be performed only after emergence; (2) visual or tactile evaluation of responses to TOF or double-burst stimulation (DBS) at the adductor pollicis (qualitative or subjective assessment); and (3) measurement of the TOFR with a device (quantitative or objective measurement).

Clinical Tests

For the conscious and cooperative patient, several clinical tests have been proposed (table 1). Sustained head lift has been studied extensively and was found to correspond to maximum inspiratory pressures ranging from 50 to 53 cm H₂O in unanesthetized volunteers partially paralyzed with *d*-tubocurarine.⁶ However, in volunteers given subparalyzing doses of mivacurium, sustained head lift for 5 s correlated with a measured TOFR ranging from 0.45 to 0.75, lower than the recommended threshold of 0.9.⁴ In patients, the sensitivity of the head-lift test was approximately 10%,

whereas specificity was excellent at 87%,⁷ which indicates that residual paralysis is likely in patients unable to maintain a sustained head lift. More recently, the ability to hold a tongue depressor between one's teeth despite the efforts of someone else to pull it out has been proposed as a more sensitive test.⁴ Volunteers given mivacurium were unable to hold the tongue depressor at a mean TOFR less than 0.86, close to the 0.9 threshold. However, the sensitivity of the tongue-depressor test in patients (13%) was not much higher than that of the head-lift test, but its specificity was higher (90%).⁷ When the head-lift or tongue-depressor tests are "passed," the persistence of a certain degree of residual paralysis cannot be excluded, suggesting that more reliable tests are required. In addition, these clinical tests cannot be performed in the anesthetized patient.

Qualitative Assessment

Tests involving a stimulator and tactile or visual subjective assessment of the clinical observer have been devised (table 1). Several studies documented that visual or tactile evaluation of the TOF responses correlated poorly with measured TOFR.^{8–10} Even experienced observers are unable to detect TOF fade visually or manually when the actual TOFR exceeds 0.4, which means that residual paralysis may be undetected if TOFR is in the range of 0.4 to 0.9.⁷ This zone of blind paralysis can be reduced somewhat with the DBS mode of stimulation. With DBS, fade can be detected visually or

Table 1. Description, Reliability, and Usefulness of Clinical and Neuromuscular Tests to Detect Residual Paralysis

Test	Reliability and Clinical Relevance
Clinical	
Respiratory	
Tidal volume: Recovery of spontaneous breathing	Not reliable. Unchanged even when peripheral muscles are fully paralyzed. ⁶
Vital capacity: Ability to take deep breaths	Not sensitive enough. Unchanged with significant levels of paralysis at peripheral muscles. ⁶
End-tidal carbon dioxide fraction: Return to normal values	Not reliable. Unchanged even when peripheral muscles are fully paralyzed. ⁶
Maximum inspiratory pressure: Ability of the patient to generate > 30–50 cm H ₂ O negative pressure	Not sensitive enough. Significant peripheral muscle paralysis present even at > 60 cm H ₂ O. ⁶
Miscellaneous	
Head- or leg-lift test > 5 s: Ability of the patient to sustain his/her head or leg against gravity for > 5 s	Not sensitive enough. Corresponds to TOFR > 0.6–0.7. ^{4,6} Response might be influenced by pain.
Tongue-depressor test: Ability to hold an object between teeth while someone is trying to remove it	Probably the most reliable clinical test. Corresponds to TOFR > 0.8–0.9. ⁴ Difficult to implement routinely.
Neuromuscular	
Qualitative	
TOF: Visual or tactile evaluation of the number of responses and fade after TOF stimulation of the ulnar nerve	Fade usually missed when TOFR > 0.4. ⁸ Useful to determine the optimal timing of reversal. ³³
DBS: Visual or tactile evaluation of DBS _{3,3} fade at the thumb	Fade usually missed when TOFR > 0.6. ⁹
Tetanus 50 Hz: Visual or tactile evaluation of fade after 50-Hz stimulation for 5 s	Fade usually missed when TOFR > 0.4. ¹²
Tetanus 100 Hz: Visual or tactile evaluation of fade after 100-Hz stimulation for 5 s	When sustained, TOFR is > 0.8–0.9. ¹³ Tetanic stimulation is painful, cannot be applied to the awake patient and leads to exaggerated responses if any stimulation is repeated within 5–10 min.
Quantitative	
Measurement of TOFR: Quantitative measurement of the TOFR at the thumb with AMG (TOF-WATCH™; Schering-Plough®, Kenilworth, NJ) or KMG (NMT™; GE Medical System®, Milwaukee, WI)	Reliable. With the AMG, a TOFR > 1.0 is required to define absence of residual paralysis. To date the gold standard in clinical practice. Probes are fragile when used routinely. KMG has not been validated in large series.

AMG = acceleromyography; DBS = double-burst stimulation; KMG = kinemyography; TOF = train-of-four; TOFR = train-of-four ratio.

manually up to a measured TOFR of 0.6, still well below the desired 0.9 threshold.⁹ The failure of these subjective methods to detect residual paralysis was confirmed more recently.^{7,11} The specificity of those two tests was good

(98–99%), but sensitivity remained poor (11 and 14% for TOF and DBS stimulation, respectively).

Therefore, when fade is detected by tactile or visual means, a certain degree of residual paralysis can be expected

with a high degree of certainty. In one study, residual paralysis (TOFR < 0.9) was present in 92–96% of subjects with demonstrated tactile or visual fade in response to TOF or DBS stimulation (positive predictive value).⁷ However, complete recovery was seen in only half the patients with no fade (negative predictive value, 53–62%).⁷ Hence, it is not surprising that the absence of clinical fade after DBS or TOF stimulation does not mean complete recovery.

Tetanic stimulation has also been used to evaluate residual paralysis. Assessing tetanic fade after a 50-Hz stimulation for 5 s does not provide any more information than TOF, because most observers do not detect tetanic fade when the TOFR is more than 0.4.¹² Tetanic fade after 100-Hz stimulation can be detected at a TOFR of 0.8–0.9, making it a more sensitive test.¹³ However, this stimulation is very painful and must not be used on the awake patient. Also, it produces a posttetanic facilitation period of 5–10 min, during which the response to any test (TOF, DBS, or tetanus) is enhanced, spuriously indicating more recovery than is actually the case. Thus, neither the clinical tests applied after emergence nor the qualitative instrumental tests are sufficiently accurate to detect the absence of residual neuromuscular block.

Quantitative Tests before Emergence

Adequate neuromuscular recovery, defined as an adductor pollicis TOFR more than or equal to 0.90, requires the quantitative evaluation of TOFR, using measurement methods such as acceleration (acceleromyography), electromyography, force (mechanomyography), or displacement (kinemyography; table 1). To be clinically acceptable, these methods must have excellent reproducibility and be simple to use. For many years, mechanomyography at the adductor pollicis was the only technique available in the operating room and the PACU. The TOFR threshold of 0.9 was established with this device. However, mechanomyography instruments are cumbersome and difficult to set up, and so the technique has never gained wide clinical acceptance. Electromyography, which is based on the measurement of electrical activity in muscle, is easier to use and less cumbersome, but it is fragile, expensive, and subject to electrical interference from cautery.

With the introduction of acceleromyography monitors in the mid-1990s, the TOFR can now be quantified objectively in routine daily practice. These monitors are inexpensive, versatile, and relatively easy to set up. However, the limits of agreement are relatively wide¹² between data measured with this device and those obtained with the gold standard, the mechanomyography. The discrepancy between mechanomyography and acceleromyography is particularly important when TOFR is in the 0.9–1.0 range, because TOFR measured by acceleromyography tends to overshoot, displaying values more than 1.0. For example, when the mechanomyography TOFR reached 0.9 after atracurium administration, the corresponding acceleromyography TOFR ranged between 0.86 and 1.0 (mean 0.95).⁵ The negative predictive

values of acceleromyography TOFRs of 0.9, 0.95, and 1.0 to detect residual paralysis were 37, 70, and 97%, respectively. Therefore, to detect residual paralysis reliably with acceleromyography, recovery of a TOFR of 0.9 is considered insufficient, and a threshold of 1.0 is now recommended to confirm complete recovery from neuromuscular block.

Quantitative Tests after Emergence

Objective tests (table 1) of neuromuscular recovery can be applied to the awake patient in the PACU, but the response is not as reliable as in anesthetized subjects, because TOFR measurements can be affected by spontaneous movements of the thumb. Thus, the values obtained with two successive measurements may vary substantially. In one study,¹⁴ the evoked thumb response was measured by acceleromyography after TOF stimulation in 253 patients after their arrival in the PACU. Current intensity was set at 30 mA, instead of the 50–70 mA commonly used in anesthetized subjects, to limit discomfort. Two TOF stimulations were applied successively and recorded at a 30-s interval. The first TOFR measurement indicated adequate neuromuscular recovery in 175 patients (TOFR \geq 0.9), but for 40 of them, the second TOFR was less than 0.9. In the 78 patients considered to be partially paralyzed after the first measurement (first TOFR < 0.9), 21 of them had a second TOFR more than or equal to 0.9. In other words, the two TOFRs were discordant in 61 patients (24%). Based on that study, it can be concluded that two isolated acceleromyography TOFR do not accurately represent the patient's neuromuscular status and that repeated measurements (> 2) are needed.

Frequency of Residual Paralysis after Emergence

The residual paralysis rate after emergence has been extensively evaluated during the last 30 yr with global frequencies ranging from 5 to more than 85%. This wide variability can be explained by substantial methodologic differences among those studies.

Evolving Criteria

Residual paralysis was first documented in the late 1970s, when the threshold for neuromuscular recovery was considered to be a TOFR more than 0.7. It is not surprising that later studies based on a higher TOFR threshold detected a greater frequency of residual paralysis. For example, in a study published in 2003, 526 patients received a single intubating dose (2 \times the ED₉₅) of atracurium, vecuronium, or rocuronium. At the end of the procedure, which lasted 1–4 h, 16% had a TOFR less than 0.7 but as many as 45% had a TOFR less than 0.9.⁷ In another study involving the same NMBDs (148 patients), the rate of residual paralysis reached 41% based on a TOFR value of 0.7 and 52% when 0.8 was considered as the threshold for recovery.¹⁵ In patients receiving pancuronium, the frequency of residual paralysis, defined as a TOFR less than 0.7, was less (40%) than if defined as a

TOFR less than 0.9 (85%).¹⁶ With rocuronium, the percentages were lower, but the difference between the threshold of 0.7 (6%) and 0.9 (29%) persisted.¹⁶

Duration of Action of NMBDs

The longer the duration of NMBD action, the higher the frequency of residual paralysis, regardless of the TOFR threshold chosen.¹⁷ In a nonrandomized study, residual paralysis, defined as a TOFR less than 0.7 in the PACU, was more frequent in patients given pancuronium (36%; 17/47) than in those who had received atracurium (4%; 2/46) or vecuronium (8%; 5/57).¹⁸

Maintenance of Neuromuscular Block: Bolus or Infusion

It seems that patients receiving NMBDs by infusion are more likely to have residual paralysis. In 150 patients given atracurium or vecuronium, 100 received the NMBD as repeated boluses and 50 others by continuous infusion.¹⁹ Neostigmine reversal was administered to 97% of cases. Residual paralysis, defined as a TOFR less than 0.7, was found in 12% of the bolus group patients and in 24% of the infusion group patients on arrival in the PACU. Fifteen minutes later, the problem persisted in 2 and 12%, respectively. These observations suggest that continuous infusion of NMBDs can increase the risk of residual paralysis at emergence.

Neuromuscular Monitoring during Anesthesia

The usefulness of intraoperative neuromuscular monitoring to reduce the frequency of residual paralysis on arrival in the PACU remains a matter of debate. The results of a recent meta-analysis indicated that the use of an intraoperative neuromuscular function monitor was not associated with a decrease of the residual paralysis rate.¹⁷ However, that study included a number of uncontrolled trials. When analyzing only studies with adequate methodology, based on a Jadad score more than or equal to 3 (*i.e.*, at least a randomized controlled trial and description of withdrawals), only five articles met these criteria and four of them demonstrated a benefit of preoperative neuromuscular transmission monitoring to decrease the residual paralysis rate, whereas only one showed the opposite.^{10,20–22} The usefulness of perioperative acceleromyography monitoring was evaluated between on two groups of patients given pancuronium and neostigmine reversal with monitoring ($n = 19$) or without ($n = 21$).²¹ Acceleromyographic TOFR were measured for both groups after extubation. The TOFR was less than 0.7 for 11/21 (52%) unmonitored patients, whereas only 1/19 (5%) monitored had a TOFR less than this threshold.

A benefit of intraoperative monitoring was also found with intermediate-acting NMBDs. In a prospective, randomized, and double-blind study, the degree of residual paralysis after rocuronium use was compared between unmonitored and acceleromyography-monitored patients (80 patients in each group).²⁰ Residual muscle paralysis, defined as a TOFR less than 0.8, was found in 16.7% of the unmoni-

tored and 3% of the monitored group. Therefore, the problem of residual paralysis can apparently be minimized by neuromuscular monitoring but cannot be definitively excluded. Finally, it was recently demonstrated in a randomized study that the incidence of incomplete neuromuscular recovery was less with quantitative (acceleromyography) than with qualitative (visual assessment of TOF) monitoring.²³

Use of Reversal

Obviously, reversal of nondepolarizing neuromuscular block seems to be one of the critical steps in reducing or to eliminating residual paralysis. To date, no prospective, randomized, and double-blinded studies have compared the rates of residual paralysis between two therapeutic arms: reversal *versus* placebo. Therefore, the efficacies of different reversal strategies can only be assessed indirectly by analysis of the existing literature.

In one study involving 148 patients receiving intermediate-duration nondepolarizing NMBDs, 101 received no reversal, whereas the remaining 74 patients received neostigmine, but the allocation was not randomized.¹⁵ Residual paralysis defined as a TOFR of less than 0.8 was found in 48% of patients who received neostigmine compared with 59% in those who did not. The difference was not statistically different. Indirect evidence of the efficacy of reversal agents can be estimated by comparing the results of Bevan *et al.*¹⁸ with those obtained by Baillard *et al.*²⁴ In the former study, 58% of 103 anesthetized patients paralyzed with either atracurium or vecuronium were given either neostigmine or edrophonium reversal, and the frequency of residual paralysis, defined as a TOFR less than 0.7, was 7%.¹⁸ In the latter study, 568 patients received vecuronium, and no subsequent reversal, and residual paralysis, defined with the same criteria, was detected in 42% of subjects.²⁴

Clinical Consequences of Residual Paralysis

The physiologic consequences of residual paralysis, such as respiratory impairment,^{1,2} upper airway collapse,^{4,6} and abnormal swallowing,³ are well documented, but the vast majority of the studies were conducted on nonanesthetized healthy volunteers in controlled conditions. However, a direct link between such residual paralysis and poorer outcome is difficult to establish, because many other factors can contribute to respiratory complications after a procedure (*i.e.*, residual effects of other anesthetic agents, type of procedure, comorbidities, and duration of the procedure). However, the adverse effects of residual paralysis after emergence have been documented in clinical studies (table 2). Some of them demonstrated poorer outcomes for anesthetized patients in terms of postoperative morbidity and mortality when residual paralysis persisted.

Thus, residual paralysis is an unwanted side effect in the immediate postoperative period and a risk factor for respira-

Table 2. Clinically Relevant Complications Associated with Residual Paralysis after Emergence from Anesthesia

Type of Complication	Reference(s)	Key Messages
Death or permanent brain damage	Tiret <i>et al.</i> ²⁷	Postanesthetic respiratory depression the most frequent cause of death attributable to anesthesia. Role of NMBDs cannot be established because of the absence of neuromuscular monitoring.
	Lunn <i>et al.</i> ²⁵ Cooper <i>et al.</i> ²⁶	Possible relation between postanesthetic respiratory depression and neuromuscular blockade was mentioned.
	Arbous <i>et al.</i> ²⁸	Deaths due to anesthesia increased 10-fold when reversal neuromuscular block was omitted.
Pulmonary complications	Berg <i>et al.</i> ³⁰	Three-fold increase of the rate of atelectasis in patients receiving long-acting NMBDs with residual paralysis at emergence.
Upper airway obstruction, severe hypoxemia (SpO ₂ < 90%), or respiratory failure necessitating emergency tracheal reintubation	Murphy <i>et al.</i> ^{23,29}	Incomplete neuromuscular recovery is an important factor contributing to the development of adverse respiratory events in the PACU.

NMBDs = neuromuscular blocking drugs; PACU = postanesthesia care unit.

tory complications. That risk could be decreased by the systematic use of neuromuscular monitoring and judicious administration of reversal agents.

Death or Permanent Brain Damage

Lunn *et al.*²⁵ demonstrated 25 yr ago in a survey based on anonymous reporting of deaths within the first 6 days after anesthesia that 11/32 (34%) deaths attributed entirely to anesthesia were caused, at least in part, by postoperative respiratory failure. Residual paralysis was considered to be contributory in six of those deaths (table 2). During the same decade, Cooper *et al.*²⁶ reported on the causes of unexpected admission to the intensive care unit because of a complication of anesthesia during a 5-yr period. There were 53 cases, and the mortality rate was 17%. The majority (33 of 53) of complications occurred in the recovery period. Twenty-four of these 33 cases were due to ventilatory inadequacy after reversal of neuromuscular block. Tiret *et al.*²⁷ conducted a French national survey on anesthesia-associated mortality by retrospectively analyzing 200,000 anesthesia procedures and found that half of the 67 anesthesia-associated deaths resulted from postanesthesia respiratory depression. More recently, a list of risk factors, directly related to anesthesia management and considered to be responsible for postoperative mortality and severe morbidity detected in the first 24 h, were identified.²⁸ Among them, omitting to reverse a residual block was associated with a 10-fold increased risk for

death or coma. This finding provides indirect evidence that residual paralysis could be implicated in death and severe morbidity.

Respiratory Complications

Direct evidence of morbidity associated with residual paralysis during emergence has been demonstrated after pancuronium administration. In a randomized study, the frequency of residual paralysis, defined as a TOFR of less than 0.9, was significantly higher in patients given pancuronium (85%) than those administered rocuronium (29%).¹⁶ Hypoxemia (defined as SpO₂ < 93%) in the PACU was found more frequently in patients who had received pancuronium. An association between residual paralysis (TOFR < 0.9) and postoperative hypoxemia was demonstrated.²⁹ According to a large controlled study on 693 patients randomized to receive pancuronium, vecuronium, or atracurium for abdominal, gynecological, or orthopedic surgery, respectively, a potential risk factor for development of postoperative pulmonary complications, defined as atelectasis on chest x-ray 2 days after surgery, was identified as a TOFR less than 0.7 on arrival in the PACU after pancuronium administration.³⁰ Significantly, more of those patients with residual paralysis developed postoperative pulmonary complications (17%; 10/59) when compared with patients without such residual paralysis (5%; 8/167). These findings demonstrate

that residual paralysis on arrival in the PACU increases the risk of subsequent pulmonary morbidity.

Avoiding Residual Paralysis

To summarize, the evidence suggests that undetected residual paralysis during emergence from anesthesia is common and may have deleterious clinical consequences. Although detection and treatment of residual paralysis are achieved with neuromuscular monitoring and/or reversal of block, surveys have shown that adherence to these principles is relatively poor. For example, a national survey conducted in France showed that 50% of anesthesiologists never use a peripheral nerve stimulator, and only 32% systematically or frequently administered an acetylcholinesterase inhibitor³¹ when an NMBD had been given. Thus, residual paralysis occurs probably more frequently in actual practice than in studies where monitoring and the use of reversal agents were standardized. It follows that it is essential to change clinicians' approach to the management of residual paralysis, and this constitutes a safety issue. To avoid residual paralysis, we must focus on management during anesthesia. No one-size-fits-all solutions are available, but a number of strategies can be applied depending on the type of procedure and the patient's medical status.

Evaluate the Real Need for NMBDs

A nondepolarizing NMBD should not be given when the procedure can be performed without paralysis and the airway secured using a supraglottic device, such as a laryngeal mask airway. However, NMBDs improve the quality and ease of tracheal intubation and lead to less subsequent laryngeal morbidity. Thus, neuromuscular block is recommended for tracheal intubation, even if relaxation is not required for surgery. If the duration of the procedure is short, succinylcholine can be an alternative to nondepolarizing NMBDs but exposes the patient to that drug's adverse effects.

Some authors have studied the usefulness of a low dose nondepolarizing NMBD ($< 2 \times$ the ED_{95}) to improve the quality of tracheal intubation,³² but the impact of this strategy on the frequency of residual paralysis at the end of the procedure has never been evaluated. When a high dose (*i.e.*, $2 \times$ the ED_{95}) of intermediate-acting nondepolarizing NMBD, for example, rocuronium, atracurium, and vecuronium, is administered to facilitate tracheal intubation, clinicians must be aware that an interval exceeding 2 h from NMBD injection to the arrival in the PACU does not guarantee an absence of residual paralysis,⁷ highlighting the need, before extubation, for neuromuscular monitoring and reversal, if needed.

If the Procedure Requires a Neuromuscular Block

When muscle paralysis is necessary during a procedure, the choice of the drug is based on the planned duration and the patient's medical status. Regardless of the duration of the procedure, long-acting NMBDs, such as pancuronium, should be avoided because the residual paraly-

sis rate on arrival in the PACU is particularly high.^{16–18,30} For short procedures, mivacurium can be a valuable option. However, mivacurium is no longer available in North America.

Because the steroidal compounds are eliminated *via* liver and/or kidney, benzyloquinolines, such as atracurium or *cis*-atracurium, seem to be a better choice for patients with liver or renal insufficiency. Bolus administration of NMDBs should be preferred to infusions because the residual paralysis rate is higher with the latter.¹⁹ Halogenated agents lower the dose of the nondepolarizing NMBD required and prolong their duration of action. To decrease the frequency of residual paralysis, intravenous anesthesia could theoretically be more appropriate than inhaled anesthesia. However, the frequency of residual paralysis associated with these two anesthesia regimens has never been compared in a well-designed study.

Prevention of hypothermia is essential because it increases the duration action of NMBDs. Although the usefulness of intraoperative neuromuscular monitoring to lower the frequency of residual remains a matter of debate,¹⁷ it seems easier and more convenient to use a nerve stimulator to adjust the degree of block during the procedure, to detect residual paralysis during emergence and assess the need for reversal.

Management at Emergence from Anesthesia

During emergence, the focus should be on preventing residual paralysis. Two options are available: (1) allowing spontaneous recovery or (2) reversing neuromuscular block with an acetylcholinesterase inhibitor or selective binding relaxant.

Spontaneous Recovery. If spontaneous recovery is chosen, there should be solid evidence that neuromuscular function has returned to a TOFR of more than or equal to 0.9 before tracheal extubation. As discussed earlier, none of the traditional clinical tests and qualitative neuromuscular tests can accurately and reliably indicate a return to a TOFR of more than or equal to 0.9. Hence, it is easier and more convenient to use objective monitoring, such as an acceleromyography device, if reversal is to be omitted. Time is not a guarantee of recovery: residual paralysis can persist more than or equal to 4 h after an intubating dose of rocuronium, vecuronium, or atracurium is given.⁷

Using a Reversal Agent. After administration of a nondepolarizing NMBD, a neuromuscular monitoring device helps greatly in deciding whether to inject a reversal agent: acetylcholinesterase inhibitors or sugammadex. Acetylcholinesterase inhibitors block the enzyme acetylcholinesterase, which normally hydrolyzes acetylcholine at the neuromuscular junction. As a result, more acetylcholine competes with the nondepolarizing NMBD for access to the receptors, so that some neuromuscular function is restored. However, the efficacy of acetylcholinesterase inhibitors is limited, because their maximum effect is reached when enzyme inhibition approaches 100%. Clinically, this ceiling effect is probably reached at neostigmine doses of 0.04–0.07 mg/kg or equiv-

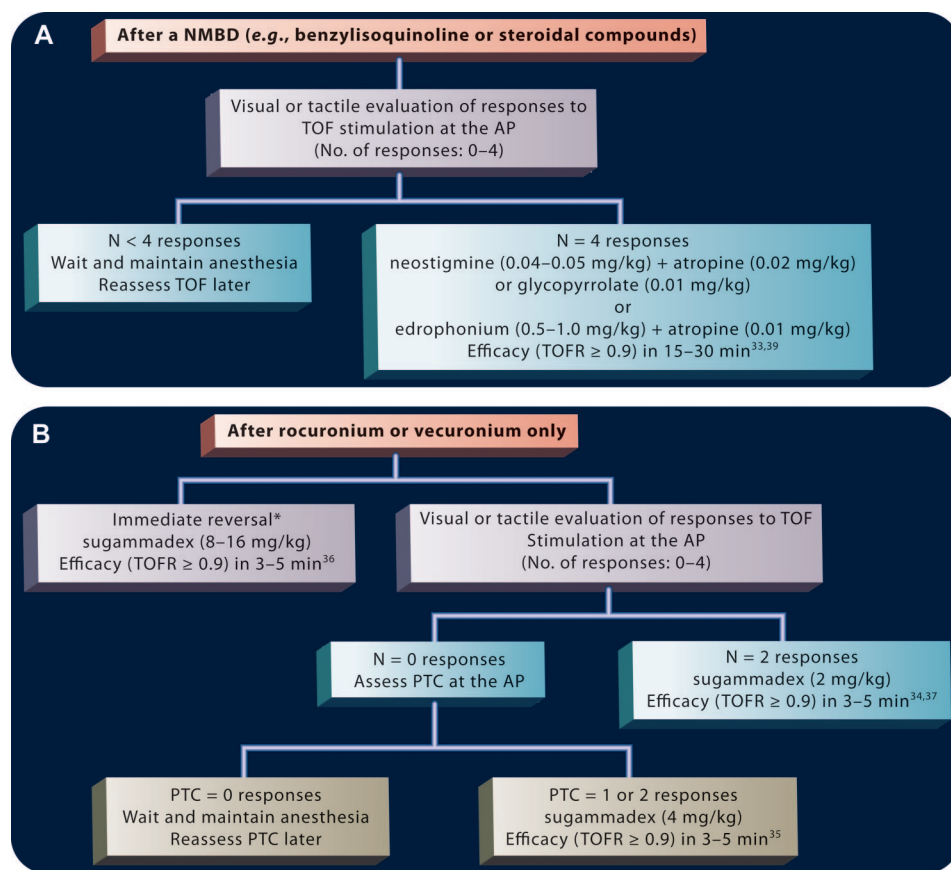


Fig. 2. Proposed decision algorithm for reversal of residual paralysis during emergence taking into account the level of neuromuscular block at that time visually or tactilely estimated with train-of-four (TOF) stimulation at the adductor pollicis (AP) and available reversal agent: (A) acetylcholinesterase inhibitor combined with an anticholinergic agent or (B) sugammadex alone. Before TOF ratio (TOFR) estimation, check the neuromuscular monitor (e.g., electrode positions and polarity, current intensity ≥ 40 mA) and central temperature (e.g., $\geq 36.5^\circ\text{C}$). When available and regardless of the therapeutic decision, quantitative assessment of TOFR is recommended. NMBD = nondepolarizing neuromuscular blocking drug; PTC = posttetanic count. * This situation has only been tested with rocuronium.

alent. This phenomenon implies that acetylcholinesterase inhibitors are not effective when the block is too intense. Therefore, it is essential to wait until some degree of spontaneous recovery has been achieved before administering the acetylcholinesterase inhibitor. Time to adequate recovery (TOF ≥ 0.9) declines from a median of 22 min, when if only one twitch is visible, to 16 min when four twitches are visible.³³ Thus, it is now recommended to wait until four twitches are visible before giving neostigmine (fig. 2A). Giving higher doses when block is intense is not effective because of the ceiling effect.

Acetylcholinesterase inhibitors also have cholinergic effects, notably bradycardia, and increased volumes of salivary and bronchial secretions. These actions can be counteracted by anticholinergic drugs, such as atropine or glycopyrrolate. However, administration of the mixture is associated with an increased frequency of arrhythmias.

Another approach can be proposed to obtain block reversal. Instead of providing more acetylcholine at the neuromuscular junction, a substance that binds selectively to the NMBD has been developed. This drug, called sugammadex, is a γ -cyclodextrin, which is a ring composed of sugars, that

selectively binds rocuronium and has a somewhat weaker affinity for vecuronium and pancuronium. Sugammadex is an abbreviation of sugar and γ -cyclodextrine. It does not bind to other classes of NMBDs, such as succinylcholine, atracurium, *cis*-atracurium, and doxacurium. At the time of writing, sugammadex had been approved for marketing in Europe, Australia but not in North America.

The main advantages of sugammadex are its rapid speed of recovery with minimal interindividual variation regardless of block level and finally lack of cholinergic side effects. In addition, it achieves recovery to TOFR more than or equal to 0.9 rapidly (3–5 min), when the appropriate dose is given. However, the sugammadex dose required depends on intensity of the block. When two twitches are visible after a TOF stimulation at the ulnar nerve, 2 mg/kg should suffice.³⁴ For more profound blocks, at reappearance of a posttetanic count of 1–2 at the adductor pollicis, 4 mg/kg is usually needed,³⁵ and as much as 8–16 mg/kg can be required if sugammadex is given a few minutes after an intubating dose of rocuronium (0.9–1.2 mg/kg; fig. 2B).³⁶ With vecuronium block, the sugammadex dose is approximately the same as with rocuronium.³⁷ No data are available for pancuronium.

Sugammadex is not effective against other NMBDs. Because the sugammadex dose depends on the level of block, it is strongly recommended to monitor neuromuscular function before and after its administration to determine the dose and evaluate its efficacy. Regardless of the strategy selected (spontaneous recovery or reversal), measured TOFR more than or equal to 0.9 is required before tracheal extubation.

Conclusion

Residual paralysis is an anesthetic complication that can be avoided by careful management. As an example, a 10-yr survey in a single hospital demonstrated that a well-implemented strategy based on promotion of neuromuscular monitoring and reversal led to a dramatically decreased residual paralysis rate in the PACU.³⁸ From 1995 to 2004, patients receiving intermediate-acting NMBDs were prospectively studied during 3-month period in 1995 (n = 435), 2000 (n = 130), 2002 (n = 101), and 2004 (n = 218). In 1995, quantitative measurement of neuromuscular block was performed in only 2% of cases, and 6% of patients received reversal agents. In 2005, corresponding figures were 60 and 42%, respectively. During the same time period, the frequency of residual paralysis, defined as a TOFR less than 0.9, decreased from 63 to only 3%, demonstrating that the systematic application of simple measures can make a difference.

References

1. Ali HH, Wilson RS, Savarese JJ, Kitz RJ: The effects of tubocurarine on indirect elicited train-of-four muscle responses and respiratory measurements in humans. *Br J Anaesth* 1975; 47:570-4
2. Eriksson LI, Lennmarken C, Wyon N, Johnson A: Attenuated ventilatory response to hypoxaemia at vecuronium-induced partial neuromuscular block. *Acta Anaesthesiol Scand* 1992; 36:710-5
3. Sundman E, Witt H, Olsson R, Ekberg O, Kuilenstierna R, Eriksson LI: The incidence and mechanism of pharyngeal and upper esophageal dysfunction in partially paralyzed humans. Pharyngeal videoradiography and simultaneous manometry after atracurium. *ANESTHESIOLOGY* 2000; 92:977-84
4. Kopman AF, Yee PS, Neuman GG: Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. *ANESTHESIOLOGY* 1997; 86:765-71
5. Capron F, Alla F, Hottier C, Meistelman C, Fuchs-Buder T: Can acceleromyography detect low levels of residual paralysis? *ANESTHESIOLOGY* 2004; 100:1119-24
6. Pavlin EG, Holle RH, Schoene R: Recovery of airway protection compared with ventilation in humans after paralysis with curare. *ANESTHESIOLOGY* 1989; 70:381-5
7. Debaene B, Plaud B, Dilly MP, Donati F: Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. *ANESTHESIOLOGY* 2003; 98:1042-8
8. Viby-Mogensen J, Jensen NH, Engbaek J, Ording H, Skovgaard LT, Chraemer-Jorgensen B: Tactile and visual evaluation of response to train-of-four nerve stimulation. *ANESTHESIOLOGY* 1985; 63:440-3
9. Drenck NE, Ueda N, Olsen NV, Jensen E, Skovgaard LT, Viby-Mogensen J: Manual evaluation of residual curarization using double burst stimulation: A comparison with train-of-four. *ANESTHESIOLOGY* 1989; 70:578-81
10. Fruergaard K, Viby-Mogensen J, Berg H, el-Mahdy AM:

- Tactile evaluation of the response to double burst stimulation decreases, but does not eliminate, the problem of postoperative residual paralysis. *Acta Anaesthesiol Scand* 1998; 42:1168-74
11. Samet A, Capron F, Alla F, Meistelman C, Fuchs-Buder T: Single acceleromyographic train-of-four, 100-Hertz tetanus or double-burst stimulation: Which test performs better to detect residual paralysis? *ANESTHESIOLOGY* 2005; 102:51-6
 12. Capron F, Fortier LP, Racine S, Donati F: Tactile fade detection with hand or wrist stimulation using train-of-four, double-burst stimulation, 50-hertz tetanus, 100-hertz tetanus, and acceleromyography. *Anesth Analg* 2006; 102:1578-84
 13. Baurain MJ, Hennart DA, Godschalx A, Huybrechts I, Nasrallah G, d'Hollander AA, Cantraine F: Visual evaluation of residual curarization in anesthetized patients using one hundred-hertz, five-second tetanic stimulation at the adductor pollicis muscle. *Anesth Analg* 1998; 87:185-9
 14. Baillaud C, Bourdieu S, Le Toumelin P, Ait KF, Riou B, Cupa M, Samama CM: Assessing residual neuromuscular block using acceleromyography can be deceptive in postoperative awake patients. *Anesth Analg* 2004; 98:854-7
 15. Hayes AH, Mirakhor RK, Breslin DS, Reid JE, McCourt KC: Postoperative residual block after intermediate-acting neuromuscular blocking drugs. *Anaesthesia* 2001; 56:213-8
 16. Murphy GS, Szokol JW, Franklin M, Marymont JH, Avram MJ, Vender JS: Postanesthesia care unit recovery times and neuromuscular blocking drugs: A prospective study of orthopedic surgical patients randomized to receive pancuronium or rocuronium. *Anesth Analg* 2004; 98:193-200
 17. Naguib M, Kopman AF, Ensor JE: Neuromuscular monitoring and postoperative residual curarisation: A meta-analysis. *Br J Anaesth* 2007; 98:302-16
 18. Bevan DR, Smith CE, Donati F: Postoperative neuromuscular block: A comparison between atracurium, vecuronium, and pancuronium. *ANESTHESIOLOGY* 1988; 69:272-6
 19. Fawcett WJ, Dash A, Francis GA, Liban JB, Cashman JN: Recovery from neuromuscular block: Residual curarisation following atracurium or vecuronium by bolus dosing or infusions. *Acta Anaesthesiol Scand* 1995; 39:288-93
 20. 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
 21. Mortensen CR, Berg H, El-Mahdi A, Viby-Mogensen J: Perioperative monitoring of neuromuscular transmission using acceleromyography prevents neuromuscular block following pancuronium. *Acta Anaesthesiol Scand* 1995; 39:797-801
 22. 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 block? *ANESTHESIOLOGY* 1990; 73:835-9
 23. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS, Nisman M: Intraoperative acceleromyographic monitoring reduces the risk of residual neuromuscular block and adverse respiratory events in the postanesthesia care unit. *ANESTHESIOLOGY* 2008; 109:389-98
 24. Baillaud C, Gehan G, Reboul-Marty J, Larmignat P, Samama CM, Cupa M: Residual curarization in the recovery room after vecuronium. *Br J Anaesth* 2000; 84:394-5
 25. Lunn JN, Hunter AR, Scott DB: Anaesthesia-related surgical mortality. *Anaesthesia* 1983; 38:1090-6
 26. Cooper AL, Leigh JM, Tring IC: Admissions to the intensive care unit after complications of anaesthetic techniques over 10 years. 1. The first 5 years. *Anaesthesia* 1989; 44:953-8
 27. Tiret L, Desmonts JM, Halton F, Vourc'h G: Complications associated with anaesthesia: A prospective survey in France. *Can J Anesth* 1986; 33:336-44
 28. Arbous MS, Meursing AEE, van Kleef JW, de Lange JJ, Spoomans HHJM, Touw P, Werner FM, Grobbee DE: Impact of anesthesia management characteristics on severe morbidity and mortality. *ANESTHESIOLOGY* 2005; 102:257-68
 29. Murphy GS, Szokol JW, Marymont JH, Greenberg SB,

- Avram MJ, Vender JS: Residual neuromuscular block and critical respiratory events in the postanesthesia care unit. *Anesth Analg* 2008; 107:130-7
30. Berg H, Viby-Mogensen J, Roed J, Mortensen CR, Engbaek J, Skovgaard LT, Krintel JJ: Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomized and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. *Acta Anaesthesiol Scand* 1997; 41:1095-103
31. Duvaldestin P, Cunin P, Plaud B, Maison P: French survey of neuromuscular relaxant use in anaesthetic practice in adults. *Ann Fr Anesth Réanim* 2008; 27:483-9
32. Kopman AF, Klewicka MM, Neuman GG: Reexamined the recommended endotracheal intubating dose for nondepolarizing neuromuscular blockers of rapid onset. *Anesth Analg* 2001; 93:954-9
33. Kirkegaard H, Heier T, Caldwell J: Efficacy of tactile-guided reversal from cisatracurium-induced neuromuscular block. *ANESTHESIOLOGY* 2002; 96:45-50
34. Sorgenfrei IF, Norrild K, Larsen PB, Stensballe J, Ostergaard D, Prins ME, Viby-Mogensen J: Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex: A dose-finding and safety study. *ANESTHESIOLOGY* 2006; 104:667-74
35. Jones RK, Caldwell JE, Brull SJ, Soto RG: Reversal of profound rocuronium-induced block with sugammadex: A randomized comparison with neostigmine. *ANESTHESIOLOGY* 2008; 109:816-24
36. Pühringer FK, Rex C, Sielenkämper AW, Claudius C, Larsen PB, Prins ME, Eikermann M, Khuenl-Brady KS: Reversal of profound, high-dose rocuronium-induced neuromuscular block by sugammadex at two different time points: An international, multicenter, randomized, dose-finding, safety assessor-blinded, phase II trial. *ANESTHESIOLOGY* 2008; 109:188-97
37. Suy K, Morias K, Cammu G, Hans P, van Duijnhoven WG, Heeringa M, Demeyer I: Effective reversal of moderate rocuronium- or vecuronium-induced neuromuscular block with sugammadex, a selective relaxant binding agent. *ANESTHESIOLOGY* 2007; 106:283-8
38. Baillard C, Clec'h C, Catineau J, Salhi F, Gehan G, Cupa M, Samama CM: Postoperative residual neuromuscular block: A survey for management. *Br J Anaesth* 2005; 95:622-6
39. Hennart D, D'Hollander A, Plasman C, De Jonckheere. Importance of the level of paralysis recovery for a rapid antagonism of atracurium neuromuscular blockade with moderate doses of edrophonium. *ANESTHESIOLOGY* 1986; 64:384-7