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Neuromuscular monitoring: Old issues, new controversies

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Abstract "Expert" editorial opinion suggests that objective or quantitative neuromuscular monitors should be used whenever nondepolarizing blocking agents are administered. It is clear that this advice has by and large fallen on deaf ears. A sizeable number of clinicians here (North America) and abroad (Europe) fail to use even conventional peripheral nerve stimulators routinely. This chapter will explore potential reasons for and consequences of this disconnect between academia and "the real world." Along the way, we will examine such questions as how do we define and measure adequate recovery from nondepolarizing block. What are the limitations of clinical tests of recovery such as the "head-lift test?" What is the incidence of undetected postoperative residual curarization (PORC)? Does neuromuscular monitoring reduce the frequency of PORC? How will the availability of sugammadex alter the above discussion?

1. Introduction

Five years ago, an editorial in *Anesthesiology* opined: "… it is time to move from discussion to action and introduce objective neuromuscular monitoring in all operating rooms, not just those occupied by researchers and aficionados of muscle relaxants. …objective neuromuscular monitoring is an evidence-based practice and should consequently be used whenever a nondepolarizing neuromuscular blocking agent is administered [1]." By "objective," the author meant the use of monitors that measured and displayed the train-of-four (TOF) ratio in real time. A similar editorial call for objective or quantitative monitoring in the *British Journal of Anaesthesia* appeared 3 years earlier with the dictum that "At a minimum, the clinician should always monitor the extent of neuromuscular recovery using objective means, whenever nondepolarizing neuromuscular block is not antagonized [2]."

Although these opinions probably represent the position of most academic neuromuscular "experts," it is clear that in the real world of day-to-day practice, these suggestions have been widely ignored. A recent survey in the United Kingdom found that 62% of clinicians never use a peripheral nerve stimulator of any kind, and less than 10% used an objective monitor on a routine basis [3]. Studies from Denmark [4], Germany [5], and Mexico [6] report that routine monitoring of neuromuscular function was used by only 43%, 28%, and 2% of clinicians, respectively. This disconnect between editorial opinion and actual clinical practice raises a question of some importance. Is there a standard of care regarding the administration of neuromuscular blockers that anesthesia providers should be held to? The American Society of Anesthesiologists offers no help. Their publication "standards for basic anesthesia monitoring"[1] makes no mention of neuromuscular monitoring. This is a little strange because the

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mission statement of the ASA that appears on the organization's Web site states: "The ASA is an educational, research, and scientific association…organized to raise and maintain the standards of the medical practice of anesthesiology and improve the care of the patient."

Does the failure to monitor neuromuscular function have clinical consequences? In the absence of any "official" guidance, a review of this question still seems relevant 50 years after the intraoperative use of nerve stimulators was first suggested [7]. A prerequisite for this discussion is an understanding of how satisfactory recovery from neuromuscular block is now measured.

2. How do we define adequate recovery of neuromuscular function?

2.1. Clinical tests

In the decade after the introduction of d-tubocurarine into anesthesia practice, the clinician's ability to recognize residual neuromuscular block in the postoperative period was very limited. In a 1959 review on the then current state of the art of muscle relaxants, Cullen [8] wrote "In the absence of any ventilatory effort by the patient, no assessment (except by history) can be made of the cause for the apnea." Nevertheless, in that year, Bendixen et al [9] suggested maximal negative inspiratory force was a useful measure of ventilatory capacity and might represent a "vital capacity measurement in the unconscious." Early attempts at defining bedside criteria for tracheal extubation and the discontinuation of mechanical ventilation were usually derived from tests of pulmonary function of patients in an ICU setting [10]. Thus, then widely accepted criteria such as the ability to generate a peak negative inspiratory force of minus 25 to 30 cm H_2O may have had applicability to the unparalyzed patient recuperating from parenchymal pulmonary disease but probably should not have been applied to healthy individuals recovering from nondepolarizing neuromuscular block. In addition, tests of pulmonary function were often impossible to use in the clinical setting.

Clinicians needed a practical bedside test of muscle strength that was simple to use in day-to-day practice. The criteria that achieved the widest acceptance was the "5-second head lift." The concept for this test may be traced back to the initial animal studies of d-tubocurarine by E.R. Squibb pharmaceuticals [11]. Drug potency was assayed by the rabbit head-drop test. The end point of the test was relaxation of the neck muscles to such a degree that the animal's head could not be raised or turned in response to a physical stimulus. It is not clear who first suggested that this test had clinical applicability, but in 1961, Dam [12] wrote "…the muscles of the neck are among the first to be influenced by the paralyzing action of muscle relaxants as shown by the fact that conscious subjects when given small doses of curare, which do not cause respiratory embarrassment are often unable to lift the head from the pillow." Shortly thereafter, Johansen et al [13] suggested that the "head lift" was a more sensitive test of neuromuscular recovery than either inspiratory/expiratory flows or pressures. Several years later, Pavlin et al [14] were able to demonstrate in 6 healthy volunteers that all subjects who could accomplish a head lift (HL) could perform airway protective measures (ability to swallow, perform a Valsalva maneuver, prevent airway obstruction). Head lift occurred at an average maximal inspiratory force (MIF) of about −55 cm H_2O vs −45 cm H_2O for airway protection. Nonetheless, it should be noted that despite a successful HL considerable weakness might still present. Control MIF values approximated −90 cm H_2O, and at −60 cm H_2O grip strength was only 40% of control.

As early as 1970, evidence began to appear that demonstrated that the HL test was not always a reliable index of recovery from d-tubocurarine. Walts et al [15] reported that despite a sustained 5-second head lift, 11 of 21 subjects had less than 90% return of vital capacity (average, 83%; range, 76%-86%), and 14 of 20 had less than 90% return of maximal voluntary ventilation. In another study evaluating "bedside tests" of neuromuscular recovery, Hutton et al [16] concluded that compared to inspiratory force, expiratory force, grip strength, or the presence of diplopia, the 5-second HL proved to be a very insensitive test of complete antagonism of residual block. Finally, it should be stressed that all bedside tests require an awake and cooperative patient. This was not a common occurrence in the immediate postoperative period in the days when halothane was considered a drug of low blood solubility.

More rigorous critiques of the 5-second HL correlating this test with the TOF fade ratio will be presented later in this chapter, but first, a brief review of the significance of evoked muscle responses to peripheral nerve stimulation may prove helpful.

2.2. Evaluating evoked responses

Although monitoring the evoked mechanical response to peripheral nerve stimulation was first suggested in the late 1950s [7] and then again in the mid-1960s [17,18] as a means of evaluating neuromuscular recovery, the first rigorous studies of the effects of neuromuscular blockers on evoked parameters (twitch height, tetanic fade, posttetanic potentiation) in man did not appear until several years later [19]. A breakthrough in neuromuscular monitoring occurred in the early 1970s with the description of the TOF stimulus [20,21]. Ali et al [22] pointed out that this sequence (4 single stimuli at half-second intervals) gave a reproducible measure of neuromuscular block without the necessity of first establishing control or baseline values. These authors were also able to show a relationship between the TOF fade ratio with the ability to perform a HL maneuver. They reported that a TOF ratio of 0.60 guaranteed that subjects had the ability to lift

their heads for at least 3 seconds. However, a closer inspection of their data (see Fig. 1) suggests a somewhat different message. A 3-second or 5-second head lift does not represent full recovery. A head lift more than 10 seconds required a TOF ratio of at least 0.70.

Four years later, Ali and coworkers [23] published a now classic study correlating the TOF ratio with 3 measurements of mechanical respiratory reserve (vital capacity, negative inspiratory force, and peak expiratory flow rate) in healthy volunteers (see Table 1). They concluded that once the TOF ratio recovered to a value of 0.70, "the magnitude of change in all variables was of minor clinical importance…since the lowest measured values were well above acceptable minimum limits required for adequate respiratory function." In a follow-up study from the same department [24] in 10 ASA III or IV patients, the authors agreed that a TOF ratio of 0.70 correlated well with clinical criteria used for tracheal extubation (see Table 2). Thus, based on less than 2 dozen subjects, a TOF ratio of at least 0.70 came to be accepted as the benchmark for adequate recovery from nondepolarizing neuromuscular block. This standard was not seriously questioned for the next 20 years.

Although there is no reason to question the validity of data of Ali [23], his study must be placed in the proper context. This work was done in an era in which early patient discharge from the hospital was uncommon. In 1975, ambulatory surgery was in its infancy. A patient entering the hospital for repair of an inguinal hernia was likely to remain an inpatient for the better part of a week. In addition, rapid recovery of cognitive function was less easily accomplished 30 years ago when diethyl ether and methoxyflurane were still widely used anesthetic agents. Thus, the issue of a patient's perceptions of residual weakness in the immediate postoperative period was not a pressing one. Today, in an environment where patients may be discharged from the hospital within 2 to 3 hours of leaving the operating room, the problem of lingering paresis takes on greater relevance.

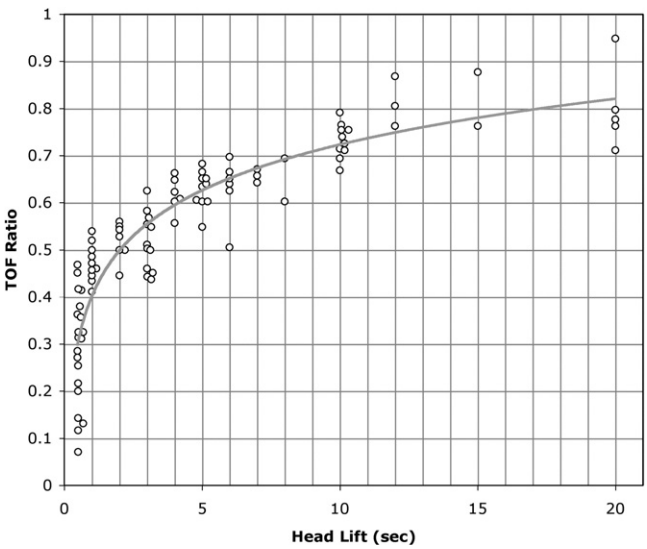

Fig. 1 The relationship between the TOF ratio and the duration of voluntary head-lifting after reversal of nondepolarizing block with neostigmine. Redrawn from Ali et al [22]. Best-fit trendline added by the present author (AFK).

Table 1 The effect of d-tubocurarine on respiratory mechanics at several TOF ratios in human volunteers [23]

TOF ratio	Vital capacity [a]	Negative inspiratory force [a]	Peak expiratory flow rate [a]
0.60	91.2	70.3	95
0.70	96.5	81.6	92.2
0.80	99.9	87.9	94.1
0.90	99.5	90.9	94.5
1.00	99.7	96.6	99.2

[a] All values expressed as % of control.

A discussion this author had with one of the subjects in Ali's volunteer study (John Savarese, MD) is instructive. He reported that at a time when his measured TOF ratio was 0.70, he was unsteady on his feet, had difficulty in climbing stairs, and experienced a feeling of generalized muscular weakness and fatigue. This conversation prompted us to investigate the signs and subjective symptoms that might accompany previously "acceptable" levels of neuromuscular block [25]. We studied 10 unsedated healthy young volunteers in whom the TOF fade ratio was recorded while receiving a mivacurium infusion titrated to TOF ratios of 0.60 to 0.70. Although no volunteer required intervention to maintain a patent airway and the oxygen hemoglobin saturation (room air) was at least 96% at all times, even small decrements in the TOF ratio were accompanied by significant signs and symptoms of muscular weakness. At TOF ratios less than 0.75, all subjects were uncomfortable, none considered themselves even remotely "street ready." Most reported that speaking required a great effort and that swallowing had become difficult. Several found it impossible to sip water through a straw because they could not maintain a tight seal with their lips. At a TOF ratio of 0.70, grip strength was decreased in all subjects. At

Table 2 Clinical criteria of Brand et al [24] for tracheal extubation

1. Ability to sustain eye opening, hand grasp, head lift, and tongue protrusion for at least 5 seconds.
2. Vital capacity of 10 to 15 mL/kg
3. Inspiratory force of at least −25 cm H_2O
4. Respiratory rate <25 to 30/min
5. $Paco_2$ between 35 and 45 torr; $AaDO_2$ between 50 and 200 torr

The criteria in this table are presented for their historic interest. They are not endorsed by the present author (AFK). $AaDO_2$, alveolar to arterial oxygen difference.

a TOF ratio of 0.70, grip strength averaged only 57% of control, with a range of 43% to 77%. This increased to 83% of control (range, 70%-105%) at a TOF ratio of 0.90. Before mivacurium administration, all subjects could easily prevent a wooden tongue depressor clenched between their incisor teeth, from being pulled out by even a vigorous effort on the part of the investigator. This ability did not return until the TOF ratio exceeded on average a value of 0.85. Train-of-four ratios less than 0.90 were also accompanied by significant visual disturbances. Below this level of recovery, every individual complained of diplopia and difficulty in tracking moving objects. Symptoms often persisted despite complete return of the TOF ratio to control values. Kopman's results confirm an earlier report by Russell [26] that demonstrated that hand grip was a more sensitive marker of residual weakness than the HL. After reversal of either d-tubocurarine or pancuronium, grip strength did not approach control values until 1 hour after all patients had successfully performed a 5-second HL. Thus, from the patient's perspective, "satisfactory" neuromuscular recovery required return of the TOF ratio to a value more than 0.90.

Nondepolarizing neuromuscular blocking drugs may have other undesirable effects at TOF ratios as high as 0.90. There is convincing evidence that even partial neuromuscular block (TOF of 0.70) impairs the ventilatory response to hypoxia suggesting an effect of nondepolarizing relaxants on carotid body hypoxic chemosensitivity [27]. Sundman et al [28] have also demonstrated that TOF ratios less than 0.90 are associated with functional impairment of the muscles of the pharynx and upper esophagus. Resting upper esophageal muscle tone is significantly decreased, and the coordination required between esophageal sphincter relaxation and contraction of the pharyngeal constrictor muscles necessary for the act of deglutition becomes dysfunctional. Their subjects showed misdirected swallowing with episodes of aspiration (penetration of contrast media into the laryngeal vestibule to the level of the vocal cords) with increasing frequency as the level of neuromuscular block intensified (8%, 25%, and 33% at TOF ratios of 0.80, 0.70, and 0.60, respectively). Thus, based on available evidence, return to a TOF ratio of 0.70 can no longer be considered optimal or even adequate neuromuscular recovery. The modern standard of recovery is now considered to be a TOF ratio of at least 0.90.

2.3. The HL vs the TOF ratio

At what TOF fade ratio can the 5-second HL be successfully performed? Kopman et al [25] found that the test was passed at an average TOF value of 0.62 ± 0.09 (range, 0.48-0.75; n = 10). However, the literature does not provide a clear-cut answer to this question (see Table 3) [29-33]. What is clear is that many individuals can sustain a 5-second HL at TOF values less than 0.60. Thus, Hutton [16] was certainly correct when he deemed the HL to be an insensitive test of neuromuscular recovery.

Table 3 Sustained 5-second HL as a function of TOF ratio

TOF	Ratio-sustained HL
0.50	6/7 individuals [30]
	6/7 individuals [32]
	0/10 individuals [33]
0.60	6/6 individuals [31]
	7/7 individuals [32]
	8/16 individuals [33]
0.70	22/23 individuals [33]
	55/62 individuals [29]

3. Postoperative residual curarization is not a rare occurrence

Almost 3 decades ago, Viby-Mogensen and coworkers [34] measured the prevalence of significant residual curarization in the recovery rooms of 3 university hospitals in Copenhagen. On different days chosen at random, these investigators studied every patient who received a nondepolarizing relaxant during anesthesia. The TOF fade ratio was determined immediately after arrival in the recovery area. Of 50 patients given neostigmine, 2.5 mg intravenously, at the end of anesthesia, 10 individuals (20%) had TOF ratios of less than 0.60, and in 6 patients, the ratio was less than 0.40. These findings have been confirmed by many other investigators [29,35]. However, all of Viby-Mogensen's patients received traditional long-acting neuromuscular blockers (eg, d-tubocurarine, pancuronium). A subsequent study with agents of intermediate action suggested that the incidence of postoperative residual curarization (PORC) was significantly lower in patients receiving these relaxants [36]. Thus, it was assumed by some that as long-acting agents were gradually replaced by newer drugs the incidence of PORC would markedly decrease. It has not worked out that way. Recent studies (the year 2000 or later) report that the incidence of PORC may actually be greater than the value reported by Viby-Mogensen. Frequencies of PORC range from a low of 16% of individuals arriving the in postanesthesia care unit (PACU) with TOF values less than 0.70 after a single dose of relaxant [37] to as high as 70% of patients who at the time of extubation still have TOF values less than 0.70 [38]. Other reports are equally alarming [39-41]. Why is PORC still such a common occurrence? Clearly, a high level of unwarranted complacency exists with regard to the ease of neostigmine-induced reversal of intermediate-duration neuromuscular blocking agents (see Dr Caldwell's chapter in this issue of *Seminars*). Much higher multiples of the ED (effective dose)$_{95}$ are now being administered than when traditional long-acting agents were the only nondepolarizing relaxants available. However, several other factors no doubt play a role.

As noted above, many clinicians still do not routinely use even simple peripheral nerve stimulators (PNS) in the perioperative period. The reasons behind this disdain for neuromuscular monitoring escape this author, but I suspect in part it reflects ignorance of the limitations of traditional "bedside" tests such as the HL and tidal volume in detecting residual muscle weakness. Clinicians do not seem to believe that PORC is a clinical problem that may affect their patients. Unfortunately, conventional PNS units even when they are used have real limitations. Subjective tactile or visual estimates of the TOF ratio are notoriously inaccurate. In fact, most clinicians cannot detect the presence of fade once the TOF ratio exceeds 0.40 [42]. Finally, in many academic centers routine reversal of neuromuscular block is still the exception rather than the rule [5,37].

3.1. Does residual neuromuscular block have clinical consequences?

In a 1985, editorial Miller [43] noted "There are…no outcome data assessing the role of residual paralysis…when the occasional case of airway obstruction or the inability of dispose of vomitus or oropharyngeal secretions occurs in the recovery room." Two decades later, despite the high incidence of residual paresis found in most PACUs, there is still remarkably little outcome information to suggest that this represents a frequent cause of major morbidity. As pointed out by Shorten [44], several factors work against obtaining reliable information. First, it is unlikely that most postoperative complications can be attributed to a single cause. Second, an ethical dilemma exists. If postoperative neuromuscular function is judged to be inadequate, the investigator is obliged to intervene and in doing so has altered the course that otherwise would have transpired. Finally, the incidence of serious adverse events associated with the administration of muscle relaxants is unknown but probably small. How then do we determine if consequential differences in outcome exist between various relaxant regimens? In practice, it may not be possible to do so. For example, assuming that protocol X has a true adverse effect rate of 1 in 500, whereas for protocol Y, this frequency is 1 in 1500; more than 10000 subjects would have to be studied to show that this difference had statistical significance. Massive studies of this magnitude are rarely carried out.

Nevertheless, some information is available. Arbous et al [45] were able to demonstrate that reversal of neuromuscular block at the end of surgery was associated with decreased risk of 24-hour mortality or coma (odds ratio, 0.10). There is also convincing evidence that postoperative pulmonary complications are more common when long-duration vs intermediate-duration nondepolarizing blockers are administered [46-48]. In a recent prospective study of 70 patients scheduled for orthopedic surgery, Murphy et al [49] compared adverse recovery room outcomes in patients who had received pancuronium vs rocuronium intraoperatively. Forty percent of patients in the pancuronium group had TOF ratios less than 0.7 on arrival to the PACU, compared with only 6% of subjects in the rocuronium group. Patients in the pancuronium group were more likely to experience symptoms of muscle weakness (blurry vision and generalized weakness) and hypoxemia (10 patients in the rocuronium group vs 21 patients in the pancuronium group) during the PACU admission. Significant delays in meeting PACU discharge criteria and achieving actual discharge were observed when the pancuronium group was compared with the rocuronium group.

In the absence of additional "hard" outcome data, how should we proceed when drawing conclusions regarding the risks associated with residual paresis in the PACU? We often are forced to accept surrogate measures as a substitute for true outcomes [50,51]. The TOF ratio is one such surrogate. There is convincing evidence that TOF values less than 0.80 result in measurable decreases in mechanical respiratory reserve [23], decreased ventilatory response to hypoxia [27], an impaired ability to swallow, and protect the upper airway from aspiration [52] and numerous subjective complaints [25]. I find it difficult to accept the position that none of this matters.

4. Does neuromuscular monitoring reduce the incidence of postoperative residual curarization?

It is a bit odd that, 50 years after the use of peripheral nerve stimulators were first suggested [7] as aids in monitoring neuromuscular function, use of these instruments is even being discussed. Nevertheless, the efficacy of these devices in preventing postoperative residual curarization is still a matter of controversy. "Common sense" suggests that even nonquantitative conventional PNS units that require a subjective evaluation of the evoked response should prove superior to "clinical" tests especially when the patient is uncooperative with the assessment. A recent meta-analysis that examined this hypothesis, however, found that the peer-reviewed literature does not necessarily support this premise [53]. The authors confirmed that the incidence of PORC was higher when long-acting neuromuscular blockers were administered. However, they could not demonstrate that the use of an intraoperative neuromuscular function monitor decreased the incidence of PORC. Because this conclusion is so counterintuitive it needs to be discussed in some detail.

4.1. Conventional (nonobjective) neuromuscular monitoring

Unfortunately, in Naguib's meta-analysis, most of the studies cited that failed to demonstrate that monitoring had a favorable effect in reducing PORC were poorly designed to do so. Examples of which are the following:

Pedersen et al [54] studied patients who received either vecuronium or pancuronium. In half of the patients, the degree of intraoperative blockade was assessed by tactile evaluation of the TOF response at the thumb. In the other half, the degree of block was evaluated solely by clinical criteria. The use of a PNS had no effect on the dose of relaxant given during anesthesia or on the incidence of postoperative residual neuromuscular blockade evaluated clinically. In the clinical criteria groups, reversal of residual paralysis was not attempted until spontaneous respiration or other indication of muscle activity was observed. However, the authors' protocol almost guaranteed that results in the monitored group would be less than optimal. Anesthetists were instructed to maintain the TOF count at 1 or 2 detectable responses and antagonism of residual block with neostigmine was initiated at this level of block. There is ample evidence that prompt and satisfactory anticholinesterase-induced antagonism at this level of block is simply not a realistic goal. Intraoperative neuromuscular monitoring should be used to help the clinician titrate doses of relaxant to avoid this level of block at the end of surgery, not the converse. The same criticism can be applied to a larger study by Fawcett et al [55]. No attempt was made to influence the conduct of anesthesia, the choice of blocking drug, or whether a neuromuscular function should be monitored. The TOF ratios were measured upon arrival in the PACU. The incidence of PORC was not decreased in patients in whom a PNS device was used. The virtue of this study is that it probably accurately reflected the then-current clinical practice of the authors' department. Its weakness is that it gives the reader no insight into how clinical decisions were made. If monitored patients were routinely kept at TOF counts of 2 or fewer detectable responses, then one may argue that use of a PNS might actually have been counterproductive.

Hayes et al [40] focused on the frequency of PORC on arrival in the PACU in patients who received vecuronium, atracurium, or rocuronium. Residual block was considered present in patients with a TOF ratio of less than 0.80. The overall incidence of PORC was 52%. Intraoperative neuromuscular monitoring was used in only 41% of patients, and reversal of residual block was omitted in one third of the patients. The authors were not able to demonstrate that the incidence of PORC was significantly less in patients in whom a PNS was used. Nevertheless, because several of their patients (no PNS device used) arrived in the PACU with TOF counts of less than 4 detectable responses, it is difficult to accept the premise that even rudimentary monitoring would not have been helpful.

I would argue that articles such as those cited above expose a basic lack of knowledge on the part of clinicians more than they indicate a lack of use of conventional PNS devices. Although it is true that subjective evaluation of the TOF ratio is subject to considerable error [42], the tactile TOF count is a very useful parameter. If the TOF count at the time reversal is initiated is known, the clinician at least has a rough "ball park" estimate of when satisfactory return of neuromuscular may be expected. If the TOF count has recovered to one detectable responses after the administration of cisatracurium or rocuronium, then neostigmine, 0.05 mg/kg, will take approximately 20 minutes will restore the TOF ratio to a value of about approximately 0.80 (with considerable individual variation) [56]. If the count has return to 2 palpable responses, then this time interval is reduced to about 15 minutes [57]. In practical terms, the maximum depth of block that can be promptly ($\leq$10 minutes) reversed by anticholinesterase antagonists approximately corresponds to the reappearance of the fourth response to TOF stimulation [58,59].

This author firmly believes that nondepolarizing relaxants can be administered quite safely to the most patients without using objective neuromuscular monitors. If drug administration is timed so that the TOF count is 3 or 4 when antagonism is initiated, then clinically significant PORC in the recovery room should be a rare event. However, there are circumstances where objective monitors are clearly preferable to conventional PNS units.

4.2. The case for objective neuromuscular monitors

Routine reversal of the residual effects of nondepolarizing blockers is not standard of care in many departments of anesthesia. Reversal agents are not without their own potential side effects. Although early concerns about lethal catastrophes after anticholinesterase administration were clearly alarmist [60,61], it is also true that atropine, glycopyrrolate, neostigmine, and edrophonium all have potentially unwanted cardiovascular effects. In addition, there is a perception among many clinicians that neostigmine increases the risk of postoperative nausea and vomiting [62], although this assertion is highly doubtful [63]. Finally, neostigmine may actually enhance TOF fade if given to the patient who has fully recovered spontaneously [64,65]. Thus, if satisfactory spontaneous recovery of neuromuscular function has occurred, there are cogent reasons to avoid administering unnecessary antagonists. Unfortunately, many clinicians believe that 90 minutes after an "intubating dose" ($2\bullet ED_{95}$) of rocuronium or vecuronium that reversal is not indicated. This is not necessarily the case. Caldwell [65] found that 4 of 20 patients given vecuronium, 0.10 mg/kg, had TOF ratios less than 0.75 after 2 hours of spontaneous recovery. Similarly, Debaene [37] in a study of more than 500 patients given various blockers of intermediate duration reported that 10% had a TOF ratio less than 0.70 at 2 hours and in 30% of individuals the value was less than 0.90. Probably in none of these individuals would palpable or visual TOF fade be detectable. Thus, it is hard to argue with the dictum of Viby-Mogensen [2] that residual neuromuscular block should always be reversed unless there is objective evidence that the TOF ratio has recovered to acceptable levels.

Objective monitoring is also strongly indicated when reversing profound neuromuscular block. If the TOF count is at most 2, prompt recovery of neuromuscular function cannot be assured by anticholinesterase administration. Nevertheless, neostigmine antagonism of deep block may result in the rapid return of all 4 evoked responses to TOF stimulation with minimal or no subjectively detectable fade (a TOF ratio >0.40). Thus, a prolonged period may exist where the TOF ratio is above 0.40 but below satisfactory recovery levels [56]. Unless the clinician is aware of this possibility, tracheal extubation may be undertaken when it is clearly inappropriate [66].

Finally, there is at least some evidence that objective monitoring does decrease the incidence of PORC. Gatke et al [67] studied 120 adult patients randomized to two 60-patient groups, one monitored acceleromyographically (AMG) and the other monitored using only clinical criteria without a nerve stimulator. Postoperatively, the TOF ratio was measured with mechanomyography; a TOF ratio of less than 0.80 indicated residual muscle paralysis. At the time of tracheal extubation, residual muscle paralysis was found in 10 patients (17%) in the group without neuromuscular monitoring and in only 2 patients (3%) in the AMG monitored group. In the control group (no monitors), the clinicians were very much aware of the goals of the study and were trying to avoid residual weakness, their results (17%) may represent a "best case scenario." The authors concluded that clinical evaluation of neuromuscular function does not rule out significant residual paralysis after the intermediate-acting muscle relaxant rocuronium, and the problem of residual block can be minimized using acceleromyography. Mortensen et al [68] in a similar study of 40 patients reported that the number of patients with a TOF ratio less than 0.7 at the time of extubation in the monitored group was significantly fewer compared to those in the nonmonitored group (1/19 patients vs 11/21 patients, respectively).

Perhaps the most convincing evidence that the use of objective neuromuscular monitors (combined with a strong educational effort at the departmental level) can decrease the incidence of PORC comes from 2 studies by Baillard et al [39]. The first was a prospective study of the incidence of PORC after the administration of vecuronium in 568 consecutive patients for a 3-month period in 1995. As was customary in the authors' department, no anticholinesterase antagonists were given, and PNS devices were rarely used (<2.0%) intraoperatively. Postoperative residual curarization (indicated by an acceleromyographic TOF ratio of <0.70) in the PACU was found in 42% of patients. Of 435 patients who had been extubated in the operating room, the incidence of PORC was 33%. As a result of these rather alarming findings, Baillard's department placed acceleromyographic monitors in all operating rooms shortly after the completion of their 1995 study. In addition, the department instituted an educational program about the use of neuromuscular monitoring and the indications for neostigmine administration. The results of their findings regarding the incidence of PORC were distributed to their staff. They then conducted repeat 3-month surveys of clinical practice in the years 2000 (n = 130), 2002 (n = 101), and 2004 (n = 218) to determine the success of their educational efforts [69]. In the 9-year interval between these studies, the use of intraoperative monitoring of neuromuscular function rose from 2% to 60% and reversal of residual antagonism increased from 6% to 42% of cases. As a result of these changes in clinical practice, the incidence of PORC (acceleromyographic TOF ratio of <0.90) in Baillard's department decreased from 62% to less than 4%. Baillard's results clearly show that when nondepolarizing neuromuscular blocking drugs are administered by knowledgeable clinicians who use objective neuromuscular monitors as adjuncts to their care and administer anticholinesterase antagonists on indication that the incidence of PORC can be reduced to very low levels.

A recent case by Claudius et al [70] is instructive. They report an 84-year-old female with no special risk factors given rocuronium, 0.60 mg/kg. At the end of surgery, 140 minutes later, the TOF count was zero (post tetanic count [PTC] was 8). A decision was made to keep the patient anesthetized until a second response to TOF stimuli could be detected. This took an additional 75 minutes, at which time neostigmine administration achieved prompt and satisfactory antagonism (TOF >0.90). It is difficult to see how this case could have been managed with intelligence in the absence of neuromuscular monitoring. The authors correctly conclude: "There are many myths and excuses for not using a nerve stimulator. The truth, however, is that there are no good reasons for not monitoring neuromuscular block whenever a [nondepolarizing] neuromuscular blocking agent is given."

Unfortunately, it is clear that large numbers of practitioners still fail to monitor neuromuscular function and to administer antagonists when appropriate. Despite intense educational campaigns, there will always be some clinicians who fail to get the message. I have on several occasions heard the comment "I haven't used a nerve stimulator in 30 years, and I see no reason to start now." To that my usual response is, "it is possible to make the same mistake for 3 decades and call it experience."

5. How may new developments alter this discussion? The future of neuromuscular monitoring

It is clear that reversal of competitive neuromuscular block by cholinesterase inhibitors has its limitations. Once inhibition of true acetylcholinesterase is complete, giving additional neostigmine does not serve any useful purpose. If concentrations of blocking drug at the neuromuscular nicotinic receptors are high enough, recovery will be incomplete. Future progress in achieving rapid return of neuromuscular function will probably result from some form of "chemical reversal" of residual block. Binding of free drug

molecules in plasma such as the encapsulation of rocuronium by sugammadex is one such example [71,72]. Another approach is exemplified by the rapid inactivation of gantacurium via cysteine adduction [73].

Initial published results of reversal of rocuronium-induced block by sugammadex are very exciting. To give just one example, after a 1.2-mg/kg dose of rocuronium, de Boer et al reported that the median time for spontaneous recovery to a TOF ratio of 0.90 was 126 minutes (range, 97-139; n = 4). By contrast, if sugammadex, 12 mg/kg, was given 5 minutes after the rocuronium bolus, recovery time was reduced to 1.3 minutes (range, 1.0-1.9; n = 7).

Reversal of this level of profound block is simply not possible with anticholinesterase inhibitors. Does this mean we can finally throw away our nerve stimulators? I think not. First of all, inadequate doses of sugammadex will result in delayed recovery. In the study of de Boer [74], when the dose of sugammadex was reduced to 2 mg/kg, recovery to a TOF ratio of 0.90 still took an average of 56 minutes. This latter dose, however, is likely to be the recommended amount when the TOF count has recovered to 2 detectable responses at the adductor pollicis [75]. If the posttetanic count is still only 1 to 2 then 4 mg/kg should be administered. Thus, intelligent administration of sugammadex necessitates some knowledge of the extent of neuromuscular block. Why not just give everyone 4 or even 12 mg/kg of sugammadex and then throw away our PNS units? First, until the drug has been given to tens of thousands of patients, its potential for producing adverse effects remains uncertain. In the interim, the fewer drugs administered the better. Second, the acquisition price of the sugammadex remains unknown, it appears that it will be marketed in 200 and 500 mg vials. Somehow, I suspect that routine administration of the later dose to a 70-kg individual (7 mg/kg) will prove to be economically unattractive. Finally, sugammadex administration may not be appropriate for all patients. It probably should be avoided in individuals with severe renal impairment, its effects in women taking hormonal contraceptives are still unclear, and it has no place in the antagonism of nonsteroidal blockers.

Thus where do we stand? I think a strong case can be made that when sugammadex is used to reverse rocuronium-induced or vecuronium-induced block that convention PNS units are adequate for safe and intelligent patient management. A knowledge of the PTC or TOF count is all that is required for selection of a dose of sugammadex that will promptly and reliably assure satisfactory neuromuscular recovery. When anticholinesterase antagonists are used for reversal of residual block the situation is more complicated. Although it is hard to argue against the virtues of objective monitors such as the TOF-Watch, I am not convinced that their use is always necessary. If the adductor pollicis TOF count has returned to 4 easily detected responses (with fade), then neostigmine in doses of 0.05 to 0.07 mg/kg will dependably achieve acceptable levels of recovery in at most 10 minutes. Four reasons outlined earlier in this chapter, quantitative monitors are most valuable in 2 situations: (1) when deciding whether to reverse neuromuscular block when no fade on TOF stimulation can be detected or (2) when evaluating the adequacy of reversal from profound nondepolarizing block (TOF count $\leq$3).

A final thought. In 1969, I joined a private practice in a nonteaching hospital on Long Island (NY). During my year there, I used an electrocardiograph only once. We did not have automated noninvasive blood pressure monitors, pulse oximetry, capnography, anesthetic agent analyzers, or cerebral function monitors. At the time, I did not feel that I lacked any essential instrumentation. All of these technologies are now considered standard of care. Today objective monitors of neuromuscular function can be purchased that are relatively inexpensive, reliable, and easy to use. They should be available in any modern anesthetizing location where neuromuscular blocking drugs are administered.

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