43 Neuromuscular Monitoring

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KEY POINTS

- Good evidence-based practice dictates that clinicians always quantitate the extent of neuromuscular block by objective monitoring.
- The neuromuscular block should be adjusted to ensure optimal surgical conditions. In most procedures, one or two responses to train-of-four (TOF) stimulation will suffice. To avoid involuntary diaphragmatic movements, a deeper level of neuromuscular block is required (i.e., one to five responses to post-tetanic count [PTC]).
- Adequate recovery of postoperative neuromuscular function cannot be guaranteed without objective neuromuscular monitoring.
- Objective neuromuscular monitoring is essential for management of neuromuscular blockade intraoperatively and its reversal for postoperative care. Muscle relaxants should not be given in the intensive care unit without proper monitoring.
- It is impossible to exclude with certainty clinically significant residual neuromuscular block by clinical evaluation of recovery of neuromuscular function.
- Residual postoperative neuromuscular block causes decreased chemoreceptor sensitivity to hypoxia, functional impairment of the pharyngeal and upper esophageal muscles, impaired ability to maintain an open upper airway, and an increased risk of hypoxemic events, as well as the development of postoperative pulmonary complications.
- Absence of tactile fade in the response to TOF stimulation, tetanic stimulation, and double-burst stimulation does not exclude significant residual block.
- To exclude clinically significant residual neuromuscular block, the TOF ratio must exceed 0.9 when measured mechanically or electromyographically and 1.0 when measured acceleromyographically.
- Antagonism of the neuromuscular block with a cholinesterase inhibitor should not be initiated before at least two to four responses to TOF stimulation are observed.
- Antagonism of the neuromuscular block achieved by rocuronium and vecuronium can be initiated at all levels of block with the selective relaxant binding agent sugammadex.
- If adequate recovery (TOF ≥0.9-1.0) has not been documented objectively at the end of the surgical procedure, the neuromuscular block should be antagonized.

Our understanding of the pathophysiologic consequences of residual paralysis has improved over the last decades, and it is now generally accepted that even small degrees of residual paralysis (i.e., a train-of-four [TOF] ratio 0.7-0.9) may be clinically harmful.[1-4] As a consequence, the benchmark of adequate neuromuscular recovery has been revised several times; an adductor pollicis TOF ratio of 0.9 or greater is now required to exclude relevant residual neuromuscular block (i.e., paralysis). Clinically significant residual paralysis cannot be excluded using clinical criteria and it can persist postoperatively.[5,6] Objective monitoring of the degree of neuromuscular block associated with pharmacologic reversal reduces the incidence of residual paralysis and should be part of standard perioperative monitoring when neuromuscular blocking agents (NMBAs) are used.[7-13]

In awake patients, muscle power can be evaluated by tests of voluntary muscle strength, but this is impossible during anesthesia and recovery from anesthesia. Historically, anesthesiologists have used clinical tests to assess muscle power directly and to estimate neuromuscular function indirectly (muscle tone; feel of the anesthesia bag as an indirect measure of pulmonary compliance, tidal volume, and inspiratory force). All these tests are influenced by factors other than the degree of neuromuscular block and, therefore, should not be used to evaluate recovery from neuromuscular blockade. Whenever precise information regarding the status of neuromuscular functioning is desired, the response of muscle to nerve stimulation should be assessed. This procedure also takes into account the considerable variation in individual response and sensitivity to muscle relaxants.

This chapter reviews the basic principles of neuromuscular monitoring and the requirements for effective use of nerve stimulators for peripheral nerve stimulation. It also describes the response to nerve stimulation during depolarizing (phase I and phase II) and nondepolarizing neuromuscular block, provides information about the level of neuromuscular blockade, and discusses the consequences of residual paralysis. Moreover, methods of evaluating evoked neuromuscular responses with and without the availability of recording equipment are discussed.

Principles of Peripheral Nerve Stimulation

Neuromuscular monitoring is used to evaluate the effect of a NMBA. The muscle response after stimulation of its corresponding motor nerve is assessed. The most frequently assessed nerve-muscle unit is the ulnar nerve and the adductor pollicis muscle. The muscle response can be evaluated either qualitatively with a peripheral nerve stimulator or quantified with objective monitors. With the peripheral nerve stimulator, the observer evaluates the muscle response either tactically or visually, whereas with the monitor the response is objectively measured and displayed on a screen. Whatever method is used for neuromuscular monitoring, the clinician should be familiar with the following terms: supramaximal stimulation, calibration, impedance, and safety margin.

SUPRAMAXIMAL STIMULATION

The reaction of a single muscle fiber to a stimulus follows an all-or-none pattern. In contrast, the response (the force of contraction) of the whole muscle depends on the number of muscle fibers activated. If a nerve is stimulated with sufficient intensity, all fibers supplied by the nerve will react, and the maximum response will be triggered. After administration of a neuromuscular blocking drug, the response of the muscle decreases in parallel with the number of fibers blocked. The reduction in response during constant stimulation reflects the degree of neuromuscular block.

For the preceding principles to work, the stimulus must be truly maximal throughout the whole period of monitoring; therefore, the electrical stimulus applied is usually at least 15% to 20% greater than that necessary for a maximal response. For this reason, the stimulus is said to be supramaximal. This compensates for potential changes in skin resistance intraoperatively and assures constant maximal stimulation throughout the procedure.

However, supramaximal electrical stimulation can be painful, which is not a concern during anesthesia, but during recovery the patient may be awake enough to experience the discomfort of nerve stimulation. Therefore, some researchers advocate stimulation with submaximal current during recovery. Although several investigations indicate that testing of neuromuscular function can be reliably performed postoperatively with submaximal stimulation,[14,15] the accuracy of such monitoring is unacceptable with that low current.[15]

CALIBRATION

A device used for objective monitoring of the neuromuscular function should be calibrated before the NMBA is administered. Calibration adjusts the gain of the device to ensure that the observed response to supramaximal stimulation is within the measurement window of the device and as close as possible to the "100% control response." The calibration procedure varies with the type of device used, but most often it is done with 1.0 Hz single-twitch stimulation. It is especially important to calibrate when the onset and recovery of the neuromuscular block are established with single-twitch stimulation.

In the TOF mode of nerve stimulation, calibration is considered less important because all four responses are amplified equally. Consequently, the TOF ratio is rarely influenced by calibration; however, in patients with very weak or strong responses to nerve stimulation, one or more responses to TOF stimulation might be out of the recording window, and the displayed TOF response might be incorrect. In some devices, supramaximal stimulation is established concurrently with the calibration procedure.

IMPEDANCE

An alternative and novel option to ensure a constant maximum stimulus throughout the whole procedure is to control the impedance (resistance) of the skin. Indeed, as long as the resistance of the skin is below a threshold value, the neuromuscular monitoring device will stimulate with the same user-selected electrical current (i.e., 60 mA). For a maximum current of 60 mA, the maximal resistance of the skin should be equal to or lower than 5 kΩ. If the resistance of the skin is above this value, the monitor will not be able to stimulate the patient with the selected current. More recently, nerve stimulators have been introduced that indicate the level of skin impedance on the screen (e.g., TofScan by iDMed, Marseille, France). Using this approach, establishment of supramaximal stimulation is not needed to assure that nerve stimulation is effective and constantly maximal through the whole procedure.

SAFETY MARGIN

Neuromuscular transmission has a substantial margin of safety. Neuromuscular block only becomes evident when 70% to 80% of acetylcholine receptors at the neuromuscular endplate are occupied by nondepolarizing NMBDs and to produce complete block, 90% to 95% of receptors must be occupied. Thus, the currently available equipment and the currently applied stimulation patterns allow only insight to this 70% to 95% range of receptor occupancy. This should be kept in mind, especially during recovery of neuromuscular block, where 70% of the acetylcholine receptors at the neuromuscular endplate may still be occupied but no longer detectable with neuromuscular monitoring.

Types of Peripheral Nerve Stimulation

Neuromuscular function is monitored by evaluating the muscular response to supramaximal stimulation of a peripheral motor nerve. Theoretically, two types of stimulation can be used: electrical and magnetic. Electrical nerve stimulation is by far the most commonly used method in clinical practice, and it is described in detail in this chapter. In theory, magnetic nerve stimulation has several advantages over electrical nerve stimulation.[2,16] It is less painful and does not require physical contact with the body; however, the equipment required is bulky and heavy, it cannot be used for TOF stimulation, and it is difficult to achieve supramaximal stimulation with this method. As a result, magnetic nerve stimulation is not used in clinical anesthesia.

Basic Considerations

STIMULATING ELECTRODES

Electrical impulses are transmitted from stimulator to nerve by means of surface or needle electrodes. Normally, disposable pre-gelled silver or silver chloride surface electrodes are used. The conducting area should be small, approximately 7 to 11 mm in diameter (Fig.43.1). Otherwise, the current produced in the underlying nerve may not be adequate.[17] Ideally, the skin should be cleansed properly and preferably rubbed with an abrasive before application of the electrodes. When the selected current cannot be obtained with surface electrodes, needle electrodes can be used in a few exceptional cases. Although specially coated needle electrodes are commercially available, ordinary steel injection needles often suffice. A sterile technique should be used, and the needles should be placed subcutaneously to avoid direct injury to the underlying nerve.

Sites of Nerve Stimulation and Different Muscle Responses

In principle, any superficially located peripheral motor nerve can be stimulated and the response to corresponding muscle measured. Choosing the site of neuromuscular monitoring depends on several factors: the site should be easily accessible during surgery, it should allow quantitative monitoring and finally, direct muscle stimulation should be avoided. Direct muscle stimulation is characterized by weak contractions without fade persisting even at a deep level of neuromuscular blockade. The risk is increased when the stimulation electrodes are directly attached over the muscle to be assessed. To prevent direct muscle stimulation, the nerve-muscle unit should be chosen so that the site of nerve stimulation and the site of the subsequent evaluation of the twitch response are topographically (anatomically) distinct.

In clinical anesthesia, the ulnar nerve is the gold standard as a stimulation site, but the median, posterior tibial, common peroneal, and facial nerves are also sometimes used. For stimulation of the ulnar nerve, the electrodes are best applied to the volar side of the wrist (see Fig. 43.1). The distal electrode should be placed approximately 1 cm proximal to the point at which the proximal flexion crease of the wrist crosses the radial side of the tendon to the flexor carpi ulnaris muscle. The proximal electrode should preferably be placed so that the distance between the centers of the two electrodes is 3 to 6 cm (see Fig. 43.1). With this placement of the electrodes, electrical stimulation normally elicits only finger flexion and thumb adduction. If one electrode is placed over the ulnar groove at the elbow, thumb adduction is often pronounced because of stimulation of the flexor carpi ulnaris muscle. When this latter placement of electrodes (sometimes preferred in small children) is used, the active negative electrode should be at the wrist to ensure maximal response. Polarity of the electrodes is less crucial when both electrodes are close to each other at the volar side of the wrist; however, placement of the negative electrode distally normally elicits the greatest neuromuscular response.[18] When the temporal branch of the facial nerve is stimulated, the negative electrode should be placed over the nerve, and the positive electrode should be placed somewhere else over the forehead. When the posterior tibial nerve is stimulated, the electrodes should be placed close to the medial malleolus, with the same distance as described above and the negative electrode being placed distally.

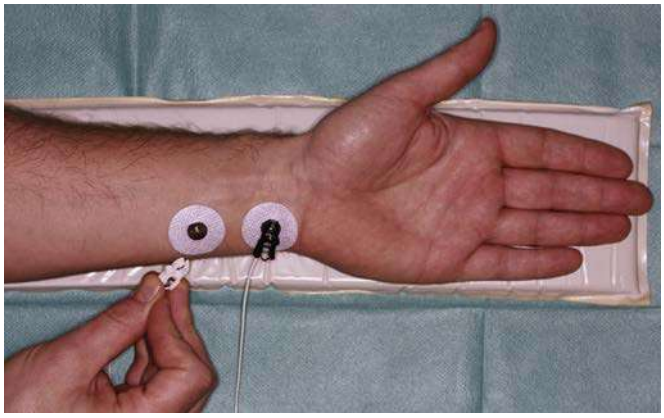

Fig. 43.1 Stimulating electrodes with the appropriate contact area in the correct position over the ulnar nerve of the left forearm.

NERVE-MUSCLE UNIT

Several nerve-muscle units may be chosen in clinical practice. Most often the ulnar nerve-adductor pollicis muscle is used.

Ulnar nerve-adductor pollicis muscle: This nerve-muscle unit is easily accessible intraoperatively if the arm is in the outstretched position and the hand in the supine position. The stimulatory response can be evaluated tactilely, visually, or by objective means. It has the lowest risk of direct muscle stimulation, because it ensures topographic separation of the stimulated nerve and the evaluated muscle by stimulating the ulnar nerve running along the median side of the arm and assessing the muscle response at the adductor pollicis muscle, which is indeed located on the lateral side of the hand.

Posterior tibial nerve-flexor hallucis brevis muscle: This nerve-muscle unit can be used for monitoring when the hands are inaccessible. The flexor hallucis brevis muscle produces flexion of the big toe following posterior tibial nerve stimulation. The characteristics (onset and recovery) of the neuromuscular block at the flexor hallucis brevis muscle is almost consistent with that of the adductor pollicis muscle.

Facial nerve-orbicularis oculi and facial nerve-corrugator supercilii muscle: When the arms are tucked under surgical drapes, quite often the only accessible site for monitoring is the head. Two facial muscles can be used as monitoring sites: the orbicularis oculi muscle and the corrugator supercilii muscle. The former encircles the orbital opening; its stimulation through the zygomatic branches of the facial nerve causes the eyelids to close. Stimulation by the temporal branch of the facial nerve of the latter one draws the medial end of the eyebrow downward, producing wrinkling of the brow. However, because the facial nerve is in direct proximity to the intrinsic mimic muscles, the risk of direct muscle stimulation is significant. Therefore, care must be

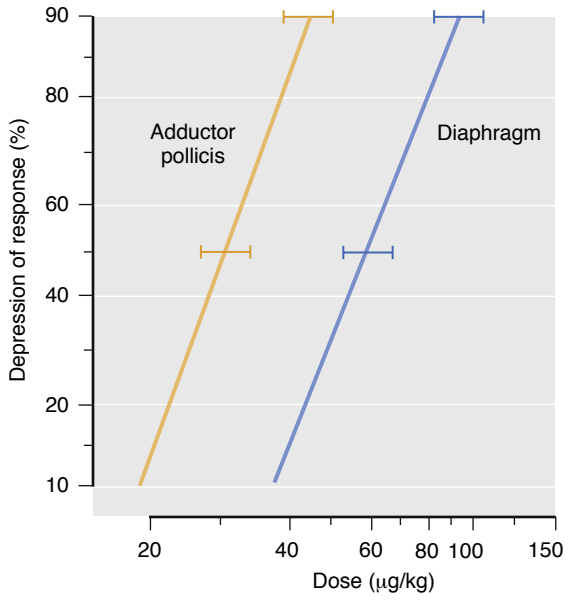

Fig. 43.2 The mean cumulative dose-response curve for pancuronium in two muscles shows that the diaphragm requires approximately twice as much pancuronium as the adductor pollicis muscle for the same amount of neuromuscular block. The depression in muscle response to the first stimulus in train-of-four nerve stimulation (probit scale) was plotted against dose (log scale). The force of contraction of the adductor pollicis was measured on a force-displacement transducer; response of the diaphragm was measured electromyographically. (From Donati F, Antzaka C, Bevan DR. Potency of pancuronium at the diaphragm and the adductor pollicis muscle in humans. *Anesthesiology*. 1986;65[1]:1–5.)

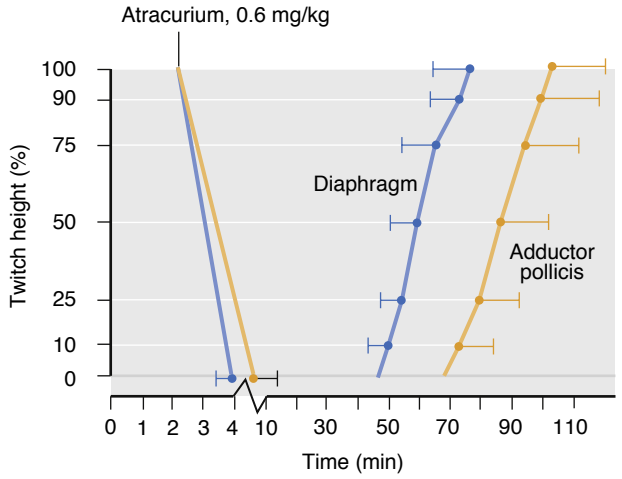

Fig. 43.3 Evolution of twitch height (mean ± SD) of the diaphragm *(blue circles)* and the adductor pollicis muscle *(yellow circles)* in 10 anesthetized patients after the administration of atracurium (0.6 mg/kg). (From Pansard J-L, Chauvin M, Lebrault C, et al. Effect of an intubating dose of succinylcholine and atracurium on the diaphragm and the adductor pollicis muscle in humans. *Anesthesiology*. 1987;67[3]:326–330.)

taken that the correct stimulatory response is assessed, and any other twitching muscle in the direct proximity of the stimulation electrodes is not falsely interpreted. Stimulation of the facial nerve can be accomplished with significantly lower currents: most often 25 to 30 mA are sufficient. Stimulation of these two muscles is technically difficult and the result often unsatisfactory in clinical practice.

Because different muscle groups have different sensitivities to neuromuscular blocking drugs, results obtained for one muscle cannot be automatically extrapolated to other muscles. However, most of the studies that are the base for dosing recommendations of NMBAs arise from measurement of the stimulation of the ulnar nerve. The diaphragm is among the most resistant of all muscles to both depolarizing[19] and nondepolarizing neuromuscular blocking drugs.[20] In general, the diaphragm requires 1.4- to 2.0-fold as much muscle relaxant as the adductor pollicis muscle for an identical degree of block (Fig. 43.2).[20] Also of clinical significance is that onset time is normally shorter for the diaphragm than for the adductor pollicis muscle, and the diaphragm recovers from paralysis more quickly than the peripheral muscles (Fig. 43.3).[21] The other respiratory muscles are less resistant than the diaphragm, as are the larynx and the corrugator supercilii muscles.[22-24] Most sensitive are the abdominal muscles, the orbicularis oculi muscle, the peripheral muscles of the limbs, and the geniohyoid, masseter, and upper airway muscles.[1,25-27] From a clinical point of view, the response of the corrugator supercilii to facial nerve stimulation reflects the extent of neuromuscular block of the laryngeal adductor muscles and abdominal muscles better than the response of the adductor pollicis to ulnar nerve stimulation.[24,28] Furthermore, the upper airway muscles seem to be more sensitive than the peripheral muscles.[25,26] Although some investigations using acceleromyography (AMG) have indicated small differences in the response to TOF nerve stimulation in the hand (adductor pollicis muscle) compared to the leg (flexor hallucis brevis muscle), these differences are probably of little clinical significance.[29,30] When comparing different sites of stimulation, there might be large differences between contralateral limbs (e.g., arm-to-arm variation of ± 20%).[31,32]

Although the precise source of these differences is unknown, possible explanations may be variations in acetylcholine receptor density, acetylcholine release, acetylcholinesterase activity, fiber composition, innervation ratio (number of neuromuscular junctions), blood flow, and muscle temperature.

Patterns of Nerve Stimulation

For the evaluation of the neuromuscular function, the most commonly used patterns are TOF stimulation, double-burst stimulation (DBS), and posttetanic count (PTC) stimulation. Single-twitch stimulation and tetanic stimulation are mainly used as a component in composite stimulation patterns (i.e., TOF, DBS, or PTC).

SINGLE-TWITCH STIMULATION

Background: Single-twitch stimulation is the earliest and simplest pattern. The first device specifically developed to monitor the neuromuscular block, the "St. Thomas's Hospital nerve stimulator," could only deliver a single twitch.[33] For decades it remained the only established stimulation pattern to assess neuromuscular blockade intraoperatively.

Stimulation pattern: In the single-twitch mode of stimulation, single electrical stimuli are applied to a peripheral motor nerve at frequencies ranging from 1.0 Hz (once every second) to 0.1 Hz (once every 10 seconds; Fig. 43.4) and

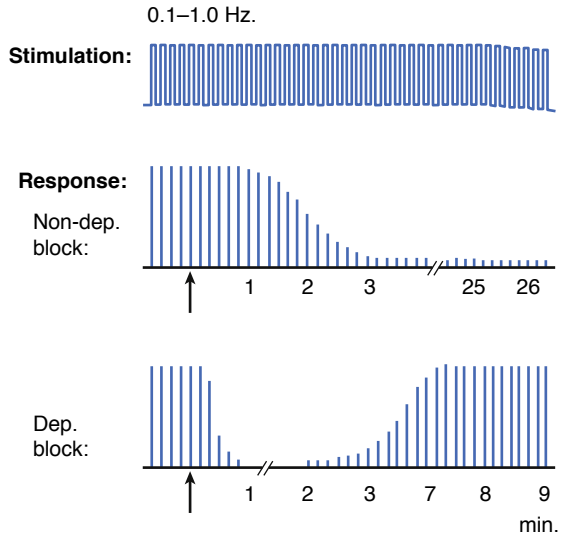

Fig. 43.4 Pattern of electrical stimulation and evoked muscle responses to single-twitch nerve stimulation (at frequencies of 0.1-1.0 Hz) after injection of nondepolarizing (Non-dep.) and depolarizing (Dep.) neuromuscular blocking drugs *(arrows)*. Note that except for the difference in time factors, no differences in the strength of the evoked responses exist between the two types of block.

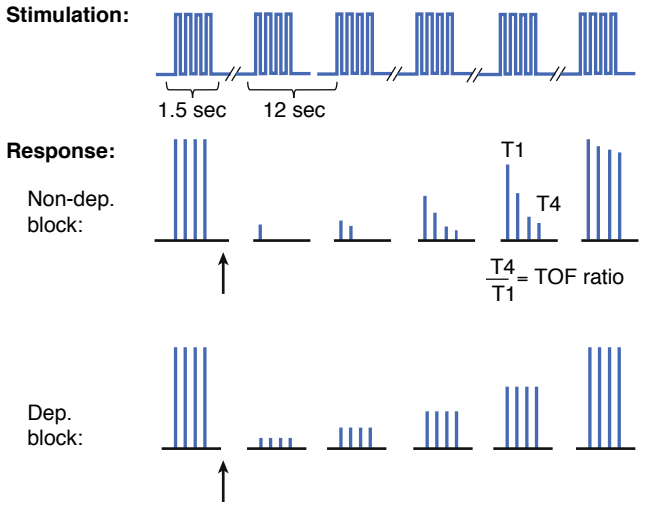

Fig. 43.5 Pattern of electrical stimulation and evoked muscle responses to train-of-four *(TOF)* nerve stimulation before and after injection of nondepolarizing (Non-dep.) and depolarizing (Dep.) neuromuscular blocking drugs *(arrows)*.

the subsequent muscle response is evaluated. The response to single-twitch stimulation depends on the frequency at which the individual stimuli are applied. If the rate of delivery is increased to greater than 0.15 Hz, the evoked response will gradually decrease and stabilize at a lower level. Therefore, results obtained with 1-Hz single-twitch stimulation cannot be compared with results obtained using, for example, 0.1-Hz single-twitch stimulation.[34] As a result, a frequency of 0.1 Hz is generally recommended.

Clinical application: To assess the degree of neuromuscular blockade after single-twitch stimulations, a comparison with a reference value recorded before administration of the NMBA is mandatory. Thus, without appropriate monitoring equipment, this stimulation pattern does not provide sufficient information of the level of block. In clinical practice, the single twitch stimulation has only limited value as a stand-alone stimulation pattern; it is mainly used as a component of the PTC stimulation and as 0.1 Hz single-twitch stimulation, it is sometimes used in scientific trials specifically to evaluate the time to onset of neuromuscular blockade. Moreover, it is the only stimulation pattern that allows, in conjunction with a monitoring device, assessing a depolarizing neuromuscular block after succinylcholine.

TRAIN-OF-FOUR STIMULATION

Background: The TOF stimulation pattern was introduced by Ali and associates[35,36] during the early 1970s. They aimed to develop a tool providing clinically reliable information throughout all phases of neuromuscular blockade with simple nerve stimulator and without the need for a monitoring device.

Stimulation pattern: TOF stimulation consists of four supramaximal stimuli given every 0.5 seconds (2 Hz; Fig.43.5) and each stimulus in the train causes the muscle to contract. The basis for evaluation is either the number of discernible responses after TOF stimulation (i.e., TOF count) or the "fade" in the train of responses—that is, dividing the amplitude of the fourth response by the amplitude of the first response (i.e., TOF ratio). Without prior administration of a muscle relaxant, all four responses are normally the same: the TOF ratio is 1.0. During a partial nondepolarizing block, the TOF ratio decreases (fades) and is inversely proportional to the degree of block. During a partial depolarizing block, no fade occurs in the TOF response and the TOF ratio remains 1.0, independently of the level of depolarizing neuromuscular blockade. Fade in the TOF response after injection of succinylcholine signifies the development of a phase II block (discussed later in the section on depolarizing neuromuscular block).

When used continuously, an interval of at least 10 seconds should be allowed between each set (train) of four stimuli to avoid fade during the measurement.

Application: TOF stimulation is still the most frequently used stimulation pattern. The advantages of TOF stimulation are most apparent during a nondepolarizing neuromuscular block because the degree of block can be read directly from the TOF response even though a preoperative value is lacking. Clinically relevant information about the onset, surgical relaxation, and neuromuscular recovery can be obtained with the same stimulation pattern by using a simple peripheral nerve stimulator; the TOF count allows reliable assessment of the onset of neuromuscular block, and moderate blockade. Moreover, the TOF ratio can be taken as a measure of neuromuscular recovery from nondepolarizing blockade. TOF stimulation has some advantages over DBS and PTC stimulation; it is less painful and, unlike tetanic stimulation, does not generally influence subsequent monitoring of the degree of neuromuscular block. There are major limitations of the TOF stimulation pattern. First, the subjective assessment of the TOF ratio overestimates neuromuscular recovery, as the tactile of visual estimation of fade is accurate only if the TOF ratio is less than 0.4; in other words, at a TOF ratio between 0.4 and 0.9, fade cannot be detected either visually or tactically. Therefore, objective monitoring devices are needed to further quantify neuromuscular recovery and to reliably exclude residual

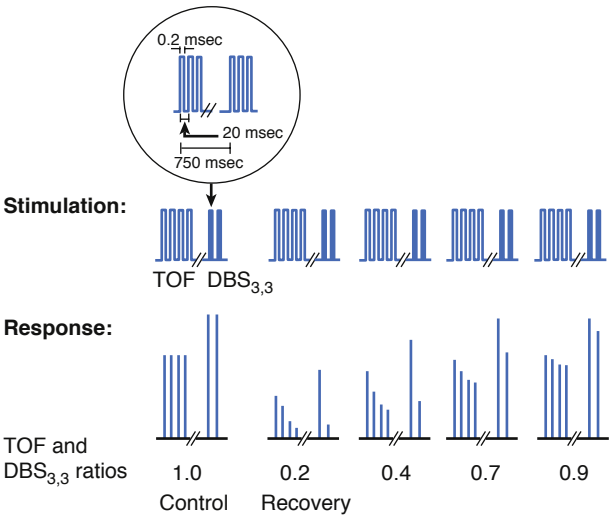

Fig. 43.6 Pattern of electrical stimulation and evoked muscle responses to train-of-four *(TOF)* nerve stimulation and double-burst nerve stimulation (i.e., three impulses in each of two tetanic bursts, *$DBS_{3,3}$*) before injection of muscle relaxants (control) and during recovery from nondepolarizing neuromuscular block. The TOF ratio is the amplitude of the fourth response to TOF divided by the amplitude of the first response. The $DBS_{3,3}$ ratio is the amplitude of the second response to $DBS_{3,3}$ divided by the amplitude of the first response. (See text for further explanation.)

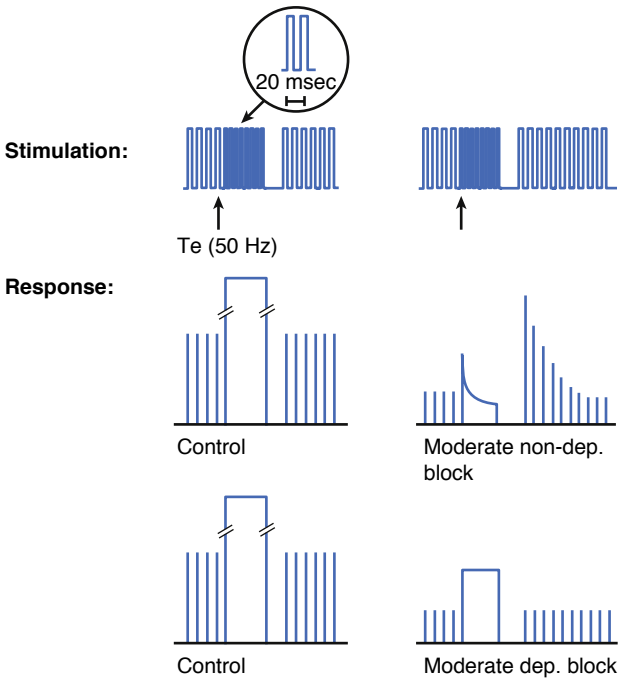

Fig. 43.7 Pattern of stimulation and evoked muscle responses to tetanic (50 Hz) nerve stimulation for 5 seconds *(Te)* and posttetanic twitch stimulation (1.0 Hz; *arrows*). Stimulation was applied before the injection of neuromuscular blocking drugs and during moderate nondepolarizing (non-dep.) and depolarizing (dep.) blocks. Note the fade in the response to tetanic stimulation, plus the posttetanic facilitation of transmission during nondepolarizing block. During depolarizing block, the tetanic response is well sustained, and no posttetanic facilitation of transmission occurs.

paralysis. Second, the TOF stimulation does not allow the clinician to quantify intense and deep levels of neuromuscular blockade (i.e., at no responses to TOF). Finally, the TOF stimulation does not allow monitoring of the depolarizing phase I blockade.

DOUBLE-BURST STIMULATION

Background: DBS was developed by Viby-Mogensen and associates in 1989 to improve the tactile or visual evaluation of recovery from nondepolarizing neuromuscular blockade.

Stimulation pattern: DBS consists of two short bursts of 50-Hz tetanic stimulation separated by 750 ms, with a 0.2-ms duration of each square wave impulse in the burst (Fig. 43.6). The number of impulses in each burst can vary: in the $DBS_{3,3}$ mode, there are three impulses in each of the two bursts, whereas in the $DBS_{3,2}$ mode, the first burst had three impulses and the second burst consisted of only two impulses.[37-39] The individual twitches elicited by each burst blend together and are felt as one single muscle contraction. Thus, the response to DBS is two short muscle contractions and fade in the second burst compared to the first one is the basis for evaluation. In nonparalyzed muscle, both muscle contractions are of equal strength. In a partially paralyzed muscle, the second response is weaker than the first and corresponds to the typical TOF fade (see Fig 43.6). When measured mechanically, the TOF ratio correlates closely with the $DBS_{3,3}$ ratio. Compared to $DBS_{3,3,}$ tactile detection of fade is slightly improved with the $DBS_{3,2}$ mode, especially at higher TOF ratios.

Clinical application: DBS was developed with the specific aim of improving manual (tactile or visual) detection of residual nondepolarizing block under clinical conditions,[38] or during recovery and immediately after surgery. Indeed, tactile evaluation of the response to DBS is more accurate in detecting fade compared to TOF. However, a DBS is still insufficient to exclude reliably residual paralysis corresponding to a TOF ratio between 0.6 and 0.9.[39-41] Accordingly, DBS cannot replace objective monitoring.

TETANIC STIMULATION

Background: Tetanic stimulation was proposed by Tassonyi in 1975[42] as an alternative method to evaluate residual neuromuscular blockade.

Stimulation pattern: Tetanic stimulation consists of high-frequency delivery of electrical stimuli (e.g., 50-100 Hz). The most commonly used pattern in clinical practice is 50-Hz stimulation given for 5 seconds, although some investigators have advocated the use of 100-Hz, or even 200-Hz stimulation for 1 second. In normal neuromuscular transmission, the observer detects one strong, sustained muscle contraction, and fade after tetanic stimulation is the basis for evaluation of nondepolarizing block. During a depolarizing block, the muscle response to 50-Hz tetanic stimulation for 5 seconds is sustained. In contrast, during a phase II block after the injection of succinylcholine, the response following tetanic stimulation is not sustained (i.e., fade occurs; Fig. 43.7).

Fade in response to tetanic stimulation is normally considered a presynaptic event. The traditional explanation is that at the start of tetanic stimulation, large amounts of acetylcholine are released from immediately available stores in the presynaptic nerve terminal. As these stores become

depleted, the rate of acetylcholine release decreases until equilibrium between mobilization and synthesis of acetylcholine is achieved. Despite this equilibrium, the muscle response to tetanic nerve stimulation is maintained (given normal neuromuscular transmission) because the acetylcholine released is many times greater than the amount necessary to evoke a response. However, when the "margin of safety"[43] at the postsynaptic membrane (i.e., the number of free cholinergic receptors) is reduced by nondepolarizing neuromuscular blocking drugs, a typical reduction in twitch height is seen with a fade, especially during repetitive stimulation. In addition to this postsynaptic block, nondepolarizing neuromuscular blocking drugs can also block presynaptic neuronal subtype acetylcholine receptors, thereby leading to impaired mobilization of acetylcholine within the nerve terminal.[44] This effect substantially contributes to fade in the response to tetanic (and TOF) stimulation. Although the degree of fade depends primarily on the degree of neuromuscular block, fade also depends on the frequency (Hz), the length (seconds) of stimulation, and on how often tetanic stimuli are applied. Unless these variables are kept constant, results from different studies using tetanic stimulation cannot be compared.

Clinical application: Traditionally, tetanic stimulation was proposed to evaluate residual neuromuscular block. While the sensitivity of tetanic stimulation to detect residual paralysis is about 70%, its specificity is only about 50%. Especially when anesthesia was maintained with volatile anesthetics, a marked fade can be observed despite adequate neuromuscular recovery or even without prior administration of a nondepolarizing NMBA. Hence, this test is of limited value for assessing neuromuscular recovery. Furthermore, tetanic stimulation is very painful, which limits its use in unanesthetized patients. In the late phase of neuromuscular recovery, tetanic stimulation can produce lasting antagonism of neuromuscular block in the stimulated muscle such that the response of the tested site may no longer be representative of other muscle groups.[45] For all these reasons, tetanic stimulation has little, if any, use in everyday clinical anesthesia, except as a component in DBS and PTC stimulation.

POSTTETANIC COUNT STIMULATION

Background: PTC stimulation was developed by Viby-Mogensen to allow tactile or visual evaluation of profound nondepolarizing neuromuscular blockade that does not respond to TOF stimulation.[46]

Stimulation pattern: PTC is a composite stimulation pattern composed by a tetanic stimulation (50 Hz for 5 seconds) followed by 10 to 15 single twitches (i.e., PTC twitches) given at 1 Hz starting 3 seconds after the end of tetanic stimulation.[46] It is based on a phenomenon called "posttetanic potentiation": tetanic stimulation leads to a transient, exaggerated release of acetylcholine that briefly shifts the ratio of acetylcholine and NMBA at the motor endplate in favor of acetylcholine. Even if no twitch response has been discernible prior to the tetanic stimulation, noticeable muscle contractions might occur briefly after tetanic stimulation (see Fig. 43.7). The basis for evaluation of the PTC is the count of these discernible posttetanic twitches.

The response to PTC stimulation depends primarily on the degree of neuromuscular block. It also depends on the frequency and duration of tetanic stimulation, the length of time between the end of tetanic stimulation and the first posttetanic stimulus, the frequency of the single-twitch stimulation, and probably the duration of single-twitch stimulation before tetanic stimulation. When the PTC method is used, these variables should be kept constant. Because of interference between PTC stimulation and the actual neuromuscular block within the monitored hand, tetanic stimulation should ideally not be performed more often than every 6 minutes.[46]

Clinical application and limitation: Moderate levels of neuromuscular blockade (i.e., TOF count between 1 and 4) are not sufficient to reliably prevent reactions of the diaphragm and/or laryngeal muscles after stimulation. Both muscles are rather resistant to the effect of nondepolarizing NMBA. Therefore, more profound levels of neuromuscular blockade are needed in clinical situations where any bucking or coughing in response to tracheal stimulation or sudden diaphragmatic movements during surgery should be avoided. Only PTC stimulation allows assessment of these degrees of neuromuscular blockade. During intense block, there is no response to either tetanic or posttetanic stimulation (Fig. 43.8). As the period of intense neuromuscular block dissipates, the first response to posttetanic twitch stimulation occurs and is followed by a gradual return of posttetanic twitches until the first response to TOF stimulation reappears. The PTC should be 3 or less if a deep block is required for clinical reasons; at 6 to 10 PTC, the return of the first TOF response is most often imminent (Fig. 43.9).[46-50] Because tetanic stimulation should not be performed more often than every 6 minutes, this stimulation pattern cannot be applied continuously.

Equipment

Although many nerve stimulators are commercially available, not all meet the basic requirements for clinical use. The stimulus should produce a monophasic and rectangular waveform, and the length of the pulse should not exceed 0.2 to 0.3 ms. A pulse exceeding 0.5 ms may stimulate the muscle directly or cause repetitive firing. Stimulation at a constant current is preferable to stimulation at a constant voltage because current is the determinant of nerve stimulation. Furthermore, for safety reasons, the nerve stimulator should be operated by a rechargeable battery, include a battery check, and be able to generate 60 to 70 mA, but not more than 80 mA. Some commercially available stimulators can deliver just 25 to 50 mA and provide a constant current only when skin resistance ranges from 0 to 2.5 kΩ. This is a limitation, as skin resistance can increase to approximately 5 kΩ, especially during lower skin temperature. The high skin resistance can cause the current delivered to the nerve to decrease below the supramaximal level and lead to a decrease in the response to stimulation. Ideally, the nerve stimulator should have a built-in warning system, or a current level display that alerts the user when the selected current is not delivered to the nerve. Alternatively, the impedance should be indicated at the screen. The polarity of the electrodes should be indicated, and the

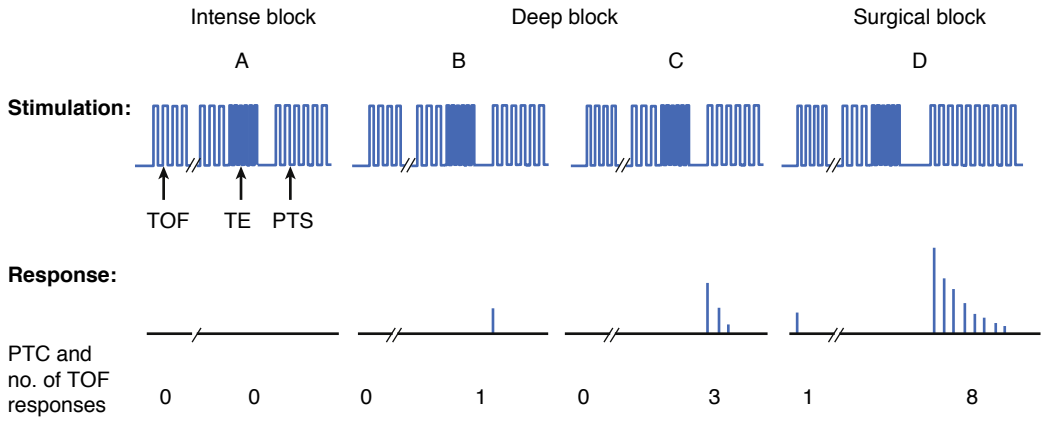

Fig. 43.8 Pattern of electrical stimulation and evoked muscle responses to train-of-four *(TOF)* nerve stimulation, 50-Hz tetanic nerve stimulation for 5 seconds *(TE)*, and 1.0-Hz posttetanic twitch stimulation *(PTS)* during four different levels of nondepolarizing neuromuscular block. During intense block of peripheral muscles (A), no response to any of the forms of stimulation occurs. During less pronounced block (deep block, B and C), there is still no response to TOF stimulation, but posttetanic facilitation of transmission is present. During surgical block (D), the first response to TOF appears and posttetanic facilitation increases further. The posttetanic count (see text) is 1 during very deep block (B), 3 during less deep block (C), and 8 during surgical (or moderate) block (D).

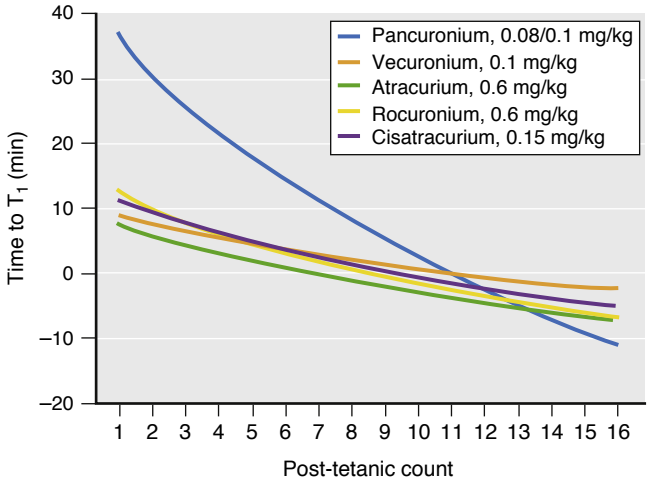

Fig. 43.9 Relationship between the posttetanic count and time when onset of train-of-four (T_1) is likely to be elicited for various neuromuscular blocking agents. (From El-Orbany MI, Joseph JN, Salem MR. The relationship of post-tetanic count and train-of-four responses during recovery from intense cisatracurium-induced neuromuscular block. *Anesth Analg.* 2003;97[1]:80–84.)

apparatus should be capable of delivering the following modes of stimulation: TOF (as both a single train and in a repetitive mode, with TOF stimulation being given every 10-20 seconds), and PTC. Some recent nerve stimulators switch automatically between TOF and PTC, depending on the level of neuromuscular blockade. If the nerve stimulator does not allow objective measurement of the response to TOF stimulation, at least one DBS mode should be available, preferably $DBS_{3,2}$.

Peripheral Nerve Stimulator

Peripheral nerve stimulators only allow stimulation of the target nerve; the subsequent muscular response is assessed subjectively either tactilely or visually. When applying TOF stimulation and evaluating the TOF count, the peripheral nerve stimulator may deliver clinically useful information about the onset of neuromuscular block or the need for an additional dose of relaxant. Moreover, the clinician could be guided for the timing and dosing of reversal agents. It is in the determination of full neuromuscular recovery these devices have clinical limitations. It is impossible to reliably exclude residual paralysis. A simple nerve stimulator acts only as a guide and should not be used as a diagnostic tool to exclude residual paralysis.

Objective Monitors

Objective monitors measure the evoked responses objectively and display it on a screen.

Several methods may be used for objective clinical monitoring of neuromuscular function: evoked mechanical response of the muscle (mechanomyography [MMG]), evoked electrical response of the muscle (electromyography [EMG]), acceleration of the muscle response (AMG), evoked electrical response in a piezoelectric film sensor attached to the muscle (kinemyography [KMG]), measurement of pressure changes in blood pressure cuff after contractions of the upper arm muscles (cuff pressure modality [CPM]), measurement of pressure change of a spherical balloon after hand contraction (compressomyography [CMG]), and measurement of low-frequency sounds evoked by the muscle contraction (phonomyography [PMG]). The different methods are described below. For further information on recording evoked responses, the reader is referred to guidelines for good clinical research practice in pharmacodynamic studies of neuromuscular blocking drugs.[17] The only objective monitors currently available are based on AMG, EMG, CPM, and KMG. The use of computer-guided administration of neuromuscular blocking drugs and "closed loop control" systems has been suggested, but no systems are commercially available.[51,52]

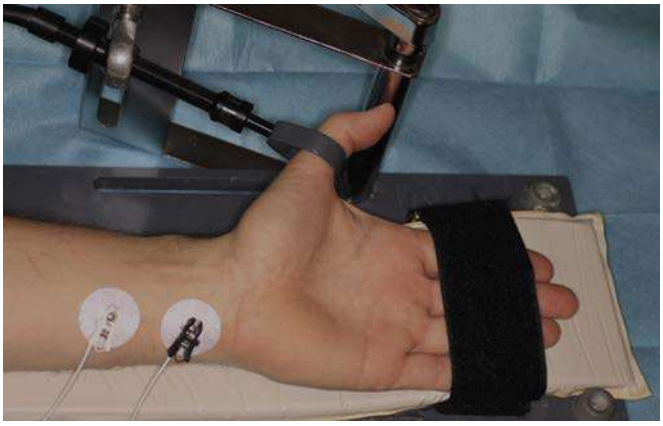

Fig. 43.10 The setup for mechanomyography. The response to nerve stimulation is measured using a force transducer (TD-100; Biometer, Odense, Denmark) placed at the proximal phalanx of the thumb.

MECHANOMYOGRAPHY

MMG measures the isometric contraction of a muscle after stimulation of the corresponding nerve. A transducer converts the force of an isometric contraction into an electrical signal. For correct and reproducible measurement, the muscle contraction needs to be isometric. In clinical anesthesia, this condition is most easily achieved by measuring the force of contraction of the thumb after the application of a resting tension of 200 to 300 g (a preload) to the thumb. When the ulnar nerve is stimulated, the thumb (the adductor pollicis muscle) acts on a force-displacement transducer (Fig. 43.10). The force of contraction is then converted into an electrical signal, which is amplified, displayed, and recorded. The arm and hand should be rigidly fixed, and care should be taken to prevent overloading of the transducer. In addition, the transducer should be placed in correct relation to the thumb (i.e., the thumb should always apply tension along the length of the transducer). It is important to remember that the response to nerve stimulation depends on the frequency with which the individual stimuli are applied and that the time used to achieve a stable control response may influence subsequent determination of the onset time and duration of block.[17] Generally, the reaction to supramaximal stimulation increases during the first 8 to 12 minutes after commencement of the stimulation (staircase phenomenon). Therefore, in clinical studies, recording of the control response (before injection of muscle relaxant) should not be made until the response has stabilized for 8 to 12 minutes or a 2- or 5-second 50-Hz tetanic stimulation has been given.[53] Even then, twitch response often recovers to 110% to 150% of the control response after paralysis with succinylcholine. This increase in response, possibly caused by a change in the contractile response of the muscle, normally disappears within 15 to 25 minutes.

Although there are numerous methods for mechanical recording of evoked mechanical responses, not all meet the criteria outlined. MMG is recognized as the gold standard of neuromuscular monitoring.[17]

Despite this status, there is no commercially available neuromuscular monitor for daily clinical use based on this principle. This type of monitor is relegated to research purpose only.

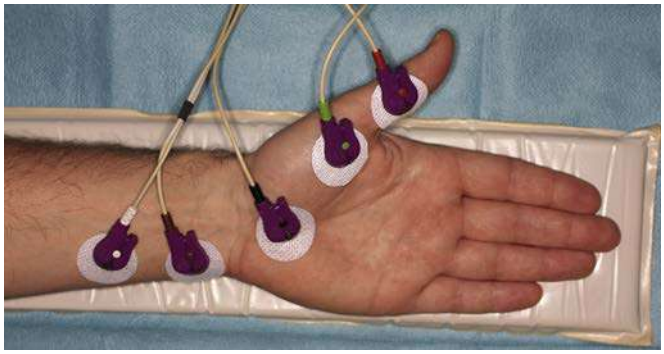

Fig. 43.11 The setup for electromyography (NMT ElectroSensor, Datex-Ohmeda, Helsinki, Finland) for recording the compound action potential from the adductor pollicis muscle.

ELECTROMYOGRAPHY

EMG is the oldest technique used for quantification of neuromuscular blockade. Evoked EMG records the compound muscle action potentials produced by stimulation of a peripheral nerve. The compound action potential is an electrical activity that for many years could be detected only by means of a preamplifier and a storage oscilloscope. Modern neuromuscular transmission analyzers are able to make online electronic analyses and graphic presentations of the EMG response.

The evoked EMG response is most often obtained from muscles innervated by the ulnar or the median nerves. Stimulating electrodes are applied as in force measurements. Most often, the evoked EMG response is obtained from the thenar or hypothenar eminence of the hand or from the first dorsal interosseous muscle of the hand, preferably with the active electrode over the motor point of the muscle (Fig. 43.11). The signal picked up by the analyzer is processed by an amplifier, a rectifier, and an electronic integrator. The results are displayed either as a percentage of control or as a TOF ratio.

Two new sites for recording the EMG response have been introduced: the larynx and the diaphragm.[54,55] Using a noninvasive disposable laryngeal electrode attached to the tracheal tube and placed between the vocal cords, it is possible to monitor the onset of neuromuscular block in the laryngeal muscles. However, the method is mainly of interest in clinical research when investigating onset times of the laryngeal muscles. In paravertebral surface diaphragmatic EMG, the recording electrodes are placed on the right of vertebrae T12/L1 or L1/L2 for monitoring the response of the right diaphragmatic crux to transcutaneous stimulation of the right phrenic nerve at the neck.[54-57] As is the case with surface laryngeal EMG, surface diaphragmatic EMG is mainly of interest in clinical research.

Evoked electrical and mechanical responses represent different physiologic events. Evoked EMG records changes in the electrical activity of one or more muscles, whereas evoked MMG records changes associated with excitation-contraction coupling and contraction of the muscle as well. For these reasons, the results obtained with these methods may differ.[57,58] Although evoked EMG responses generally correlate well with evoked mechanical responses,[38] marked differences can occur, especially in the response to succinylcholine and in the TOF ratio during recovery from a nondepolarizing block.[38,57,59]

In theory, recording of evoked EMG responses has several advantages over recording of evoked mechanical responses. Equipment for measuring-evoked EMG responses is easier to set up, the response reflects only factors influencing neuromuscular transmission, and the response can be obtained from muscles not accessible to mechanical recording. However, evoked EMG does entail some difficulties. Although high-quality recordings are possible in most patients, the results are not always reliable. For one thing, improper placement of electrodes can result in inadequate pickup of the compound EMG signal. If the neuromuscular transmission analyzer does not allow observation of the actual waveform of the compound EMG, determining optimal placement of the electrodes is difficult. Another source of unreliable results may be that fixation of the hand with a preload on the thumb might be more important than is generally appreciated, inasmuch as changes in the position of the electrodes in relation to the muscle can affect the EMG response. In addition, direct muscle stimulation sometimes occurs. If muscles close to the stimulating electrodes are stimulated directly, the recording electrodes can pick up an electrical signal even though neuromuscular transmission is completely blocked. Another difficulty is that the EMG response often does not return to the control value. Whether this situation is the result of technical problems, inadequate fixation of the hand, or changes in temperature is unknown (Fig. 43.12). Finally, the evoked EMG response is highly sensitive to electrical interference, such as that caused by diathermy.

Currently, to our knowledge, there are only a few EMG-based monitors available for clinical use, but more devices are under development.

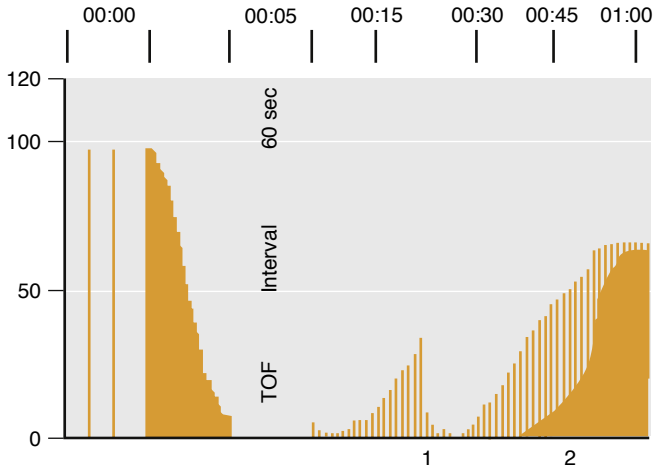

Fig. 43.12 Evoked electromyographic printout from a Relaxograph (Datex-Ohmeda, Helsinki, Finland). Initially, single-twitch stimulation was given at 0.1 Hz, and vecuronium (70 μg/kg) was administered intravenously for tracheal intubation. After approximately 5 minutes, the mode of stimulation was changed to train-of-four *(TOF)* stimulation every 60 seconds. At a twitch height (first twitch in the TOF response) of approximately 30% of control (marker 1), 1 mg of vecuronium was given intravenously. At marker 2, 1 mg of neostigmine was given intravenously, preceded by 2 mg of glycopyrrolate. The printout also illustrates the common problem of failure of the electromyographic response to return to the control level. (Courtesy Datex-Ohmeda, Helsinki, Finland.)

ACCELEROMYOGRAPHY

AMG was developed specifically for clinical use and is widely practiced. The technique of AMG is based on Newton's second law: force = mass × acceleration, it measures the isotonic acceleration of the stimulated muscle.[60] If mass is constant, acceleration is directly proportional to force. Accordingly, after nerve stimulation, one can measure not only the evoked force but also acceleration of the thumb.

AMG uses a piezoelectric ceramic wafer with electrodes on both sides. Exposure of the electrode to a force generates an electrical voltage proportional to acceleration of the electrode. Consequently, when an accelerometer is fixed to the thumb and the ulnar nerve is stimulated, an electrical signal is produced whenever the thumb moves (Fig. 43.13). This signal can be analyzed in a specially designed analyzer[61] or displayed on a recording system.

AMG is a simple method of analyzing neuromuscular function, both in the operating room and in the intensive care unit. Although good correlation exists between the TOF ratio measured by this method and the TOF ratio measured with a force-displacement transducer or EMG,[60,62,63] measurements made via AMG are not directly comparable with results obtained by the other two methods.[63-69] When AMG is used with a free-moving thumb, as originally suggested,[60] wide limits of agreements in twitch height (T1) and TOF ratio and differences in the onset and recovery course of block between AMG and MMG have been found. Moreover, the AMG control TOF ratio is consistently higher than

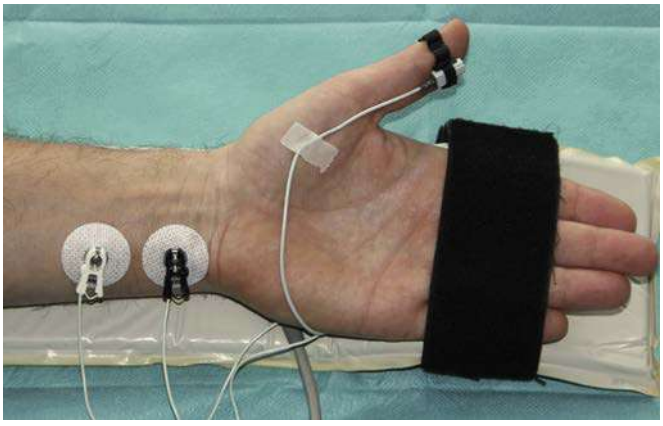

Fig. 43.13 The setup of acceleromyography without preload (TOF Watch, Biometer, Odense, Denmark). The response to nerve stimulation is measured with a small piezoelectric acceleration transducer placed distally on the volar site of the thumb.

when measured with a force-displacement transducer. In accordance with this, several studies have indicated that when using AMG, the TOF ratio indicative of sufficient postoperative neuromuscular recovery is 1.0 rather than 0.90, as when measured by MMG or EMG in the adductor pollicis muscle.[6,68,70-72] In contrast to MMG and EMG, the control baseline TOF value before administration of a neuromuscular blocking drug is most often 1.1 to 1.2 when measured with AMG, and in some patients is as high as 1.4. A high control baseline value probably indicates that the TOF ratio necessary for excluding residual curarization is equally higher. For instance, in a patient with a high control baseline value (e.g., TOF = 1.2), it is to be expected that a higher TOF ratio during recovery is necessary to exclude residual

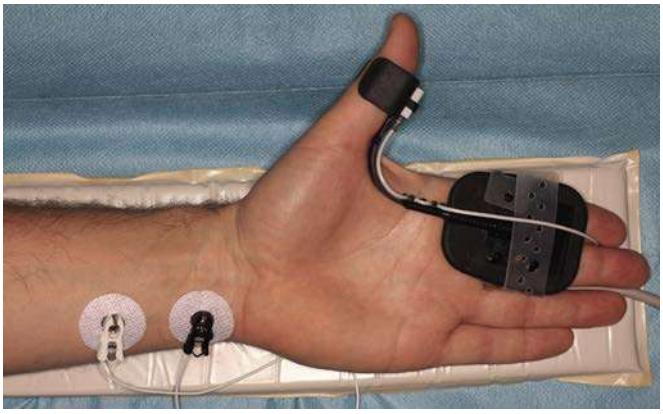

Fig. 43.14 The setup of acceleromyography with preload (TOF Watch with Hand Adapter, Biometer, Odense, Denmark). The piezoelectric acceleration transducer is placed in the Hand Adapter. The stretching wing ensures that the thumb does not touch the palm of the hand.

block compared with a patient with a low control baseline value (e.g., TOF = 0.95). It is generally accepted that the TOF ratio should be at least 0.90 to exclude clinically significant residual paralysis; using the preceding example, a TOF ratio of 1.08 (90% of 1.2) would represent safe recovery in the first patient, whereas a TOF ratio of 0.86 (90% of 0.95) would suffice in the other patient. To overcome such problems, it has been suggested to refer the actually obtained TOF ratios during recovery to the baseline control TOF ratio (normalization).[67,72-76] Currently, no commercially available monitors can "normalize" the TOF ratio automatically. Intuitively, for excluding residual block using AMG, a TOF ratio of at least 1.0 should be targeted to exclude residual block.[67,68,72,74]

One reason for the wide limits of agreement between AMG and MMG is probably and paradoxically connected with one of the originally claimed advantages of the method, that fixation of the hand could be reduced to a minimum as long as the thumb could move freely.[60] In clinical practice, it is often not possible to ensure that the thumb can move freely and that the position of the hand does not change during the surgical procedure. The evoked response can therefore vary considerably. Several solutions have been proposed, but the use of an elastic preload on the thumb improves the precision without compromising the agreement between results obtained with AMG and MMG (Fig. 43.14).[67,68] Several studies have indicated that objective monitoring with AMG reduces and almost eliminates the problem of postoperative residual neuromuscular block.[67,77-81]

When the thumb is not available for monitoring during surgery, some clinicians prefer to monitor the AMG response of the orbicularis oculi or the corrugator supercilii in response to facial nerve stimulation.[28] However, neuromuscular monitoring of both sites with AMG is subject to both large uncertainty regarding the extent of paralysis and high risk of direct muscle stimulation, and it cannot be recommended for routine monitoring. It provides only a rough estimate of the degree of block of the peripheral muscles.[82,83]

AMG was one of the first widely distributed commercially available monitors and has therefore become the standard for qualitative monitoring in the clinical setting. Today, AMG devices are available as portable monitors as well as integrated in the anesthesia monitor.

Recently, AMG monitors with three-dimensional piezoelectric transducers were introduced, which sense the motion of the thumb in all directions,[83a,83b] and not just in one plane. This might further improve the reliability of the AMG technology. This novel method has been compared to the TOF-Watch (one-dimensional AMG) in two small studies. Although both studies showed some disagreement between the two methods, the authors agreed that the three-dimensional monitor may be used in clinical practice. An advantage seems to be that the monitors' integrated internal check-up ensuring that all components including the piezoelectric element are functional is developed. The newest monitors also display the impedance and calculate automatically a modified normalized TOF ratio. Hopefully, the new generation of AMG monitors becomes even more user-friendly and more reliable.

KINEMYOGRAPHY

The technique of KMG is based on the principle that stretching or bending a flexible piezoelectric film (e.g., one attached to the thumb) in response to nerve stimulation generates a voltage that is proportional to the amount of stretching or bending.[84,85]

Few studies have evaluated the function of these monitors.[84-86] Limited data indicate not only a good relationship between results obtained with KMG, AMG, and MMG, but also wide limits of agreement between the methods. Therefore, although KMG may be a valuable clinical tool, the values obtained in an individual patient with this method can vary from those obtained with MMG or AMG. Only one device based on this principle is available commercially in two sizes (adult and pediatric): the NMT MechanoSensor (Datex-Ohmeda, Helsinki, Finland).

CUFF PRESSURE MODALITY (CPM)

The cuff modality detects changes in cuff pressure due to muscle contraction. Electrodes integrated into a blood pressure cuff stimulate the brachial plexus at the humeral level. The subsequent bulk contraction of the upper arm generates pressure change in the blood pressure cuff which is analyzed and displayed at the monitor. However, only limited data are currently available and further clinical investigations are needed to prove the reliability and reproducibility of the new monitoring modality. One monitor based on this technology is commercially available: the TOF-Cuff NMT monitor (RGB Medical devices, Madrid, Spain).

COMPRESSOMYOGRAPHY

CMG measures pressure changes in a hand-held balloon. Following ulnar nerve stimulation, the force of muscle contraction of the hand muscles is transmitted to a balloon secured in the patient's hand. Despite encouraging results of the only publication investigating the device,[49] this technique has not been further developed and is not commercially available.

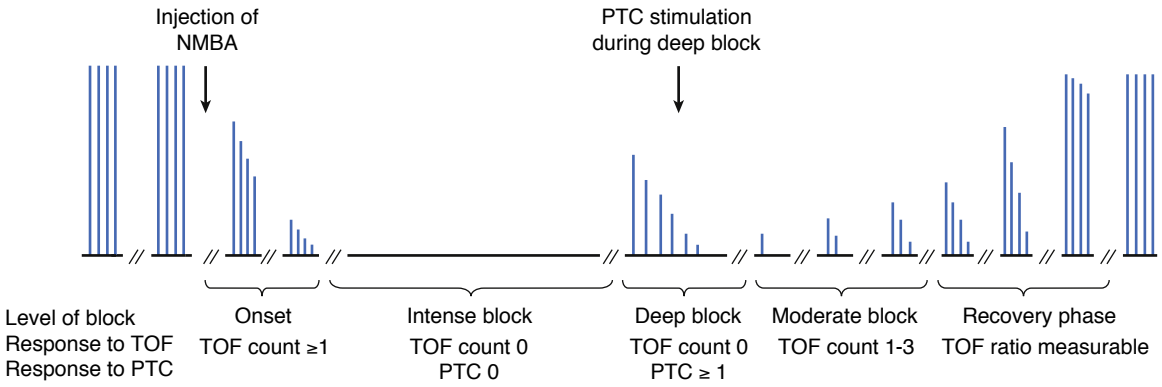

Fig. 43.15 Levels of block after a normal intubating dose of a nondepolarizing neuromuscular blocking agent *(NMBA)* as classified by posttetanic count *(PTC)* and train-of-four *(TOF)* stimulation. During intense (profound) block, there are no responses to either TOF or PTC stimulation. During deep block, there is response to PTC but not to TOF stimulation. Intense (profound) block and deep block together constitute the "period of no response to TOF stimulation." Reappearance of the response to TOF stimulation heralds the start of moderate block. Finally, when all four responses to TOF stimulation are present and a TOF ratio can be measured, the recovery period has started. (From Fuchs-Buder T, Claudius C, Skovgaard LT, et al. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: The Stockholm revision. *Acta Anaesthesiol Scand*. 2007;51[7]:789–808.)

PHONOMYOGRAPHY

PMG measures the intrinsic low-frequency sounds of muscle contraction with special microphones following nerve stimulation. PMG has been evaluated for clinical and research purposes by one study group. This group reports good correlation between evoked acoustic responses and those obtained with more traditional methods of recording, such as MMG, EMG, and AMG.[31,87-92] A potential advantage of PMG, however, is that the method can be applied not only to the adductor pollicis muscle, but also to other muscles of clinical interest such as the diaphragm, larynx, and eye muscles. In addition, the ease of application is attractive. However, PMG-based monitors are not currently commercially available.

Evaluation of Recorded Evoked Responses

In daily clinical practice, the recorded response to TOF stimulation and PTC stimulation are typically used to explain how to evaluate the degree of neuromuscular block during clinical anesthesia.

NONDEPOLARIZING NEUROMUSCULAR BLOCK

After injection of a nondepolarizing neuromuscular blocking drug in a dose sufficient for smooth tracheal intubation, TOF recording demonstrates four phases, or levels, of neuromuscular block: intense block, deep block, moderate or surgical block, and recovery (Fig. 43.15).

Intense Neuromuscular Block

Intense or profound neuromuscular block occurs within 3 to 6 minutes of injection of an intubating dose of a nondepolarizing muscle relaxant, depending on the drug and the dose given. This phase is also called the "period of no response" because no response to any pattern of nerve stimulation occurs. The length of this period varies, again depending primarily on the duration of action of the muscle relaxant and the dose given. The sensitivity of the patient to the drug also affects the period of no response. An intense block cannot be antagonized with a cholinesterase inhibitor (e.g., neostigmine), and only a high dose of sugammadex (16 mg/kg) can antagonize an intense block caused by rocuronium or vecuronium.[93,94]

Deep Neuromuscular Block

Intense neuromuscular block is followed by a period of deep neuromuscular block, characterized by absence of response to TOF stimulation, but with the presence of at least one response to PTC stimulation (i.e., PTC ≥1; compare with Fig. 43.8). To avoid diaphragmatic movements and thus, to assure surgical stillness and improve surgical space conditions during laparoscopic abdominal procedures, deep neuromuscular blockade corresponding to ≤3 PTC responses is recommended.[49] Although prediction of the duration of a deep neuromuscular block is difficult, correlation usually exists between PTC stimulation and the time until reappearance of the first response to TOF stimulation (see Fig. 43.9). Attempts to reverse a deep neuromuscular block with neostigmine are usually impossible. However, a deep neuromuscular block caused by rocuronium or vecuronium can be antagonized completely within a few minutes using a dose of sugammadex of 4 mg/kg.[95-97]

Moderate Neuromuscular Block

Moderate neuromuscular block begins when the first response to TOF stimulation appears. This phase is characterized by a gradual return of the four responses to TOF stimulation. Furthermore, good correlation exists between the degree of neuromuscular block and the number of responses to TOF stimulation. When only one response is detectable, the degree of neuromuscular block (the depression in twitch tension) is 90% to 95%. When the fourth response reappears, neuromuscular block is usually 60% to 85%.[98,99] The presence of one or two responses in the TOF pattern normally indicates sufficient relaxation for most surgical procedures. During light anesthesia, however, patients may move, buck, or cough; therefore, a deeper block (or a deeper level of anesthesia) may be necessary when elimination of sudden movements or facilitation of surgery is necessary.

Antagonism of neuromuscular block with neostigmine should usually not be attempted when the block is intense or deep. Even if some reversal occurs, it will often be inadequate, regardless of the dose of neostigmine administered.[100] Furthermore, after the administration of large doses of muscle relaxants, reversal of the block with neostigmine to clinically normal activity is not always possible if only one TOF response is present. In general, antagonism with neostigmine should not be initiated before all four responses after TOF stimulation are observed. Even then, sufficient recovery may take time and cannot be guaranteed unless documented using objective monitoring.[101-103]

Antagonism of moderate block induced by rocuronium and vecuronium can be achieved with a small dose of sugammadex (2 mg/kg) within a few minutes.[104-106] However, the reappearance of neuromuscular blockade has been reported by anesthesiologists from Japan[107] when the 2 mg/kg dose has been used. However, they did not monitor the degree of neuromuscular blockade; did the reappearance of neuromuscular blockade occur because of inadequate monitoring or too small a dose of sugammadex? Although the antagonism of neuromuscular block from sugammadex seems to be fast and predictable, neuromuscular monitoring is mandatory for proper dosing, and objective monitoring should still be used until the TOF ratio is 0.9 to 1.0.

Recovery from Neuromuscular Block

Return of the fourth response in the TOF heralds the recovery phase. During neuromuscular recovery, a reasonably good correlation exists between the actual TOF ratio and clinical observation, but the relationship between the TOF ratio and signs and symptoms of residual block varies greatly among patients.[81,100] When the TOF ratio is 0.4 or less, the patient is generally unable to lift the head or arm. Tidal volume may be normal, but vital capacity and inspiratory force is reduced. When the ratio is 0.6, most patients are able to lift their head for 3 seconds, open their eyes widely, and stick out their tongue, but vital capacity and inspiratory force are often still reduced. At a TOF ratio of 0.7 to 0.75, the patient can normally cough sufficiently and lift the head for at least 5 seconds, but grip strength may still be as low as about 60% of control.[108] When the ratio is 0.8 and higher, vital capacity and inspiratory force are normal.[36,109-111] The patient may, however, still have diplopia, blurred vision, and facial weakness (Table 43.1).[81,108]

However, the TOF ratio must exceed 0.90 when recorded with MMG or EMG, and 1.0 when using AMG to exclude clinically important residual neuromuscular block.[1,3,38,67,68,70,112-116] Moderate degrees of neuromuscular block can impair carotid body chemosensitivity to hypoxia with absent ventilatory response to arterial desaturation.[3,112,114,116] Moreover, residual block (TOF < 0.90) is associated with functional impairment of the pharyngeal and upper esophageal muscles, which most probably predisposes to regurgitation and aspiration of gastric contents.[1] Eikermann and colleagues[4] have documented that partial neuromuscular block, even to a degree that does not evoke dyspnea or oxygen desaturation, can decrease inspiratory upper airway volume and can evoke partial inspiratory airway collapse.[4] Also, residual block (TOF < 0.70) caused by the long-acting muscle relaxant pancuronium is a significant risk factor for the development of postoperative pulmonary complications (Table 43.2 and Fig. 43.16).[113] Intraoperative neuromuscular monitoring, followed by appropriate pharmacological reversal, reduces the risk of residual neuromuscular block and results in fewer patients with hypoxemic events or airway obstruction in the postanesthesia care unit.[80] Even in volunteers without sedation or impaired consciousness, a TOF ratio of 0.90 or less can impair the ability to maintain the airway.[77,108,117] Even small degrees of residual block are unpleasant for patients, causing symptoms such as general weakness and blurred vision.[81] In summary, adequate recovery of neuromuscular function requires the return of an MMG or EMG TOF ratio to at least 0.90, and an AMG TOF ratio to at least 1.0 (or normalized to 0.90),[74] which cannot be guaranteed without objective neuromuscular monitoring.[78,79,81,118-121]

TABLE 43.1 Clinical Signs and Symptoms of Residual Paralysis in Awake Volunteers after Mivacurium-Induced Neuromuscular Block

Train-of-Four Ratio	Signs and Symptoms
0.70-0.75	Diplopia and visual disturbances
	Decreased handgrip strength
	Inability to maintain apposition of the incisor teeth
	"Tongue depressor test" negative
	Inability to sit up without assistance
	Severe facial weakness
	Speaking a major effort
	Overall weakness and tiredness
0.85-0.90	Diplopia and visual disturbances
	Generalized fatigue

From 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(4):765–761.

DEPOLARIZING NEUROMUSCULAR BLOCK (PHASE I AND II BLOCKS)

Fade and posttetanic facilitation are the basis for evaluation of all stimulation patterns applied in clinical practice (i.e., TOF, DBS, and PTC stimulation). It is important to realize that during depolarizing neuromuscular phase I block, neither fade nor posttetanic facilitation occurred. Thus, the usually applied stimulation patterns do not allow assessment of depolarizing neuromuscular block. After TOF stimulation, all four responses are reduced at the same degree, no fade occurred, and all four disappear simultaneously. Thus, independently of the degree of depolarizing neuromuscular block, the TOF-ratio remains 1 and the TOF-count is either 4 or 0.

Patients with normal plasma cholinesterase activity who are given a moderate dose of succinylcholine (0.5-1.5 mg/kg) undergo a typical depolarizing neuromuscular block (phase I block; i.e., the response to TOF or tetanic stimulation does not fade, and no posttetanic facilitation of

TABLE 43.2 Relationship Between Train-of-Four Ratio at the First Postoperative Recording and Postoperative Pulmonary Complications

	PANCURONIUM (n = 226)			ATRACURIUM OR VECURONIUM (n = 450)		
		PATIENTS WITH POPC			PATIENTS WITH POPC	
	No. of patients	***n***	**%**	**No. of Patients**	***n***	**%**
TOF ≥ 0.70	167	8	4.8	426	23	5.4
TOF < 0.70	59	10	16.9*	24	1	4.2

*P < .02 versus patients in the same group with a train-of-four ratio of 0.70 or greater.

Results from a prospective, randomized, and blinded study of postoperative pulmonary complications (POPC) in a total of 691 adult patients undergoing abdominal, gynecologic, or orthopedic surgery and receiving either pancuronium, atracurium, or vecuronium.[82] In 4 of the 46 patients with POPC (1 in the pancuronium group and 3 in the atracurium and vecuronium groups), the train-of-four (TOF) ratio was not available. Because there were no significant differences in the two groups of patients given the intermediate-acting muscle relaxants, the data from these groups are pooled.

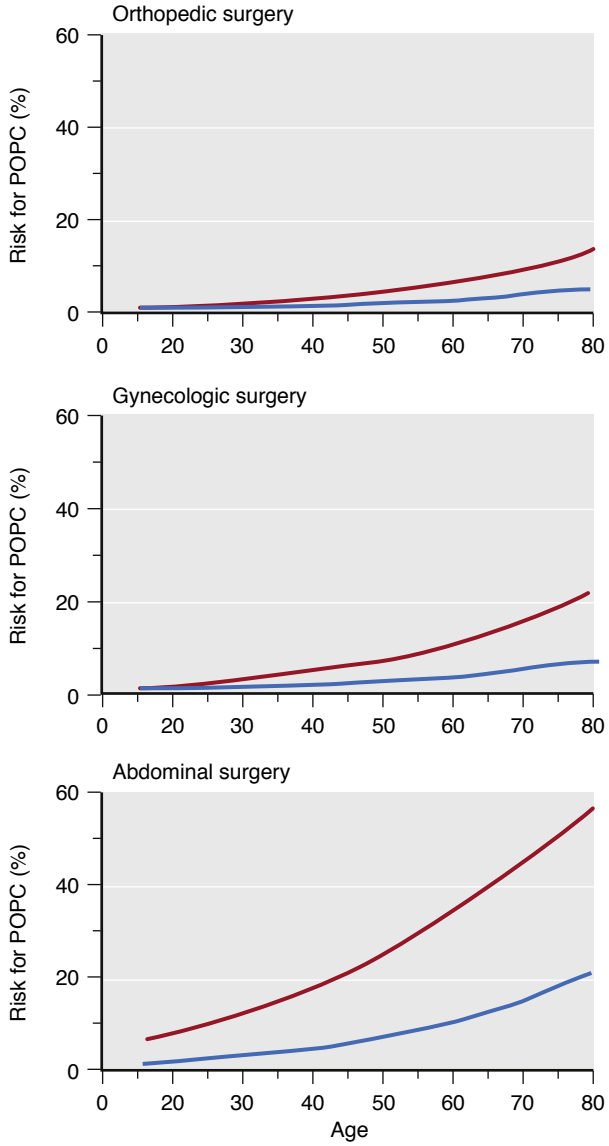

Fig. 43.16 Predicted probabilities of a postoperative pulmonary complication *(POPC)* in different age groups in orthopedic, gynecologic, and major abdominal surgery with duration of anesthesia of less than 200 minutes. The *red lines* represent patients with residual neuromuscular block (train-of-four [TOF] < 0.70) after the administration of pancuronium; the *blue lines* represent patients with a TOF of 0.70 or greater after the administration of pancuronium, as well as all patients after the administration of atracurium and vecuronium, independent of the TOF ratio at the end of anesthesia.[113]

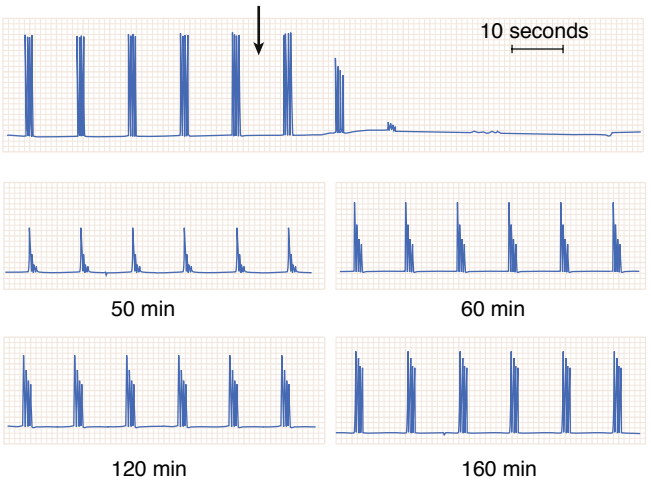

Fig. 43.17 Typical recording of the mechanical response to train-of-four ulnar nerve stimulation after injection of 1 mg/kg of succinylcholine *(arrow)* in a patient with genetically determined abnormal plasma cholinesterase activity. The prolonged duration of action and the pronounced fade in the response indicate a phase II block.

transmission occurs. All four responses are reduced at the same degree [TOF ratio is 1.0] or 0). In contrast, some patients with genetically determined abnormal plasma cholinesterase activity who are given the same dose of succinylcholine undergo a nondepolarizing-like block characterized by fade in the response to TOF and tetanic stimulation and the occurrence of posttetanic facilitation of transmission (Fig. 43.17). This type of block is called a *phase II block* (dual, mixed, or desensitizing block). In addition, phase II blocks sometimes occur in genetically normal patients after repetitive bolus doses or a prolonged infusion of succinylcholine. Therefore, in a clinical setting, TOF stimulation can be used to distinguish depolarizing phase I block and phase II block. Patients with normal plasma cholinesterase activity would recover from the neuromuscular block within a few minutes, showing four equally weak responses (TOF ratio 1.0), which quickly become stronger (still at TOF ratio 1.0). In contrast, patients with abnormal plasma cholinesterase activity and subsequent phase II block would not recover quickly and will return with a TOF count of 1, slowly increasing to 2, 3, and last 4 counts—then having a fade of TOF (TOF-ratio <1.0) during recovery as seen with nondepolarizing block.

From a therapeutic point of view, a phase II block in normal patients must be differentiated from a phase II block in patients with abnormal cholinesterase activity. In healthy patients, a phase II block can be antagonized by administering a cholinesterase inhibitor a few minutes after discontinuation of succinylcholine. In patients with abnormal genotypes, however, the effect of intravenous injection of a cholinesterase inhibitor (e.g., neostigmine) is unpredictable because it inhibits acetylcholinesterase and plasma-cholinesterase. For example, neostigmine can potentiate the block dramatically, temporarily improve neuromuscular transmission, and then potentiate the block or partially reverse the block, all depending on the time elapsed since administration of succinylcholine and the dose of neostigmine given. Therefore, unless the cholinesterase genotype is known to be normal, antagonism of a phase II block with a cholinesterase inhibitor should be undertaken with extreme caution. Even if neuromuscular function improves promptly, patient surveillance should continue for at least 1 hour.

Use of Nerve Stimulators in Daily Clinical Practice

Whenever a neuromuscular blocking drug is administered to a patient, objective monitoring of the evoked response using recording equipment is the best way to evaluate the neuromuscular block.[121a] However, tactile and visual evaluation are still common forms of clinical neuromuscular monitoring, not least when recording equipment is not available or considered unreliable. The following is a description of how to use nerve stimulators with or without recording equipment (objective monitoring).

PREPARATIONS BEFORE INDUCTION OF ANESTHESIA AND ADMINISTRATION OF THE NEUROMUSCULAR BLOCKING AGENT

First, for reliable stimulation, careful cleansing of the skin and proper placement and fixation of electrodes are essential. When the ulnar nerve is used for nerve stimulation, one should take advantage of the fact that the nerve follows the artery by placing the electrodes above the pulse. This placement gives the best response (see Fig. 43.1). Second, every effort should be taken to prevent central cooling, as well as cooling of the extremity being evaluated. Both central and local surface cooling of the adductor pollicis muscle can reduce twitch tension and the TOF ratio.[122-124] Peripheral cooling can affect nerve conduction, decrease the rate of release of acetylcholine and muscle contractility, increase skin impedance, and reduce blood flow to the muscles, thus decreasing the rate of removal of muscle relaxant from the neuromuscular junction. These factors might account for the occasional and pronounced difference in muscle response between a cold extremity and the contralateral warm extremity.[125]

USE OF A NERVE STIMULATOR DURING INDUCTION OF ANESTHESIA

The nerve stimulator should be attached to the patient before induction of anesthesia but should not be turned on until after the patient is unconscious.

Single-twitch stimulation at 1 Hz can be used initially when seeking supramaximal stimulation. However, after supramaximal stimulation has been ensured and before the muscle relaxant is injected, the recording equipment (when using objective monitoring) should be calibrated to ensure that the response is in the measurement window and the response to 1 Hz stimulation is set to 100%. Currently, all commercially available devices have an automatic calibration modus. Without calibration, the recorded response to nerve stimulation might differ significantly from the visual or tactile response throughout all levels of neuromuscular block; therefore, the mode of stimulation should be changed to TOF (or 0.1-Hz twitch stimulation). When the response to this stimulation is observed (the control response), the neuromuscular blocking drug is injected. However, devices with integrated impedance measurement do not need calibration, but at least one TOF stimulation without NMBA should be registered, allowing to normalize the recovery TOF-ratio. Although the trachea is often intubated when the response to TOF stimulation disappears, postponement of this procedure for 30 to 90 seconds, depending on the muscle relaxant used, usually produces better conditions.

When possible, the response to nerve stimulation should be evaluated at the thumb (rather than at the fifth finger). Direct stimulation of the muscle often causes subtle movement of the fifth finger when no response is present at the thumb. Finally, the different sensitivities of various muscle groups to neuromuscular blocking drugs should always be kept in mind.

USE OF A NERVE STIMULATOR DURING SURGERY

If tracheal intubation is facilitated by the administration of succinylcholine, no more muscle relaxant should be given until the response to nerve stimulation reappears or the patient shows other signs of returning neuromuscular function. If plasma cholinesterase activity is normal, the muscle response to TOF nerve stimulation reappears within 4 to 8 minutes.

When a nondepolarizing neuromuscular drug is used for tracheal intubation, a longer-lasting period of intense block usually follows. During this period of no response to TOF and single-twitch stimulation, the time until the return of response to TOF stimulation can be evaluated by PTC (see Fig. 43.9 and Fig. 43.18).

For most surgical procedures requiring muscle relaxation, it is not necessary to have a deep or intense block, provided that the patient is adequately anesthetized. If a nondepolarizing relaxant is used, a moderate level of neuromuscular block with one or two responses to TOF stimulation is sufficient. However, because the respiratory muscles (including the diaphragm) are more resistant to neuromuscular blocking drugs than the peripheral muscles are, the patient may breathe, hiccup, or even cough at this moderate level of block. Moreover, tonus of the diaphragm might impede the surgical conditions, especially during abdominal laparoscopic surgery. To ensure paralysis of the diaphragm, neuromuscular block of the peripheral muscles must be deep so that the PTC is 1-3 at the thumb.

The disadvantages of sustaining a deep or intense neuromuscular block is that at these levels of block, the muscles

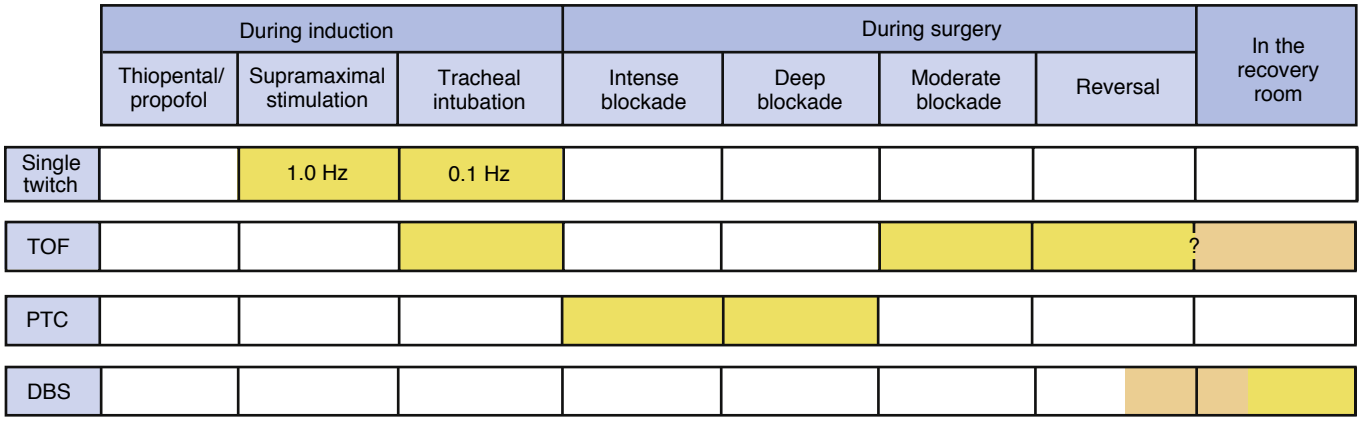

Fig. 43.18 Diagram showing when the different modes of electrical nerve stimulation can be used during clinical anesthesia. *Dark areas* indicate appropriate use and *light areas*, less effective use. Modes of nerve stimulation are train-of-four *(TOF)* stimulation; posttetanic count *(PTC)*; double-burst stimulation *(DBS)*; and the question mark (?), indicating that TOF is less useful in the recovery room unless measured with mechanomyography, electromyography, or acceleromyography. (See text for further explanation.)

are completely paralyzed and the patient cannot signal awareness with voluntary or involuntary movements. Another disadvantage is that deep or intense block cannot readily be reversed by neostigmine. Only sugammadex can reverse a deep or intense neuromuscular block (if caused by rocuronium or vecuronium).

USE OF A NERVE STIMULATOR DURING REVERSAL OF NEUROMUSCULAR BLOCK

Antagonism of nondepolarizing neuromuscular block is most often facilitated with a cholinesterase inhibitor, such as neostigmine, or with the selective relaxant binding agent sugammadex when the neuromuscular block is achieved using rocuronium or vecuronium.

Antagonism with neostigmine should not be initiated before at least all four responses to TOF stimulation are present. Reversal of neuromuscular block will not be hastened and can possibly be delayed by giving neostigmine when no response to peripheral nerve stimulation is present. Moreover, even when there are four responses to TOF stimulation, the reversal is slow and insufficient in some patients. With a large dose of neostigmine (e.g., 5 mg/70 kg), the median time to achieve a TOF ratio of 0.90 is 15 to 20 minutes, and it will take approximately 90 to 120 minutes to achieve a TOF ratio of 0.90 in 95% of the patients after an intermediate-acting neuromuscular blocking drug (e.g., rocuronium).[126] Conversely, a large dose of neostigmine after full recovery might give a paradoxical block with decreasing TOF ratio.[127-131]

When rocuronium or vecuronium is used, the selective relaxant binding drug sugammadex can be used for reversal.[104,105] Sugammadex encapsulates rocuronium and vecuronium with a high affinity, thereby antagonizing the neuromuscular blocking effect. Three different doses of sugammadex are recommended according to the level of block. A large dose (16 mg/kg) is given during intense block (no response to PTC stimulation),[93,94] a medium dose (4 mg/kg) during deep block (at least one response to PTC),[95-97] and a low dose (2 mg/kg) during moderate block (two or more responses to TOF stimulation).[104-106] In most patients, all levels of neuromuscular block are reversed within 2 to 5 minutes. However, appropriate dosing requires neuromuscular monitoring and residual neuromuscular block can be excluded only with objective monitoring (TOF ratio, 0.9-1.0), even after routine use of sugammadex.[107,132]

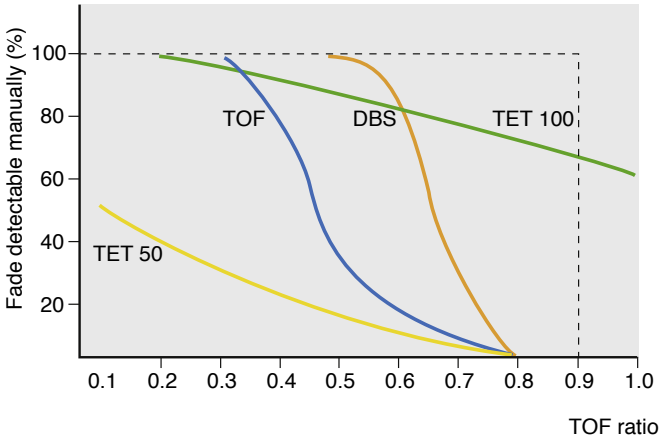

Fig. 43.19 Fade detectable by feel in the response to train-of-four *(TOF)*, double-burst stimulation ($DBS_{3,3}$), and 50- and 100-Hz tetanic stimulation (*TET* 50 and TET 100) in relation to the true TOF ratio, as measured mechanically. The axis indicates the percentage of instances in which fade can be detected at a given TOF ratio.[37,39,72] It appears that it is not possible to exclude residual neuromuscular block by any of the methods. (See text for further explanation.)

During recovery of neuromuscular function, when all four responses to TOF stimulation can be felt, an estimation of the TOF ratio can be attempted. However, manual (tactile) evaluation of the response to TOF stimulation (Fig. 43.19) is not sensitive enough to exclude the possibility of residual neuromuscular block.[37,72,118,133] Greater sensitivity is achieved with $DBS_{3,3}$, but even absence of manual fade in the $DBS_{3,3}$ response does not exclude clinically significant residual block (i.e., TOF 0.6-0.9).[41,72] Moreover, some patients might suffer from residual block, even after recovery to a TOF ratio of 0.9 to 1.0.[77,81] Therefore, manual evaluation of responses to nerve stimulation should always be considered in relation to reliable clinical signs and symptoms of residual neuromuscular block (Box 43.1).

BOX 43.1 Clinical Tests of Postoperative Neuromuscular Recovery

Unreliable

- Sustained eye opening
- Protrusion of the tongue
- Arm lift to the opposite shoulder
- Normal tidal volume
- Normal or nearly normal vital capacity
- Maximum inspiratory pressure less than 40-50 cm H_2O

More Reliable, But Still Not Excluding Residual Neuromuscular Block

- Sustained head lift for 5 s
- Sustained leg lift for 5 s
- Sustained handgrip for 5 s
- Sustained "tongue depressor test"
- Maximum inspiratory pressure

When to Use a Peripheral Nerve Stimulator

In clinical practice, significant residual block can be excluded with certainty only if an objective method of neuromuscular monitoring is used.[78,79] Therefore, good evidence-based practice dictates that clinicians should always quantitate the extent of neuromuscular recovery by objective monitoring.[7-13] Only a TOF ratio of 0.90 to 1.00 measured by objective monitoring ensures a low risk of clinically significant residual block.

However, in many departments, clinicians do not have access to equipment for measuring the degree of block.[134] How then to evaluate and, as far as possible, exclude a clinically significant postoperative block? First, long-acting neuromuscular blocking drugs should not be used. Second, the tactile response to TOF nerve stimulation should be evaluated during surgery. Third, if possible, total twitch suppression should be avoided. The neuromuscular block should be managed so that there are always one or two tactile TOF responses. Fourth, the block should be antagonized at the end of the procedure, preferably with sugammadex if rocuronium or vecuronium have been used. When using neostigmine, reversal should not be initiated before at least two to four responses to TOF stimulation are present. Fifth, during recovery, tactile evaluation of the response to DBS is preferable to tactile evaluation of the response to TOF stimulation because it is easier to manually assess fade in the DBS than in the TOF response. Sixth, the clinician should recognize that the absence of tactile fade in both the TOF and DBS responses does not exclude significant residual block. Finally, reliable clinical signs and symptoms of residual block (see Box 43.1) should be considered in relation to the response to nerve stimulation. Fig. 43.20 shows how to minimize the risk of residual block with or without objective monitoring.[135]

In view of the uncertainty connected with the use of clinical tests of postoperative neuromuscular recovery and tactile evaluation of the response to nerve stimulation, all patients receiving neuromuscular blocking drugs should be monitored with an objective monitor. Whether the functioning of such a neuromuscular transmission analyzer is based on EMG, MMG, AMG, CPM, CMG, or PMG is not crucial as long as the apparatus is used appropriately.

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Complete references available online at expertconsult.com.

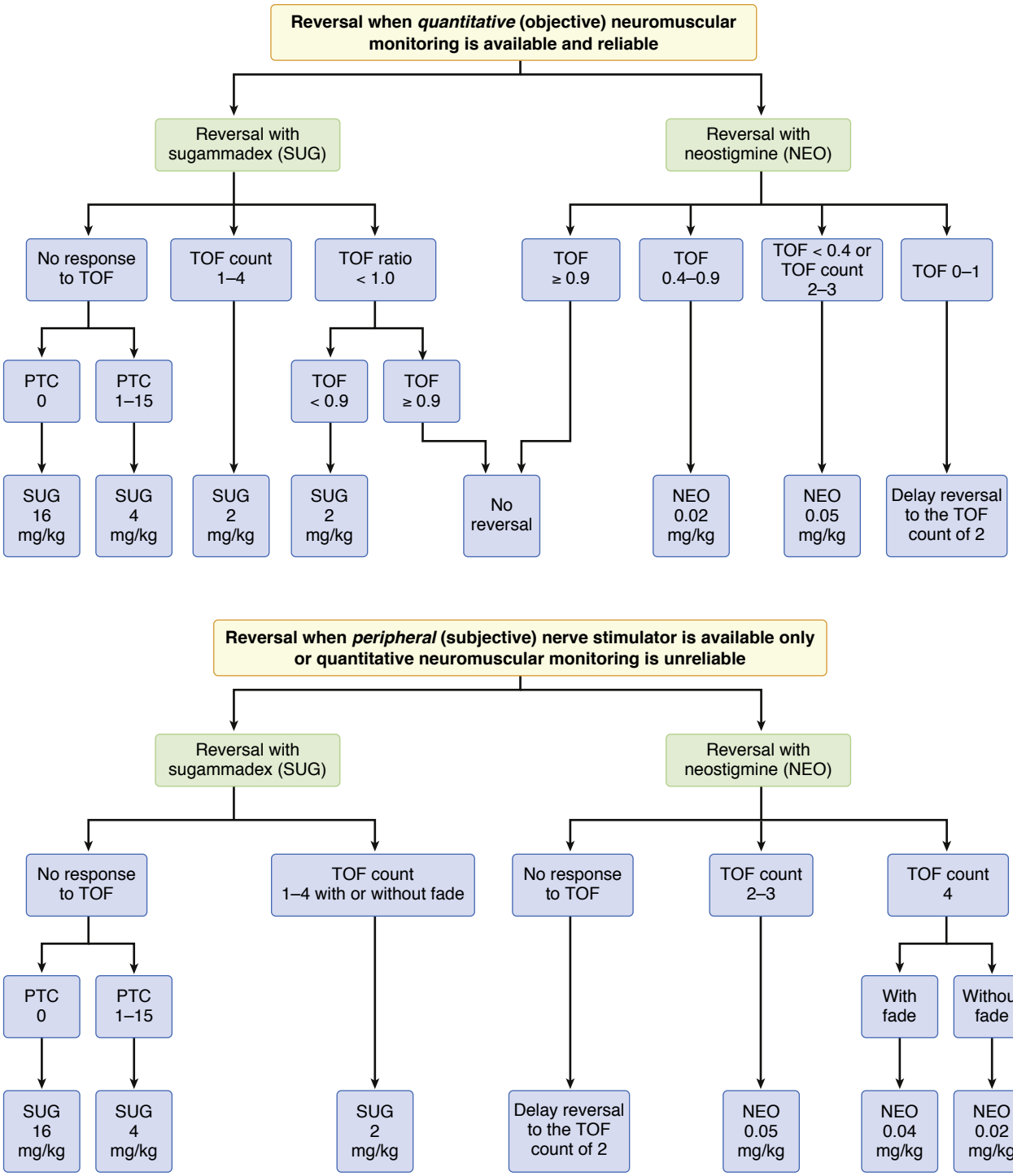

Fig. 43.20 Suggestion to diminish the incidence of residual curarization by neostigmine (NEO) or sugammadex (SUG) according to the level of block, determined with a nerve stimulator (quantitative or peripheral). Note that only a quantitative measured TOF ratio of 0.90 to 1.00 ensures low risk of clinically significant residual block. *PTC,* Posttetanic count; *TOF,* train-of-four. (Modified from Kopman AF, Eikermann M. Antagonism of non-depolarising neuromuscular block: current practice. *Anaesthesia*. 2009;64[Suppl 1]:22–30.)

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