Monitoring of Neuromuscular Function in the Clinical Setting

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This paper will review the basics of neurostimulation in the perioperative period. Following a brief overview of neuromuscular physiology, the mechanism of action of depolarizing and non-depolarizing relaxants will be discussed. The principles of neurostimulation will then be applied clinically when different patterns of stimulation (single twitch, train-of-four, post-tetanic twitch count, double burst) are described. Clinical assessment of neuromuscular function will then be compared with both subjective and objective means of assessment of adequacy of intraoperative relaxation and postoperative reversal. The principles reviewed in this paper will then be applied in the clinical setting, and risks and benefits associated with perioperative use of muscle relaxants will be discussed.

Muscle relaxants have been used in clinical anesthesia ever since Griffith and Johnson reported that "curare may prove to be a drug which will occasionally be of great value" [1]. The intervening period has taught us the usefulness of muscle relaxants, and that the response to these agents varies widely between individuals [2, 3]. The response may be further altered by certain disease states, electrolyte imbalances and/or drug interactions [4, 5, 6, 7, 8].

To minimize patient morbidity and optimize use of operating room time, monitoring of neuromuscular blockade is essential during the perioperative period. Clinical assessment of neuromuscular function and use of nerve stimulators are the most common monitoring methods, but despite their use, residual curarization occurs with various relaxant regimens [9, 10, 11, 12, 13, 14]. An understanding of the techniques used to monitor neuromuscular function, coupled with knowledge of the relevant physiology and pharmacology, will enable anesthesiologists to pursue our goal of optimal patient care.

NEUROMUSCULAR PHYSIOLOGY

Skeletal muscle fibers are innervated by motor neurons, whose cell bodies lie in the anterior horn of the spinal cord or in the corresponding motor nuclei of cranial nerves. These somatic motor neurons are typically thick, myelinated, fast conducting fibers. As the axon approaches its termination, it loses its myelin sheath and divides into a number of terminal branches. Each neural branch supplies a single muscle fiber, via the intervening neuromuscular junction.

At the neuromuscular junction, the membrane of the muscle fiber is thickened and is known as the motor end plate. The terminal nerve filaments are swollen and fit into depressions in the motor end plate. The narrow space between the nerve terminal and the

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\textsuperscript{b}Abbreviations used: ACh, acetylcholine; EPP, end-plate potential; NMJ, neuromuscular junction; TOF, train-of-four; DBS, double burst stimulation; EMG, electromyography; PTP, post-tetanic potentiation.
muscle membrane is analogous to the synaptic cleft between neurons. The entire region of the neuromuscular junction is enclosed by Schwann cells which separate it from the surrounding extracellular fluid [15].

The nerve terminal synthesizes ACh⁶ and stores it in vesicles [16]. When the nerve is stimulated, its action potential travels downwards and opens Ca++ channels in the nerve terminal membrane [17]. The inward movement of Ca++ triggers fusion of the synaptic vesicles with the nerve membrane (exocytosis) and ACh is released into the synaptic cleft. ACh is released in standard amounts, known as quanta.

The ACh diffuses across the synaptic cleft to the nicotinic ACh receptors on the membrane of the muscle end plate. The ACh receptor straddles the muscle membrane and consists of 5 subunits (2 alpha, 1 beta, 1 delta and 1 epsilon) arranged as in a cylinder around a central channel [18]. When both alpha subunits are occupied by ACh molecules (or a depolarizing relaxant), the channel opens. This is an "all or none" response. Na⁺ and Ca++ ions enter the muscle cell, and K⁺ ions exit through the open channel. The resultant ion flux generates an EPP₅. Individual EPPs may summate and once the local potential depolarizes the adjacent muscle membrane to its firing threshold, a muscle action potential is generated. The muscle action potential (an all-or-none response) is conducted along the muscle fiber. Subthreshold stimuli are not propagated along the muscle fiber, but do cause a localized depolarizing potential, which either summates with other EPPs (eventually reaching threshold), or gradually decays with time.

The post-synaptic end plate contains approximately 5 million ACh receptors [19]. When 5–10% of these are open, the EPP typically reaches threshold and a muscle action potential is produced [20]. Each ACh vesicle contains about 10,000 ACh molecules, and a nerve impulse typically releases 50–60 ACh vesicles [21]. This amount of neurotransmitter is sufficient to activate about 10 times the number of the ACh receptors required to produce a muscle action potential [21].

A single muscle action potential causes a brief contraction of the fiber (known as a muscle twitch), followed by relaxation. The depolarization of the muscle membrane is transmitted to all the fibrils in the muscle fiber by a collection of tubules (T system) and triggers release of Ca++ from the sarcoplasmic reticulum [22]. The Ca++ release initiates interaction of the actin and myosin filaments, and results in contraction of the muscle [22]. The complete process by which depolarization of the muscle membrane initiates contraction is known as excitation-contraction coupling. The depolarization of the membrane and the mechanical process which results are separate entities.

**MECHANISM OF ACTION OF MUSCLE RELAXANTS**

The muscle relaxants used in clinical anesthesia may be classified into two groups, depolarizing and non-depolarizing. Curare is the prototype of the non-depolarizing group, which includes atracurium, vecuronium, and pancuronium amongst others. These agents bind to the alpha subunit of the post-synaptic nicotinic receptor and competitively block the transmitter action of ACh. By increasing the concentration of these competitive antagonists at the synaptic cleft, the amplitude of the EPP is progressively diminished. The EPP may have to fall below 70% of its initial value before it is insufficient to initiate a muscle action potential, which provides a safety factor in neuromuscular transmission [23]. Binding of two agonist molecules, one on each alpha subunit, is needed for receptor activation, whereas binding of one antagonist molecule to the receptor is sufficient to render it non-functional [24, 25]. In addition, pre-synaptic binding of non-depolarizing relaxants may oppose mobilization and release of ACh [26, 27]. During a non-depolarizing block the muscle continues to respond to direct electrical stimulation.

Depolarizing relaxants, such as succinylcholine and decamethonium, initially depo-
larize the membrane by opening receptor channels, in a similar manner as ACh. However, they persist at the NMJ and result in prolonged end-plate depolarization [23]. This brief period of repetitive excitation is manifested by transient muscle fasciculations, followed by blockade of neuromuscular transmission and flaccid paralysis. Prolonged stimulation of the receptor by ACh will produce a similar response.

At the perimeter of the muscle end-plate, a grouping of Na+ channels is responsible for propagation of the action potential [28]. Each Na+ channel consists of two "gates." In resting muscle, the lower (time-dependent) gate is open, while the upper (voltage dependent) gate is closed [20, 29]. Depolarization of the end-plate opens the upper gate, allowing ion exchange and propagation of the muscle action potential. Soon after the upper gate opens, the lower gate closes, thereby terminating the ion exchange. The lower gate remains closed until the upper gate shuts, and the cell returns to its resting state. However, the persistent end-plate depolarization produced by succinylcholine is maintained until the lower gate closes, thereby preventing further action potential propagation beyond the junctional rim. Thus, after an initial period of muscle fasciculations, flaccid paralysis results [23].

The nicotinic receptor may also be inactivated by channel block, which involves interference with the transfer of ions through the transmembrane channels. Open channel block and closed channel block are the two principal types [30, 31]. The latter involves direct occlusion of the channel mouth, independent of channel opening. Ion transfer is prevented and end-plate depolarization fails to occur [30, 32]. In open channel block, after the channel has been opened by an agonist, a molecule enters and occludes the channel thereby preventing end-plate depolarization. The intensity of open channel block varies with the frequency of channel activation, as only open channels can be affected. The potential across the end plate draws the molecule, which is usually charged, into the channel. The receptor is tunnel shaped and the molecule is unable to traverse its narrow portion. The duration of the block varies with the size and shape of the molecule: some leave the channel quickly, whereas others bind to it and produce a longer lasting effect [33]. Open channel block does not occur at the ACh binding site, and so this process is not competitive antagonism [19, 30, 32, 34].

Desensitization may also inactivate the nicotinic receptors; this occurs when the receptors bind agonists in the normal fashion, but the receptors do not undergo the structural changes that normally open the channel. Desensitization involves a conformational change in the structure of the receptor [33]. Receptor proteins are constantly changing between the resting and desensitized states, and some agonists may promote the transition to the desensitized state [33].

During prolonged exposure to a depolarizing relaxant, the typical (phase 1) block may assume the characteristics of a non-depolarizing (phase 2) block. Persistent binding of depolarizing agents to the alpha subunits of the receptor induces desensitization [33, 35, 36]. This is thought to be the mechanism responsible for phase 2 block, but other factors may contribute (e.g., abnormal transmembrane electrolyte balance). In addition, many agents that enhance neuromuscular blockade also promote desensitization of the nicotinic receptor and/or cause channel block (e.g., barbiturates, volatile anesthetics, local anesthetics, and cholinesterase inhibitors) [20, 37, 39].

**PRINCIPLES OF NERVE STIMULATION**

The nerve stimulator generates an electric current which is delivered to a nerve fiber via surface or subcutaneous (needle) electrodes. The aim of the stimulator is to induce equal degrees of nerve depolarization over time. This is best achieved by using a supra-maximal current which stimulates all fibers in the nerve bundle. Using surface electrodes,
a current of 30–50 mA is typically needed to ensure supramaximal stimulation, while using subcutaneous electrodes this value is typically around 10 mA. Production of a neural action potential depends on the current applied by the stimulator, and not the voltage. Ohm's Law states that the amount of current (I) that flows through a body is equal to the driving voltage (V) divided by the electrical resistance (R). Thus, any change in skin impedance requires a proportional change in the applied voltage to ensure a constant current, and hence a constant level of nerve depolarization. Ideally, the stimulator should have a current display unit which alerts the operator when the current selected is not being delivered, or else the degree of blockade may be misjudged.

Skin resistance is reduced by applying a conducting solution (usually silver/silver chloride gel) to clean, dry skin. The impedance may change intraoperatively due to drying of electrolyte gel, cooling of skin or displacement of electrodes. Therefore, constant-voltage stimulators have been replaced by constant-current ones, thus ensuring consistency of response. A constant current can be delivered more effectively via needle electrodes placed subcutaneously. The electrodes are in close proximity to the nerve and more likely to stimulate all the neural fibers, being less affected by physical factors such as obesity and increased skin impedance.

Other important features of the electrical pulse delivered by the stimulator are the wave form and its duration. The stimulus should be monophasic (i.e., square wave) because biphasic waves may result in repetitive nerve firing. The intensity of the stimulus (in milliamperes, mA) required to initiate nerve firing increases exponentially as the pulse duration decreases: a short impulse requires a higher current to cause the nerve to fire. However, if the pulse width exceeds 0.5 msec, direct muscle stimulation or repetitive neural firing may result. In addition, the amplitude of the evoked response shows little change with pulse durations exceeding 0.1 msec if the current intensity is kept constant. In clinical practice, pulse widths of 0.1–0.3 msec are usually employed, as this range is optimal for assessment of depth of neuromuscular block.

The rate of stimulus application to the nerve also influences the evoked response. At the unblocked NMJ, supraphysiological stimulation rates (e.g., above 70–200 Hz) will cause fatigue in the muscle [40, 41]. This fatigue is due to inability to mobilize sufficient ACh at the presynaptic nerve terminal to sustain the high frequency response. A brief tetanic stimulation at 50–100 Hz, in the setting of normal neuromuscular transmission, results in a sustained contraction without fade. In the presence of a non-depolarizing block, fatigue (i.e., fade) is noted at slower stimulation rates. This characteristic is utilized in the train-of-four and tetanic stimulation (see below) to estimate the extent of neuromuscular block [42, 43].

In addition to inducing fatigue, frequent stimulation increases local blood flow, thus speeding delivery of relaxant to the stimulated muscle [44, 45, 46]. In the clinical setting, the frequency of neurostimulation and the rate of onset of depolarizing and non-depolarizing block are directly proportional, such that an increase in stimulation frequency will result in a falsely elevated rate of onset [46, 47, 48, 49, 50]. Both these effects (induction of fatigue and increase in blood flow) can reduce the apparent dose requirements for muscle relaxants [47].

**PATTERNS OF NERVE STIMULATION**

The extent of neuromuscular blockade may be assessed by several different patterns of stimulation. These include single twitch, train-of-four, double burst, and tetanic stimulation, and post-tetanic twitch count (Table 1).
Table 1. Features of different patterns of neurostimulation.

| Pattern                        | Features                                                                                                                                 |
|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Single Twitch                 | • A supramaximal stimulus delivered at 0.1 to 1.0 Hz.                                                                                     |
|                               | • Rate of stimulus delivery affects muscle response.                                                                                      |
|                               | • Baseline twitch height required; subsequent accuracy may be impaired.                                                                    |
|                               | • Narrow range of receptor block detection (75–95%).                                                                                      |
|                               | • Does not differentiate depolarizing & non-depolarizing block.                                                                        |
| Train-of-Four                 | • Four supramaximal stimuli at 2 Hz.                                                                                                     |
|                               | • Less painful than tetanic stimulation and may be used in awake patients (ICU).                                                         |
|                               | • Differentiates depolarizing & non-depolarizing block.                                                                                    |
|                               | • Useful for detection of block in the range of surgical relaxation (70–100% receptor occupancy).                                          |
|                               | • Does not induce potentiation of subsequent responses or recovery.                                                                      |
|                               | • No baseline (pre-relaxant) response needed.                                                                                             |
| Double Burst Stimulation      | • Two short tetanic bursts (2 or 3 impulses at 50 Hz) separated by 750 msec.                                                            |
|                               | • Clinical assessment (tactile & visual) of DBS superior to TOF in detecting fade.                                                       |
|                               | • No control baseline necessary.                                                                                                        |
|                               | • May induce potentiation of subsequent responses.                                                                                       |
|                               | • Painful to awake patients.                                                                                                             |
| Tetanus                       | • Typically 50 Hz for 5 sec                                                                                                                |
|                               | • Differentiates depolarizing & non-depolarizing block.                                                                                   |
|                               | • May induce direct muscle stimulation.                                                                                                   |
|                               | • Painful; therefore less useful in awake patients.                                                                                      |
|                               | • Enhances subsequent neuromuscular responses and recovery.                                                                               |
|                               | • Degree of fade varies with frequency and duration of applied stimulus.                                                                |
| Post-Tetanic Count            | • Tetanus (50 Hz for 5 sec) followed 3 sec later by single supramaximal stimuli at 1 Hz.                                                  |
|                               | • Allows profound degrees of block to be assessed.                                                                                       |
|                               | • Useful to ensure "complete" block.                                                                                                      |
|                               | • Accuracy of PTC depends on many variables (eg. duration & frequency of tetanic stimulation, latency period between tetanus & single stimuli, frequency of single twitches, etc) |
|                               | • Frequent tetanic stimuli may antagonize the apparent neuromuscular block.                                                             |

**Single twitch**

With this mode, a supramaximal stimulus is applied to the nerve prior to the administration of muscle relaxant and a baseline amplitude of the muscle twitch is established. The degree of block produced by the relaxant can be estimated by comparing any subsequent twitch height to that of the baseline. The frequency of the applied stimulus affects the response of the muscle to single twitch stimulation (see above). Changing the stimulus frequency from 0.1 Hz to 1.0 Hz can decrease the ED95 of d-tubocurarine (the effective dose for 95% twitch depression of the thumb adduction) by a factor of 3 or more [47]. A supramaximal stimulus lasting 0.2 msec with a frequency of 0.1 Hz is the commonest single twitch technique. However, a frequency between 0.1 and 1.0 Hz may be selected.

The response to single twitch stimulation disappears completely once 90–95% of the
receptors are blocked, but the response is not reduced until 75–80% of the receptors are occupied. Thus, the range of receptor blockade detected by single twitch stimulus (i.e., approximately 75–95%) is narrow [51], limiting its clinical usefulness.

Other factors limiting the clinical usefulness of single twitch include its sensitivity to variations in current, skin temperature, and resting muscle tension (preload). In addition, careful documentation of baseline twitch height is needed for comparison with subsequent twitches. When the control height is evaluated visually or by palpation (as often occurs in clinical practice), subsequent responses are difficult to assess and compare accurately.

**Train-of-four**

In the train-of-four (TOF) pattern, four supramaximal stimuli are applied at a frequency of 2 Hz. In the presence of a non-depolarizing block, this frequency is associated with clearly separated muscle responses which exhibit fade. The degree of fade is proportional to the extent of the neuromuscular block. Thus, the ratio of the amplitude of the fourth response (T4) to that of the first response (T1) estimates the extent of non-depolarizing block. This ratio is known as the T4/T1 ratio or TOF ratio.

At the unblocked NMJ, the T4/T1 ratio approximates 1.0. During a partial depolarizing block, the twitch height is reduced to the same extent in all four responses, and no fade is induced, the T4/T1 ratio approximating 1.0. If a phase 2 block develops after succinylcholine administration, the TOF response will show "fade", as the depolarizing agent exhibits features of a competitive blocker. During a partial non-depolarizing block, the T4 amplitude starts to decrease when 70–75% of the receptors are occupied. The T1 response may not decline until the T4/T1 ratio falls below 0.7.

When the T4 response is lost completely, approximately 80% of the receptors are blocked. Disappearance of the T3 and T2 responses corresponds to 85% and 85–90% receptor occupancy, respectively [52]. When 90–95% of the receptors are blocked, T1 disappears, its amplitude having decreased progressively with increasing receptor occupancy [51, 52].

Since its introduction in the 1970's [53], TOF stimulation has become the most popular method of assessing neuromuscular block in clinical practice. It is considerably less painful than tetanic stimulation and may be used in awake patients to detect residual block. Once the T4 and T1 responses are detectable, the TOF ratio is consistent at submaximal and supramaximal intensities [54, 55]. This makes TOF more comfortable for awake patients, as the pain experienced is directly related to the intensity of the stimulating current [56].

TOF does result in fade during a partial non-depolarizing block but, unlike tetanus, it does not facilitate subsequent neuromuscular responses [42, 43, 57]. Thus, TOF does not induce changes in subsequent recovery. It also does not require a preoperative control height, as the degree of block is proportional to the T4/T1 ratio [52, 58, 59]. A T4/T1 ratio of 0.75 generally correlates with a sustained muscle response to 50 Hz (for 5 sec) and with a single twitch height which has returned to baseline. This degree of block also correlates with clinically adequate neuromuscular function, although a greater degree of recovery may be necessary in some patients.

**Tetanic stimulation**

In the normal individual, high frequency neurostimulation (30–100 Hz) results in repetitive muscle action potentials and a sustained muscle contraction [40]. Initially, large quantities of ACh are released from preformed vesicles in the nerve endings. As the stimulus persists, the rate of ACh release decreases. Normally, greater quantities of ACh are
released from pre-synaptic stores than are necessary; therefore, muscle depolarization in response to tetanic stimulation persists despite decreasing ACh release, and muscle contraction is sustained. In clinical practice, a stimulus of 50 Hz for 5 sec is usually selected, as the muscle tension evoked approximates that achieved during maximal voluntary effort [40].

During a pure depolarizing block, the peak muscle tension is reduced, but it is sustained for the 5-sec duration. With non-depolarizing (and phase 2) block, the peak tension is reduced and "fades" with sustained stimulus [53, 60]. The degree of fade depends primarily on the extent of the neuromuscular block and, thus, may be used to quantify the block. Fade also varies proportionately with the frequency of the applied stimulus, being greater at higher frequencies. In addition, the longer the duration of the tetanic stimulus, the greater the extent of fade. Recent studies suggest that the degree of fade is not significantly altered by a preceding tetanic stimulus given as recently as 2 min earlier [61].

Tetanic fade is generally thought to be a pre-synaptic phenomenon, though controversy exists as to its exact nature. One explanation is that the competitive block of the relaxant at the post-synaptic receptor narrows the safety margin and that, despite repetitive stimulation, the nerve terminal is unable to mobilize ACh quickly enough to overcome the block [62]. Competitive antagonism of pre-synaptic cholinergic receptors with alteration in Ca++ fluxes in the nerve terminal also may play a role by altering ACh mobilization [20]. Moreover, open-channel block has been proposed as an alternative mechanism, in which the antagonist may physically block the open postsynaptic channels [34].

In the presence of a non-depolarizing or phase 2 block tetanic stimulation may result in an enhanced subsequent neuromuscular response (i.e., the evoked twitch tension is increased). This effect usually occurs if the stimulus is applied within 60–120 sec following the tetanic stimulus. The duration and magnitude of this PTP is a function of the degree of neuromuscular block [63] and may result in underestimation of the degree of block if evoked responses are assessed during the period of potentiation. The muscle block induced by succinylcholine does not exhibit PTP.

Thus, tetanic stimulation shortens the time to recovery of neuromuscular transmission as measured by TOF and double burst stimulation (DBS, see below), such that the evoked response of the tested site may no longer be representative of other muscle groups [63, 64]. Since tetanic stimulation is painful, it should be applied to anesthetized patients only, thus limiting its usefulness in settings in which patients are awake (i.e., intensive care or postanesthesia care units).

Post tetanic twitch count

When the non-depolarizing blockade is profound, TOF or single twitch stimulation evoke no response and cannot quantify the extent of the block. However, the potentiation of neuromuscular transmission that occurs after tetanic stimulation may enable single stimuli to produce a response [65, 66]. PTC method takes advantage of this period of enhanced evoked responses to assess the duration until return of neuromuscular function even when single-twitch, TOF or DBS evoke no response. PTC is generally used to ensure profound muscle block, such as during microsurgery, ophthalmic surgery, and when "bucking" on the endotracheal tube could have disastrous consequences [67]. A tetanic stimulus (50 Hz for 5 sec) is delivered, and 3 sec later, single supramaximal stimuli are delivered once every second (i.e., at 1 Hz). The number of twitches elicited is inversely proportional to the degree of block, and is known as the post tetanic twitch count [65].

For each non-depolarizing relaxant, the first response to the TOF stimulation typically occurs when the post tetanic twitch count has reached a certain value. The PTC,
therefore, allows the time to recovery of a profound block to be estimated and allows reversal with anticholinesterases to be planned.

While the PTC depends primarily on the degree of neuromuscular block, it varies with other factors which must be controlled, in order for PTC to be clinically useful. Thus, the frequency and duration of the tetanic stimulus, the time interval between the tetanic stimulus and the first twitch stimulus and the frequency of the single twitch stimulus all must be standardized. In addition, as noted above, repetitive tetanic stimulation may antagonize the neuromuscular block such that the blocked muscle is not truly representative of the extent of the block at other muscle groups. Thus, the tetanic stimulus should not be applied any more frequently than once every 3 or 4 min [68].

**Double burst stimulation**

DBS was introduced in the late 1980's as an alternative method of monitoring neuromuscular blockade [69, 70, 71]. It involves two short bursts of 50-Hz tetanic stimuli separated by 750 msec. While the duration of each individual twitch is 0.2 msec, the number of impulses in each of the two bursts may vary; the pattern using 3 impulses in each burst (DBS3,3) has gained widest use in clinical practice. When DBS3,3 is applied to the unblocked NMJ, two short muscle contractions of equal strength are induced. In the partially blocked patient, DBS3,3 results in a weaker second response (i.e., the response fades), the degree of fade being proportional to the extent of the neuromuscular block. DBS and TOF correlate closely over a wide range of block and stimulating currents [70, 71, 72].

When the TOF response is evaluated by visual and tactile means, minor degrees of neuromuscular block cannot be excluded with certainty [73]. The main advantage of DBS in clinical practice is that fade of DBS-evoked responses may be easier to evaluate by subjective means than with TOF [72].

**THE NERVE STIMULATOR AND ELECTRODES**

As mentioned previously, the nerve stimulator should provide a constant current stimulus as opposed to a constant voltage. The wave form should be monophasic, and its duration should not exceed 0.5 msec. Supramaximal stimulation of the nerve is desirable when assessing single twitch responses and, thus, the stimulator should be capable of delivering a current of 60–70 mA. A current display unit should ideally be incorporated, and the selected current should be maintained for the duration of the impulse. Multiple patterns of stimulation (single twitch, train-of-four, double burst, tetanic, post-tetanic twitch count) should be possible. For safety purposes, the stimulator should be battery-operated, it should include a means to test the battery, and should be enclosed in a plastic case. During use, the stimulator should be placed on a non-conductive surface, and its electrodes should always be regarded as a potential route for unintentional electrocautery grounding. The polarity of the electrodes should be clearly indicated. Other desirable features include an audible signal with each stimulus delivered and the ability to calculate and display fade ratio and/or percent depression of single twitch amplitude from baseline.

Skin or subcutaneous electrodes may be used to transmit the electrical current from the stimulator to the nerve. The electrodes reduce the resistance to the electric impulse. In clinical practice, the skin electrodes used are usually disposable, and use silver/silver chloride as the conducting electrolyte solution. They should be firmly applied to clean dry skin. When a supramaximal response cannot be obtained with skin electrodes, needle electrodes may be placed subcutaneously in close proximity to, but never in, the nerve.
SITES OF STIMULATION

Essentially any superficial peripheral nerve may be stimulated. The ulnar nerve is the most popular, and the response of the adductor pollicis muscle (thumb) is monitored. This site is well suited for visual, tactile, and mechanomyographic assessments. In addition, this muscle is on the side of the arm opposite the site of stimulation; therefore, there is little chance of direct muscle stimulation, suggesting an incomplete block. To stimulate the ulnar nerve, one electrode is placed on the radial side of the flexor carpi ulnaris tendon about 1 cm proximal to the wrist skin crease. The other electrode may be placed 3–4 cm proximal to the distal electrode, or over the ulnar groove on the medial epicondyle of the elbow. When the latter placement is used, the flexor carpi ulnaris muscle may be stimulated and result in augmented thumb adduction. Polarity of the electrodes is not important when both electrodes are in close proximity to the wrist. However, if one electrode is placed over the elbow, the active (negative) electrode should be placed at the wrist to ensure maximum stimulation of the ulnar nerve [74, 75].

Muscle groups differ in their sensitivity to muscle relaxants [76]. The exact cause of these differences is multifactorial and has not been fully elucidated. Proposed mechanisms include different regional blood flow, differences in muscle temperature and density of receptors, varying margins of safety at the NMJ, and differences in muscle fiber composition. Compared to the adductor pollicis muscle, the diaphragm requires 1.5–2 times the amount of relaxant to achieve paralysis due to its resistance to depolarizing and nondepolarizing agents [77, 78]. After a bolus dose of relaxant, the diaphragm and upper airway muscles achieve onset and recovery of block quicker than peripheral muscles, possibly because of their higher blood flow [79, 80, 81, 82]. Differences in sensitivity to relaxants and in onset times have clinical implications when peripheral sites are monitored. When high doses of relaxants are used (> 2 times the ED₉₅), the faster onset time at the diaphragm tends to predominate, and adequate blockade should be achieved before it is evidenced by the adductor pollicis muscle response [81]. However, if lower doses of relaxant are used, the lesser sensitivity of the diaphragm may predominate, and the adductor pollicis twitch may be ablated 30–60 sec before maximal diaphragmatic relaxation is achieved [83].

The response of the orbicularis oculi muscle to facial nerve stimulation reflects more closely the sensitivity of, and time course at, the airway musculature [80, 81, 84, 85]. The electrodes are placed 2–3 cm posterior to the lateral border of the orbit. However, direct muscle stimulation may occur, resulting in an enhanced response and underestimation of the degree of blockade. In addition, the orbicularis oculi response is not readily quantified mechanographically.

CLINICAL ASSESSMENT OF NEUROMUSCULAR FUNCTION

A variety of clinical signs have been employed to estimate the degree of neuromuscular block and adequacy of reversal: patients' ability to open their eyes, protrude their tongue, swallow, lift the head for 5 sec, or to sustain a hand grip. An initial strong contraction which weakens over time is characteristic of residual paralysis; such patients will be unable to sustain muscle activity, and their movements may appear "jerky." While clinical tests of neuromuscular integrity are useful in assessing the degree of blockade, they require patient's cooperation and cannot be performed in unconscious patients. The adequacy of the tidal volume, vital capacity, and inspiratory pressure, as well as the pattern of respiration, have been used as markers for neuromuscular integrity. Patients with partial blockade may, however, have adequate ventilation and a normal tidal volume, but their airway reflexes and ability to cough can still be impaired. In addition, perioperative respiratory depression may be due to central blunting of the respiratory drive by opioids,
Mechanomyography

anesthetic agents, and/or low arterial CO₂ levels. Residual blockade can only be confirmed as a cause of respiratory depression by demonstrating impairment of neuromuscular transmission.

Studies have shown that the Tₐ/T₁ ratio correlates with some clinical criteria used to assess recovery from neuromuscular block. When the Tₐ/T₁ ratio was greater than 60%, patients achieved sustained head lift for 3 sec or more [86]. When this ratio exceeded 75%, eye opening, cough, and tongue protrusion were clinically normal. In addition, at this Tₐ/T₁ ratio, after d-tubocurarine and N₂O/narcotic anesthesia, a vital capacity of 15–20 ml/kg, a negative inspiratory pressure of 20–25 cm H₂O and a sustained head lift for 5 sec were present [57, 87]. Neuromuscular monitoring provides objective evidence of the degree of block and may be used in unconscious patients. It should not replace clinical judgment, but rather the two modes complement each other in assessment of the status of neuromuscular transmission.

MONITORING OF THE RESPONSE TO NERVE STIMULATION

After the nerve has been stimulated using one of the patterns outlined above, the evoked muscle response is monitored in the clinical setting using various means, either objective or subjective, or a combination.

SUBJECTIVE MEANS

Visual and tactile assessment

Visual and/or tactile assessment remain the most popular method of monitoring neuromuscular fade in response to TOF stimulation in clinical practice. For visual assessment, the observer should be at an angle of 90° to the plane of muscle movement. For tactile assessment, the thumb should be held in full abduction, and the observer's fingertips placed over the distal phalanx in the direction of movement. However, such subjective assessments will not be consistent in detecting neuromuscular fade even when performed by experienced observers [13, 88, 89]. DBS, as mentioned above, has been introduced in an attempt to improve non-mechanographic detection of fade.

Studies of DBS have reported more accurate detection of neuromuscular fade, and its usefulness in this regard is now generally accepted. Such testing may be performed with submaximal nerve stimulation without loss of accuracy and with less patient discomfort [90]. Recent investigations have reported that regardless of pattern of neurostimulation or the current intensity delivered, there was no significant difference in the ability to detect fade between visual and tactile means [90].

OBJECTIVE MEANS

Precise assessment of neuromuscular blockade can be quantified by mechanomyography, electromyography, and accelerography; these measure evoked mechanical response, electrical response, and muscle acceleration, respectively. These techniques are much more accurate in quantifying the muscular blockade than visual or tactile assessment. However, they are infrequently used in clinical anesthesia due to time constraints, lack of availability, and their expense.

Mechanomyography

With this method, a force translation monitor is used to measure the evoked muscle tension. The isometric contraction of the muscle (usually the adductor pollicis muscle is selected) in response to stimulation of its innervating nerve is translated via a force transducer into an electrical signal. The signal is recorded and quantified on a pressure monitor, and the amplitude of the signal is proportional to the strength of muscle contraction.
By measuring the T₄/T₁ signal ratio, the degree of fade can be accurately recorded.

For consistent measurement of muscle response, certain precautions should be undertaken. The hand must be fully immobilized to reduce movement artifact, while movement of the thumb in the force transducer unit must be unencumbered. The thumb must always apply tension along the axis of the transducer, so that the degree of movement is fully appreciated. A preload of 200–300 g should be applied to the abducted thumb before ulnar nerve stimulation to ensure isometric contraction. The recording monitor must be adjusted to account for the predicted response; the tension developed after tetanic stimulation can be four times that achieved by a single twitch. A transducer with a suitable tension range should be selected. In most clinical settings a tension range of 0–5 kg is adequate for monitoring a non-depolarizing block, but tetanus at the unblocked NMJ generates a force of 7.1–22.0 kg [41] which can overload some transducers [91].

**Electromyography**

EMG is the process of recording the electrical activity of a muscle. The signal obtained depends on the location of the recording electrodes relative to the muscle. Usually one electrode is placed over the midpoint of the muscle (close to the neuromuscular junction) and the other is placed over the tendon of insertion. The third (neutral) electrode's placement is variable. Such positioning gives the most consistent EMG signals [92]. After stimulation of the innervating nerve, electrical activity of the muscle is inversely proportional to the degree of block at the NMJ. The compound action potential evoked is recorded in the EMG: the amplitude of the compound action potential represents the sum of the amplitudes of the individual muscle fibers activated by the stimulus. The time between application of the stimulus and the initial deflection of the evoked response is known as the latency period. It represents the nerve conduction time and the time needed for neuromuscular transmission (muscle contraction is not required for EMG recordings). The duration and shape of the compound action potential depends upon the distance from the stimulating electrode to the recording device. Most EMG devices compute the area under the EMG curve, as it is a better representation of overall muscular activity. This area is then represented numerically.

When the EMG signal is recorded from the thenar eminence, studies have shown a good correlation between the EMG and the adductor pollicis force transducer. However, movement artifact at this monitoring site may make the EMG recording unreliable. The hypothenar muscles are usually used for electromyography as a result, but these muscles are less sensitive than the adductor pollicis to non-depolarizing relaxants (as measured by the force transducer) [93, 94, 95]. The EMG electrodes can be placed over the first dorsal interosseous space; in this location, the EMG response correlates well with adductor pollicis force transduction.

The differences between EMG and mechanomyography may be due to the sensitivity of the latter to factors affecting muscle contraction (e.g., mechanical). The EMG, on the other hand, is influenced by those factors involved in nerve conduction and neuromuscular transmission but is relatively independent of mechanical events. Therefore, the factors influencing excitation-contraction coupling (e.g., dantrolene) will not alter the EMG, but will modify the mechanomyograph.

The advantages of the EMG over mechanomyography are its accuracy and reliability, the fact that it is less bulky and time consuming than a force transducer, and that it can be used to monitor a larger number of sites than the latter. It is, however, more expensive, and electrical diathermy produces artifact. To date, EMG monitors can record the response to single twitch and train-of-four stimulation, but do not monitor double burst
stimulation, tetanus or the post-tetanic twitch count.

Accelerography

The principle of accelerography is based on Newton's Law that force equals mass times acceleration. If mass is constant, force is then directly proportional to acceleration. Thus, the acceleration of the thumb after ulnar nerve stimulation is directly proportional to the evoked force of contraction. A thin transducer (piezoelectric wafer) is attached to the thumb. Whenever the thumb moves, a voltage is generated, its height is proportional to the degree of angular acceleration. The signal is amplified and displayed on a monitor screen.

Accelerography yields comparable results to mechanomyographic TOF monitoring at varying current amplitudes [55, 96, 97, 98]. Accelerometers are less bulky and easier to use than force transducers, and because they measure isotonic contraction, they do not require a preload. Results may be altered by thumb movement or failure of the thumb to return to its baseline position after a contraction, and this may account for a $T_4/T_1$ greater than 1.0 in the unblocked state [55]. Any impedance of free thumb movement will reduce the accuracy of the accelerometer. While the future role of accelerography in anesthesia looks promising, further studies are necessary to fully evaluate its usefulness in the clinical setting.

CLINICAL APPLICATIONS AND RISKS OF NEUROMUSCULAR MONITORING

Recent studies have highlighted the wide variability in onset and recovery times with various relaxant regimens [2, 3]. The incidence of "residual curarization" when clinical means of assessment are used is unacceptably high; infusion techniques with both depolarizing and non-depolarizing agents are notoriously difficult to titrate accurately; the onset of phase 2 block following succinylcholine requires the use of a nerve stimulator for its diagnosis. The newer non-depolarizing agents with short half lives (especially mivacurium) may have such rapid offset that monitoring is needed to guide intraoperative dosing regimens. Patient response is even more difficult to predict accurately in certain disease states: myasthenia gravis, Eaton-Lambert Syndrome, hypothermia and hypokalemia, among others [4, 5, 6, 99]. The pharmacokinetic parameters of relaxants are altered in the elderly, those with renal or hepatic impairment and patients with atypical or reduced pseudocholinesterase levels [7, 100, 101]. Drug interactions may affect the extent of neuromuscular block induction agents, while inhalational anesthetics, nitrous oxide, succinylcholine, local anesthetics, anti-arrhythmics, aminoglycosides and calcium channel blockers can modify the response to both relaxants and reversal agents [8, 102–115]. Given the wide variation in patient response to a dose of muscle relaxant and the possible alteration in the pharmacodynamic and pharmacokinetic profile, it seems prudent to monitor neuromuscular function whenever muscle relaxants are employed.

SUMMARY

Muscle relaxants play a key role in modern anesthetic practice. Both depolarizing and non-depolarizing agents exhibit wide pharmacodynamic variability, which makes their effects unpredictable. Furthermore, the lone clinical assessment of intraoperative block or adequacy of reversal is unreliable. Nerve stimulators allow assessment of the response of the neuromuscular unit to various patterns of stimulation and complement clinical assessment. The evoked response is proportional to the extent of neuromuscular block, and can be quantified by visual and/or tactile means or by objective means, since the former methods may give misleading results. It is hoped that greater understanding and wider application of neuromuscular monitoring techniques perioperatively will
reduce patient morbidity and improve standards of anesthetic care.

REFERENCES
1. Griffith, H. R. and Johnson, G. E. The use of curare in general anesthesia. Anesthesiology 3:418–420, 1942.
2. Katz, R. L. Neuromuscular effects of d-tubocurarine, edrophonium and neostigmine in man. Anesthesiology 28:327–336, 1967.
3. Silverman, D. G., Swift, C. A., and Dubow, H. D., O’Connor, T. Z., and Brull, S. J. Variability of onset times within and among relaxant regimens. J. Clin. Anaesth. 4:28–33, 1992.
4. Grob, D. and Namba, T. Characteristics and mechanisms of neuromuscular block in myasthenia gravis. Ann. N. Y. Acad. Sci. 274:143, 1976.
5. Mitchell, M. M., Ali, H. H., and Savarese, J. J. Myotonia and neuromuscular blocking agents. Anesthesiology 49:44–48, 1978.
6. Martyn, J. A. J., Szfelbein, S. K., Ali, H. H., Matteo, R. S., and Savarese, J. J. Increased d-tubocurarine requirement following major thermal injury. Anesthesiology 52:352–365, 1980.
7. Feldman, S. A. Effect of changes in electrolytes, hydration and pH upon the reactions to muscle relaxants. Br. J. Anaesth. 35:546–551, 1963.
8. Argov, Z. and Mastaglia, F. L. Disorders of neuromuscular transmission caused by drugs. N. Engl. J. Med. 301:409–413, 1979.
9. Viby-Mogensen, J., Jorgensen, B. C., and Ording, H. Residual curarization in the recovery room. Anesthesiology 50:539–541, 1979.
10. Lennmarken, C. and Lofstrom, J. B. Partial curarization in the postoperative period. Acta Anaesthesiol. Scand. 28:260–262, 1984.
11. Beemer, G. H. and Rozental, P. Postoperative neuromuscular function. Anaesth. Intensive Care 14:41–45, 1986.
12. Andersen, B. N., Madsen, J. V., Schurizek, B. A., and Juhl, B. Residual curarisation: a comparative study of atracurium and pancuronium. Acta Anaesthesiol. Scand. 32:79–81, 1988.
13. Bevan, D. R., Smith, C. E., and Donati, F. Postoperative neuromuscular blockade: a comparison between atracurium, vecuronium, and pancuronium. Anesthesiology 69:272–276, 1988.
14. Brull, S. J., Ehrenwerth, J., Connelly, N. R., and Silverman, D. G. Assessment of residual curarization using low-current stimulation. Can J. Anaesth. 38:164–168, 1991.
15. Birks, R., Huxley, H. E., and Katz, B. The fine structure of the neuromuscular junction of the frog. J. Physiol. (Lond) 150:134–144, 1960.
16. Hubbard, J. I. Mechanism of transmitter release. Prog. Biophys. Mol. Biol. 21:35, 1970.
17. Katz, B. and Miledi, R. Further study of the role of calcium in synaptic transmission. J. Physiol. (Lond) 207:789–801, 1970.
18. Raftery, M. A., Hunkapiller, M. W., Strader, C. D., and Hood, L. E. Acetylcholine receptor: a complex of homologous subunits. Science 208:1454–1456, 1980.
19. Peper, K., Bradley, R. J., and Dreyer, F. The acetylcholine receptor at the neuromuscular junction. Physiol. Rev. 62:1271–1340, 1982.
20. Standaert, F. G. Neuromuscular physiology. In: Miller, R. D., ed. Anesthesia, 3rd Ed., New York: Churchill-Livingstone, 1990, pp. 659–684.
21. Ganong, W. F. Synaptic and junctional transmission. In: Review of Medical Physiology, 13th Ed, Appleton & Lange, Norwalk, 1987, pp 65–89.
22. Ganong, W. F. Excitable Tissue: Muscle. In: Review of Medical Physiology, 13th Ed, Appleton & Lange, Norwalk, 1987, pp. 48–64.
23. Taylor, P. Agents acting at the neuromuscular junction and autonomic ganglia. In: Gilman, A. G., Rall, T. W., Nies, A. S., and Taylor, P., eds., Goodman and Gilman’s The Pharmacological Basis of Therapeutics, New York, 8th Ed., Pergamon Press, 1990, pp. 166–186.
24. Sine, S. and Taylor, P. Relationship between reversible antagonist occupancy and the functional capacity of the acetylcholine receptor. J. Biol. Chem. 256:6692–6698, 1981.
25. Taylor, P., Brown, R. D., and Johnson, D. A. The linkage between ligand occupation and response of the nicotinic acetylcholine receptor. In: Kleinzeller, A., Martin, B. R., eds. Current Topics in Membranes and Transport, Volume 18. New York: Academic Press, Inc.; 1983, pp. 407–444.
26. Bowman, W. C. Prejunctional and postjunctional cholinoreceptors at the neuromuscular junction. Anesth. Analg. 59:935–943, 1980.
27. Bowman, W. C., Marshall, I. G., and Gigg, A. J. Is there feedback control of transmitter release at the neuromuscular junction? Semin. Anesth. 3:275–283, 1984.
28. Betz, W. J., Caldwell, J. H., and Kinnunen, S. C. Increased sodium conductance in the synaptic region of rat skeletal muscle fibres. J. Physiol. (Lond) 352:189–202, 1984.
29. Katz, A. M., Messiniso, F. C., and Herbette, L. Ion channels in membranes. Circulation 65:2–10, 1982.
30. Spivak, C. E. and Albuquerque, E. X. Dynamic properties of the nicotinic acetylcholine receptors ion channel complex: Activation and blockade. In: Hannin, I. and Goldberg, A. M., eds. Progress in Cholinergic Biology: Model Cholinergic Synapses. New York: Raven Press, 1982, pp. 323.
31. Albuquerque, E. X., Akaike, A., Shaw, K. P., and Rickett, D. L. The interaction of anticholinesterase agents with the acetylcholine receptor-ionic channel complex. Fund. Appl. Toxicol. 4:527, 1984.
32. Lamberts, J. J., Durant, N. N., and Henderson, E. G. Drug-induced modifications of ionic conductance at the neuromuscular junction. Ann. Rev. Pharmacol. Toxicol. 23:505–539, 1983.
33. Standaert, F. G. Donuts and Holes: Molecules and muscle relaxants. Semin. Anesth. 3:251–261, 1984.
34. Dreyer, F. Acetylcholine receptor. Br. J. Anaesth. 54:115–130, 1982.
35. Gage, P. W. and Hammill, O. P. Effects of anesthetics on ion channels in synapses. Int. Rev. Physiol. 25 (Neurophysiol 4): 1–46, 1981.
36. Neubig, R. R., Boyd, N. D., and Cohen, J. B. Conformations of torpedo acetylcholine receptor associated with ion transport and desensitization. Biochemistry 21:3460–3467, 1982.
37. Sakmann, B., Patlak, J., and Neher, E. Single acetylcholine-activated channels show burst-kinetics in presence of desensitizing concentrations of agonist. Nature 286:71–73, 1980.
38. Brown, R. D. and Taylor, P. The influence of antibiotics on agonist occupation and functional states of the nicotinic acetylcholine receptor. Mol. Pharmacol. 23:8–16, 1983.
39. Pascuzzo, G. J., Akaike, A., Maleque, M. A., Shaw, K-P, Aronstam, R. S., Rickett, D. L., and Albuquerque, E. X. The nature of the interactions of pyridostigmine with the nicotinic receptor-ionic channel complex. Mol. Pharmacol. 25:92–101, 1984.
40. Merton, P. A. Voluntary strength and fatigue. J. Physiol. (Lond) 123:553–564, 1954.
41. Stanec, A., Heyduk, J., Stanec, G., and Orkin, L. R. Tetanic fade and posttetanic tension in the absence of neuromuscular blocking agents in anesthetized man. Anesth. Analg. 57:102–107, 1978.
42. Ali, H. H., Savarese, J. J., Lebowitz, P. W., and Ramsey, F. M. Twitch, tetanus and train-of-four as indices of recovery from nondepolarizing neuromuscular blockade. Anesthesiology 54:294–297, 1981.
43. Lee, C., Barnes, A., and Katz, R. L. Neuromuscular sensitivity to tubocurarine: a comparison of 10 parameters. Br. J. Anaesth. 48:1045–1051, 1976.
44. Goat, V. A., Yeung, M. L., Blakeney, C., and Feldman, S. A. The effect of blood flow upon the activity of gallamine triethiodide. Br. J. Anaesth. 48:69–73, 1976.
45. Saxena, P. R., Dhasmana, K. M., and Prakash, O. A comparison of systemic and regional hemodynamic effects of d-tubocurarine, pancuronium, and vecuronium. Anesthesiology 59:102–108, 1983.
46. Curran, M. J., Donati, F., and Bevan, D. R. Onset and recovery of atracurium and suxamethonium-induced neuromuscular blockade with simultaneous train-of-four and single twitch stimulation. Br. J. Anaesth. 59:989–994, 1987.
47. Ali, H. H. and Savarese, J. J. Stimulus frequency and dose-response curve to d-tubocurarine in man. Anesthesiology 52:36–39, 1980.
48. Connelly, N. R., Silverman, D. G., and Brull, S. J. Temporal correlation of succinylcholine-induced fasciculations to loss of twitch response at different stimulating frequencies. J. Clin. Anesth. 4:190–193, 1992.
49. Ali, H. H. and Savarese, J. J. Stimulus frequency is essential information. Anesthesiology 50:76–77, 1979.
50. Blackman, J. G. Stimulus frequency and neuromuscular block. Br. J. Pharmacol. 20:5–16, 1963.
51. Waud, B. E. and Waud, D. R. The margin of safety of neuromuscular transmission in the muscle of the diaphragm. Anesthesiology 37:417–422, 1972.
52. Lee, C. Train-of-four quantitation of competitive neuromuscular block. Anesth. Analg. 54:649–653, 1975.
53. Ali, H. H., Utting, J. E., and Gray, T. C. Stimulus frequency in the detection of neuromuscular block in humans. Br. J. Anaesth. 42:967–978, 1970.
54. Brull, S. J., Ehrenwerth, J., and Silverman, D. G. Stimulation with submaximal current for train-of-four monitoring. Anesthesiology 72:629–632, 1990.
55. Silverman, D. G., Connelly, N. R., O'Connor, T. Z., Garcia, R. and Brull, S. J. Accellographic train-of-four at near-threshold currents. Anesthesiology 76:34–38, 1992.
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56. Connelly, N. R., Silverman, D. G., O’Connor, T. Z., and Brull, S. J. Subjective responses to train-of-four and double burst stimulation in awake patients. Anesth. Analg. 70:650–653, 1990.
57. Ali, H. H. and Kitz, R. J. Evaluation of recovery from nondepolarizing neuromuscular block, using a digital neuromuscular transmission analyzer: preliminary report. Anesth. Analg. 52:740–745, 1973.
58. Ali, H. H., Utting, J. E., and Gray, T. C. Quantitative assessment of residual antidepolarizing block. Br. J. Anaesth. 43:473–477, 1971.
59. Ali, H. H. and Savarese, J. J. Monitoring of neuromuscular function. Anesthesiology 45:216, 1976.
60. Lee, C. and Katz, R. L. Fade of neurally evoked compound electromyogram during neuromuscular block by d-tubocurarine. Anesth. Analg. 56:271–275, 1977.
61. Silverman, D. G. and Brull, S. J. The effect of a tetanic stimulus on the response to subsequent tetanic stimulation. Anesth. Analg. 76:1284–1287, 1993.
62. Paton, W. D. M., and Waud, D. R. The margin of safety of neuromuscular transmission. J. Physiol. (Lond) 191:59–90, 1967.
63. Brull, S. J., Connelly, N. R., O’Connor, T. Z., and Silverman, D. G. Effect of tetanus on subsequent neuromuscular monitoring in patients receiving vecuronium. Anesthesiology 74:64–70, 1991.
64. Brull, S. J. and Silverman, D. G. Tetanus-induced changes in apparent recovery after bolus doses of atracurium or vecuronium. Anesthesiology 77:642–645, 1992.
65. Viby-Mogensen, J., Howardy-Hansen, P., Chræmmer-Jørgensen, B., Ørding, H., Engbæk, J. and Nielsen, A. Posttetanic count (PTC): a new method of evaluating an intense nondepolarizing neuromuscular blockade. Anesthesiology 55:458–461, 1981.
66. Bonsu, A. K., Viby-Mogensen, J., Fernando, P. U. E., Muhhal, K. Tamilara-San, A., and Lambourne, A. Relationship of posttetanic count and train-of-four response during intense neuromuscular blockade caused by atracurium. Br. J. Anaesth. 59:1089–1092, 1987.
67. Fernando, P. U. E., Viby-Mogensen, J., Bonsu, A. K., Tamilarasan, A., Mochhal, K. K., and Lambourne, A. Relationship between post-tetanic count and response to carinal stimulation during vecuronium-induced neuromuscular blockade. Acta Anaesthesiol. Scand. 31:593–596, 1987.
68. Howardy-Hansen, P., Viby-Mogensen, J., Gottshau, A., Theil-Skovgaard, L., Chemmer, Jørgensen, B., and Engbæk, J. Tactile evaluation of the posttetanic count (PTC). Anesthesiology 60:372–374, 1984.
69. Drenck, N. E., Ueda, N., Olsen, N. V., Engbæk, J. Jensen, E., Skovgard, L. T., and Viby-Mogensen, J. Manual evaluation of residual curarization using double burst stimulation: a comparison with train-of-four. Anesthesiology 70:578–581, 1989.
70. Engbæk, J., Ostergaard, D., and Viby-Mogensen, J. Double burst stimulation (DBS): a new pattern of nerve stimulation to identify residual neuromuscular transmission. Br. J. Anaesth. 62:274–278, 1989.
71. Ueda, N., Viby-Mogensen, J., V-Olsen, N., E-Drenck, N. Tsuda, H., and Muteki, T. The best choice of double burst stimulation pattern for manual evaluation of neuromuscular transmission. J. Anaesth. 3:94–99, 1989.
72. Brull, S. J., Connelly, N. R., and Silverman, D. G. Correlation of train-of-four and double burst stimulation ratios at varying amperages. Anesth. Analg. 71:489–492, 1990.
73. Viby-Mogensen, J., Jensen, N. H., Engbæk, J., Ørding, H. Skovgaard, L. T., Chræmmer-Jørgensen, B. Tactile and visual evaluation of the response to train-of-four nerve stimulation. Anesthesiology 63:440–443, 1985.
74. Berger, J. J., Gravenstein, J. S., and Munson, E. S. Electrode polarity and peripheral nerve stimulation. Anesthesiology 56:402–404, 1982.
75. Rosenberg, H. and Greenhow, D. E. Peripheral nerve stimulator performance: the influence of output polarity and electrode placement. Can. Anaesth. Soc. J. 25:424–426, 1978.
76. Johansen, S. H., Jorgensen, M., and Molbeck, S. Effect of tubocurarine on respiratory and non respiratory muscle power in man. J. Appl. Physiol. 19:990–994, 1964.
77. Smith, C. E., Donati, F., and Bevan, D. R. Potency of succinylcholine at the diaphragm and the adductor pollicis muscle. Anesth. Analg. 67:625–630, 1988.
78. Donati, F., Antzaka, C., and Bevan, D. R. Potency of pancuronium at the diaphragm and the adductor pollicis muscle in humans. Anesthesiology 65:1–5, 1986.
79. Chauvin, M., Lebrault, C., and Duvaldestin, P. The neuromuscular blocking effect of vecuronium on the human diaphragm. Anesth. Analg. 66:117–122, 1987.
80. Donati, F., Meistelman, C., and Plaud, B. Vecuronium neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis. Anesthesiology 74:833–837, 1991.
81. Donati, F., Meistelman, C., and Plaud, B. Vecuronium neuromuscular blockade at the diaphragm, the orbicularis oculi, and adductor pollicis muscles. Anesthesiology 73:870–875, 1990.
82. Meistelman, C., Plaud, B., and Donati, F. Neuromuscular effects of succinylcholine on the vocal cords and adductor pollicis muscles. Anesth. Analg. 73:278–282, 1991.
83. Brull, S. J. and Silverman, D. S. Intraoperative use of muscle relaxants. Anesth. Clin. of North Amer. 11(2):325–344, 1993.
84. Caffrey, R. R., Warren, M. L., and Becker, K. E., Jr. Neuromuscular blockade monitoring comparing the orbicularis oculi and adductor pollicis muscles. Anesthesiology 65:95–97, 1986.
85. Suffel, P., Hameroff, S. R., Blits, C. D., Cork, R. C. Variability in assessment of neuromuscular blockade. Anesthesiology 52:436–437, 1980.
86. Epstein, R. A. and Epstein, R. M. The electromyographic and the mechanical response of indirectly stimulated muscle in anesthetized man following curarization. Anesthesiology 38:212–223, 1973.
87. Brand, J. B., Cullen, D. J., Wilson, N. E., and Ali, H. H. Spontaneous recovery from nondepolarizing neuromuscular blockade: correlation between clinical and evoked responses. Anesth. Analg. 56:55–58, 1977.
88. Drenck, N. E., Ueda, N., Olsen, N. V., Engbaek, J., Jensen, E., Skovgaard, L. T., and Viby-Mogensen, J. Manual evaluation using double burst stimulation: a comparison with train-of-four. Anesthesiology 70:578–581, 1989.
89. Gill, S. S., Donati, F., and Bevan, D. R. Clinical evaluation of double-burst stimulation. Anaesthesia 45:543–548, 1990.
90. Brull, S. J. and Silverman, D. G. Visual assessment of train-of-four and double burst induced fade at submaximal currents. Anesth. Analg. 73:627–632, 1991.
91. Freund, F. G. and Merati, J. K. A source of errors in assessing neuromuscular blockade. Anesthesiology 39:540–542, 1973.
92. Donlon, J. V., Newfield, P., Sreter, F., and Ryan, J. F. Implications of masseter spasm after succinylcholine. Anesthesiology 49:298–301, 1978.
93. Kopman, A. F. The relationship of evoked electromyographic and mechanical responses following atracurium in humans. Anesthesiology 63:208–211, 1985.
94. Dupuis, J., Martin, R., and Tetrault, J. P. Clinical, electrical and mechanical correlations during recovery from neuromuscular blockade with vecuronium. Can. J. Anaesth. 37:192–196, 1990.
95. Kalli, I. Effect of surface electrode position on the compound action potential evoked by ulnar nerve stimulation during isoflurane anaesthesia. Br. J. Anaesth. 65:494, 1990 (abstract).
96. Torres, F. P., Lee, B. H., and Steen, S. N. Evaluation of a new handheld neuromuscular transmission monitor. J. Clin. Monit. 7:209–211, 1991.
97. Werner, M. U. A methods-comparison study of acceleration, EMG and force responses during recovery from a non-depolarizing block in children. Anesthesiology 73:A911, 1990.
98. Viby-Mogensen, J., Jensen, E., Werner, M., and Nielsen, H. K. Measurement of acceleration: a new method of monitoring neuromuscular function. Acta Anaesthesiol. Scand. 32:45–48, 1988.
99. Heier, T., Caldwell, J. E., Sessler, D. I., and Miller, R. D. Mild intraoperative hypothermia increases duration of action and spontaneous recovery of vecuronium blockade during nitrous oxide-isoflurane anesthesia in humans. Anesthesiology 74:815–819, 1991.
100. Foldes, F. F., Rendell-Baker, L., and Birch, J. H. Causes and prevention of prolonged apnea with succinylcholine. Anesth. Analg. 35:609, 1956.
101. Gramstad, L. Atracurium, vecuronium, and pancuronium in end-stage renal failure. Br. J. Anaesth. 59:995–1003, 1987.
102. Lee, C. and de Silva, A. J. C. Acute and subchronic neuromuscular blocking characteristics of streptomycin: A comparison with neomycin. Br. J. Anaesth. 51:431–434, 1979.
103. Singh, Y. N., Harvey, A. L., and Marshall, I. G. Antibiotic-induced paralysis of the mouse phrenic nerve-hemidiaphragm preparation, and reversibility by calcium and by neostigmine. Anesthesiology 48:418–474, 1978.
104. Singh, Y. N., Marshall, I. G., and Harvey, A. L. Depression of transmitter release and postjunctional sensitivity during neuromuscular block produced by antibiotics. Br. J. Anaesth. 51:1027–1033, 1979.
105. Sokoll, M. D. and Gergis, S. D. Antibiotics and neuromuscular function. Anesthesiology 55:148–159, 1981.
106. Ghoneim, M. M. and Long, J. P. The interaction between magnesium and other neuromuscular blocking agents. Anesthesiology 32:23–29, 1970.
107. Usubiaga, J. E. and Standaert, F. The effects of local anesthetics on motor nerve terminals. J. Pharmacol. Exp. Ther. 159:353–361, 1968.
108. Gelser, R. M. and Matsuba, M. Neuromuscular blocking actions of local anesthetics. J. Pharmacol. Exp. Ther. 103:314, 1951.
109. Harrah, M. D. Way, W. L., and Katzung, B. G. The interaction of d-tubocurarine with antiarrhythmic drugs. Anesthesiology 33:406-410, 1970.
110. Bikhazi, G. B., Leung, I., Flores, C., Mikati, H. M. J., and Foldes, F. F. Potentiation of neuromuscular blocking agents by calcium channel blockers in rats. Anesth. Analg. 67:1–8, 1988.
111. Martin, B. A. and Kramer, P. M. Clinical significance of interaction between lithium and a neuromuscular blocker. Am. J. Psychiatry 139:1326–1328, 1982.
112. Ornstein, E., Matteo, R. S., Schwartz, A. E., Silvergerg, P. A. Young, W. L., and Diaz, J. The effect of phenytoin on the magnitude and duration of neuromuscular block following atracurium or vecuronium. Anesthesiology 67:191–196, 1987.
113. Deacock, A.R. and Hargrove R.L. The influence of certain ganglionic blocking agents on neuromuscular transmission. Br. J. Anaesth. 34:357–362, 1962.
114. Glisson, S. N., El-Etr, A. A., and Lim, R. Prolongation of pancuronium induced neuromuscular blockade by intravenous infusion of nitroglycerine. Anesthesiology 51:47–49, 1979.
115. Miller, R. D., Sohn, Y. J., and Matteo, R. S. Enhancement of d-tubocurarine neuromuscular blockade by diuretics in man. Anesthesiology 45:442–445, 1976.