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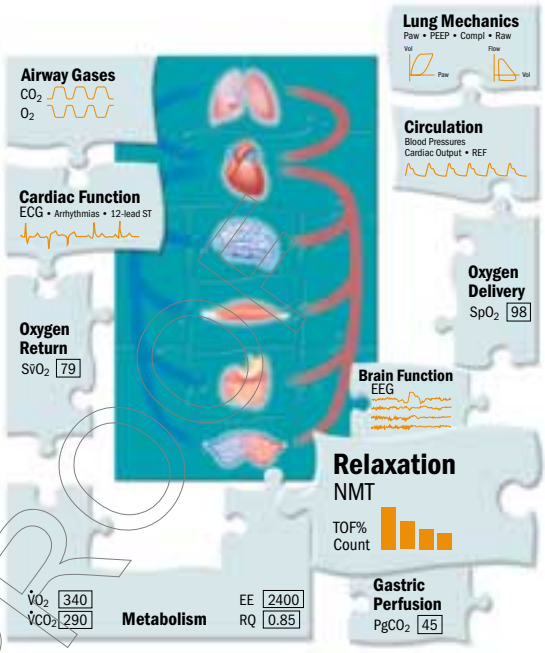

Neuromuscular monitoring

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MEDICAL SYSTEMS

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Abbreviations

AP	adductor pollicis
Ach	acetylcholine
ACG	accelerography
cMAP	compound muscle action potential
DBA	depolarizing blocking agent
DBS	double burst stimulation
EMG	electromyography
Impedance	the opposition to the flow of alternating current
KMG	kinemyography
MAP	muscle action potential
MEP	motor end plate = post-synaptic membrane
MEPP	miniature end-plate potential
MMG	mechanomyography
NDBA	non-depolarizing blocking agent
NMBA	neuromuscular blocking agent
NMJ	neuromuscular junction
NMT	neuromuscular transmission
PTC	post-tetanic count
PTF	post-tetanic facilitation
PTP	post-tetanic potentiation
ST	single-twitch
TOF	train-of-four

Introduction

Muscle relaxants have been used in clinical settings for almost 60 years. Still, neuromuscular blocking agents are associated with a significant incidence of postoperative residual effects in the operating room (OR) and in critical care (Intensive Care Unit, ICU). Monitoring the effect of neuromuscular blocking agents helps ensure appropriate intraoperative use and effective antagonism of these agents. However, for many years, clinical criteria alone was used to determine the degree of block and the adequacy of recovery.

Clinical testing of the recovery from a neuromuscular block is performed by evaluating muscle strength (e.g., head or leg-lift, hand-grip, tongue protrusion). In patients recovering from anesthesia and in the critical care areas, muscle strength can be affected by many variables other than the depth of neuromuscular block. Additionally, clinical signs alone are not an adequate and sensitive means of detecting residual block. Thus, it is essential to monitor neuromuscular recovery following the administration of neuromuscular blocking drugs. Monitoring of neuromuscular block is particularly useful in any types of surgery where patient movement absolutely has to be avoided e.g. in ophtalmic and neurosurgery.

The appropriate assessment of the degree of block allows the anesthesiologist to correctly time intubation, guide intraoperative administration of neuromuscular blocking agents, maintain a desired degree of intraoperative block, predict spontaneous recovery or antagonism of block, and ultimately prevent the occurrence of residual weakness. In the ICU, the appropriate assessment of the degree of block enhances adequate ventilation, diminishes the incidence of traumatic extubation, shortens the ICU stay, and was shown to decrease drug costs.

Neuromuscular Physiology

Anatomy of the Nerve

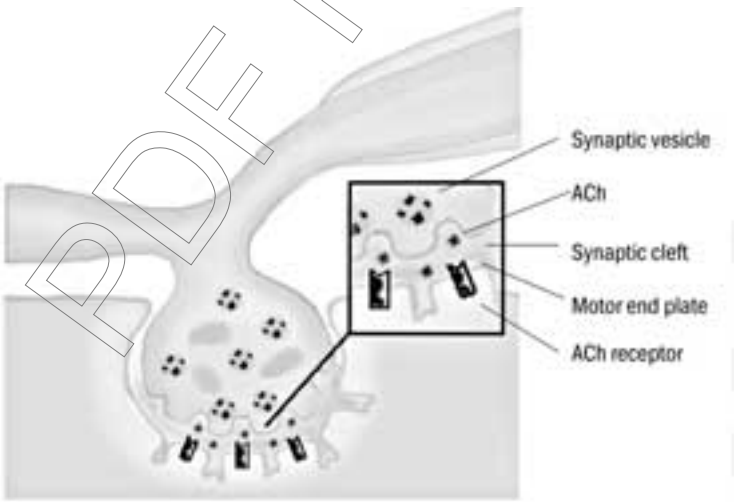
All skeletal muscle fibers that form a muscle are innervated by motor neurons, whose cell bodies lie in the anterior horn of the spinal cord or in the corresponding motor nuclei of cranial nerves. These somatic motor neurons are typically myelinated and thus, are fast conducting fibers. Each neural branch supplies a single muscle fiber, via the intervening neuromuscular junction (NMJ). The innervation ratio relates to the number of muscle fibers that are innervated by a single motor neuron (motor unit). An example of a low innervation ratio would be the extraocular muscles where a neuron innervates only a few fibers; this allows for very fine control of a single muscle group whose function is modulated by many neurons. A high innervation ratio, such as the postural muscles of the back, have hundreds of muscle fibers innervated by only one neuron.

Neuromuscular Junction

The components of the neuromuscular junction are the pre-synaptic region of the motor neuron, the intervening cleft, and the receptors that are located on the post–synaptic membrane, the motor end plate (MEP). At the motor end plate, the membrane of the muscle fiber is thickened. The narrow space between the nerve terminal and the muscle membrane is analogous to the synaptic cleft between neurons. Acetylcholine (ACh) is synthesized in the nerve terminal and is stored in vesicles. Each vesicle stored in the terminal contains a quantum of ACh. ACh is released into the synaptic cleft and diffuses across the synaptic cleft to bind to the ACh receptors in the muscle end plate. Each vesicle contains between 6,000 and 10,000 ACh molecules, and a nerve impulse typically releases 50–60 ACh vesicles *(Figure 1)*. The end plate contains approximately 5 million receptor channels, each consisting of 5 subunits (2 alpha, 1 beta, 1 delta and 1 epsilon) arranged as a rosette around a central

channel. Both of the alpha subunits need to be occupied by ACh molecules (or an agonist) for the channel to open *(Figure 2A)*. If ACh binds to both alpha subunits, the open channel allows passage of Na^{+} and Ca^{++} ions into, and K^{+} ions out of, the muscle cell, leading to a miniature end-plate potential (MEPP). If enough channels are open, the individual MEPPs summate and the end plate potential reaches a threshold. Then, a self-propagating muscle action potential (MAP) will be produced, and an "all or none" muscle fiber contraction (muscle twitch) will result followed by relaxation.

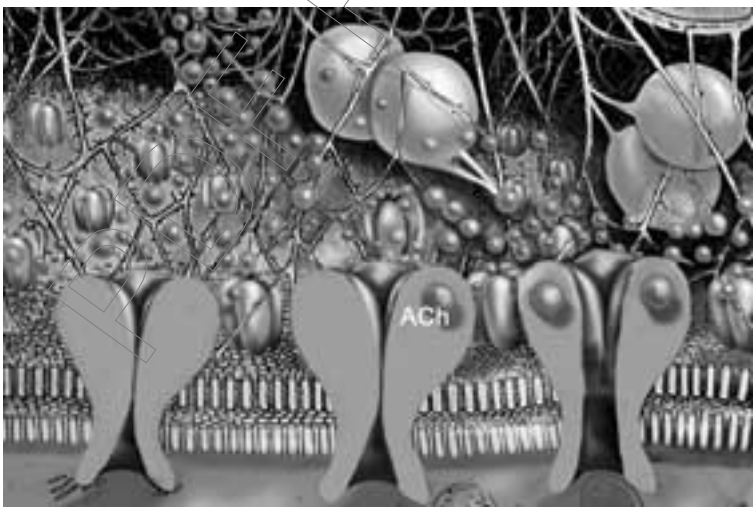
Figure 1



Mechanism of Action of Neuromuscular Blocking Drugs

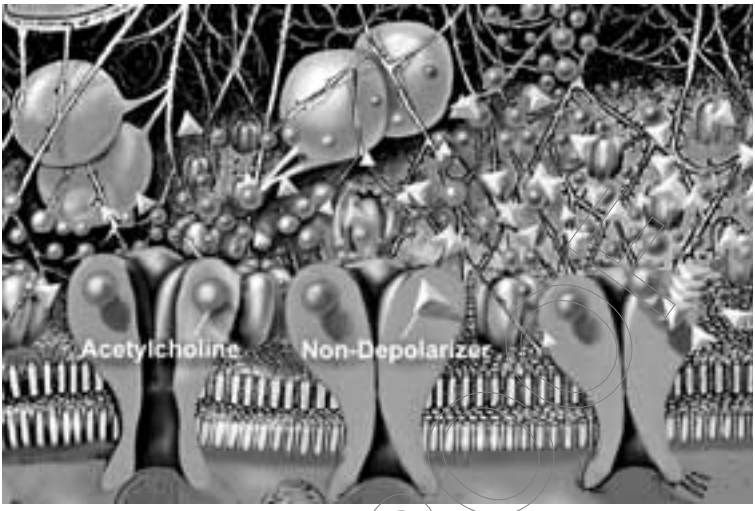
There are 2 groups of neuromuscular blocking agents (NMBA, "muscle relaxants") used in clinical practice: depolarizing and non-depolarizing. Curare is the prototype of the non-depolarizing (NDBA) group (e.g. atracurium, doxacurium, mivacurium, pancuronium, rapacuronium, cisatracurium, pipecuronium, rocuronium, and vecuronium). These agents (also called competitive blockers) compete with ACh for binding to the alpha subunit of the post-synaptic nicotinic receptor, blocking the action of ACh. NDBAs have no appreciable agonist activity. By increasing the concentration of non-depolarizing molecules at the NMJ, the amplitude of the end-plate potential (EPP) decreases progressively. While both two alpha subunits need to be bound by ACh for receptor activation, binding of only one NDBA molecule to one alpha subunit renders the receptor non-functional. In addition, NDBAs may also bind to pre-synaptic receptors, opposing mobilization and release of ACh *(Figure 2)*.

Figure 2 A



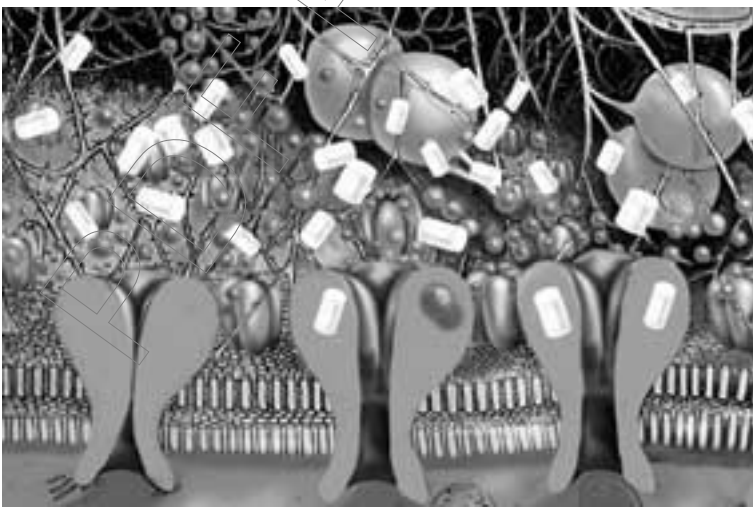
Normal ACh receptor response. Two ACh molecules are needed to open the channel, as shown at right.

Figure 2 B



Non-depolarizer competitive block. One pyramid is enough to cause the block. ACh and blocking molecule compete at right.

Figure 2 C



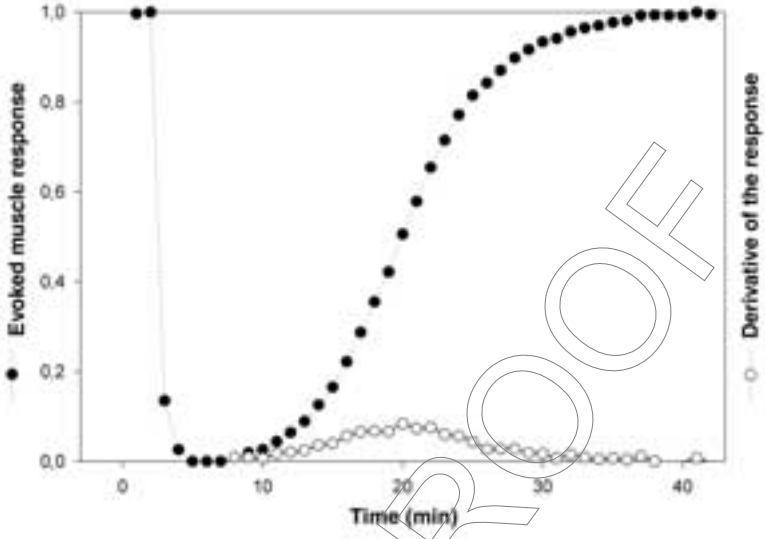
Depolarizing receptor response.Cylinders represent depolarizing agonist e.g. succinylcholine

Depolarizing blocking agents (DBAs), such as succinylcholine and decamethonium, initially depolarize the post-synaptic membrane by opening receptor channels, in a similar manner as ACh. However, because they are not hydrolyzed by acetylcholinesterases at the NMJ, their action persists, resulting in prolonged end-plate depolarization. This brief period of consecutive excitations is manifested clinically by transient muscle fasciculations, followed shortly by neuromuscular transmission block and spastic paralysis. During both a depolarizing and a non-depolarizing block, the muscle continues to respond to direct electrical stimulation (e.g., electrocautery) despite the inactivation of the receptors,

If the exposure to a depolarizing relaxant is prolonged (by administering relaxants in large or repeated doses or by infusion), the typical depolarizing (phase 1) block may assume the characteristics of a non-depolarizing (phase 2) block. Desensitization is thought to be the primary mechanism responsible for phase 2 block. Desensitization may occur when the receptors are no longer responsive to the presence of agonists on both alpha subunits, thus inactivating the receptors. Desensitization involves a conformational change in the structure of the receptor, preventing it from opening the channel normally. In addition, many agents that enhance neuromuscular block also promote desensitization of the nicotinic receptor and/or may cause an open channel receptor block (e.g., barbiturates, volatile anesthetics, local anesthetics, and cholinesterase inhibitors).

The ratio of blocked receptors to unblocked receptors rendering the junction inactive varies between muscle fibers, which explains the sigmoid form of relaxation and recovery curves. The fibers are normally distributed in respect to this characteristic and the cumulative distribution curve is sigmoidal *(Figure 3)*.

Figure 3



Principles of Nerve Stimulation

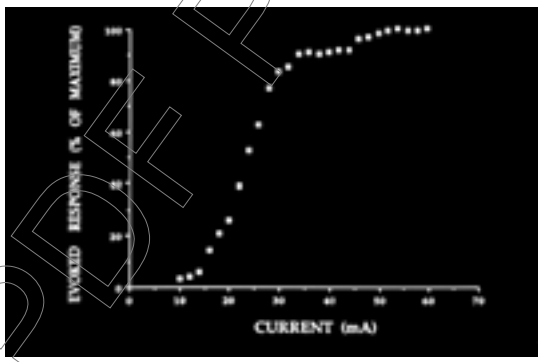
Ohm's Law (U = I • R, where U=voltage, I=current, and R=electrical resistance) describes the factors involved in production of an action potential (AP). The nerve stimulator must provide constant current intensity, as opposed to constant voltage. The strength or total charge, in microCoulombs (μC), of the stimulus depends on its duration (pulse width in microseconds, μsec), and current amplitude (intensity in milliamperes, mA) that reaches the nerve fiber.

One of the most important determinants of the evoked muscle response is the stimulation current amplitude, which depends on the impedance between the electrode and the skin. Using stainless steel needle electrodes, tissue impedance generally is between 500 and 2,000 ohms. Similar impedance is obtained when using silver/silver chloride surface electrodes if the skin is adequately prepared by wiping the skin with alcohol swabs to remove insulating natural skin oils. In neuromuscular research,

rubbing an electrolyte solution into the skin, abrading the skin, and/or applying a conducting paste may be necessary. When using disposable ECG-electrodes, it may be necessary to moisten the pads that have dried out during storage. Despite meticulous skin preparation, a constant current is seldom obtained in the clinical setting.

Another important determinant of the evoked muscle response is the current intensity. When pulse duration and skin-electrode resistance are constant, the stimulating current required to depolarize all fibers of a nerve bundle is called the maximal current. Below this value, the relationship between the number of nerve fibers recruited and the intensity of stimulating current is sigmoidal *(Figure 4)*. This reflects the distribution of individual nerve fiber sensitivities in response to various current intensities. To ensure consistent and maximal recruitment of fibers despite minor variations in skin resistance over time, a supramaximal current (i.e., 10-30% higher than the maximal current) is delivered.

Figure 4



Evoked Response vs. Current Intensity

In addition to skin impedance and current intensity, the duration of the stimulus (pulse width) is also important in determining the amplitude of the evoked muscle response. The relationship between pulse duration and the amplitude of evoked single twitch

response is also sigmoidal; if the current intensity is kept constant, the amplitude of the evoked response shows little change when pulse duration exceeds 0.15-0.30 ms. In clinical practice, pulse widths of 0.2-0.3 ms are used. Durations longer than that may cause repetitive firing and therefore are not recommended. Some devices that deliver a pulse of only 0.1 ms duration may achieve less than maximal fiber recruitment, possibly influencing assessment.

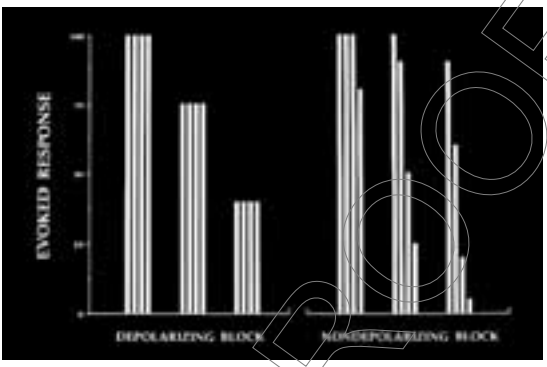
The effect of muscle temperature must also be appreciated. Peripheral cooling decreases the evoked muscle twitch response and increases the electromyographic (EMG) response area, while local heating increases muscle force and decreases the compound EMG response.

The stimulus application rate to the nerve (stimulation frequency) also induces changes in muscle response. At the normal, unblocked NMJ, supraphysiological stimulation rates (e.g. above 70-200 Hz) cause muscle fatigue. Stimulation at physiologic rates (brief tetanus at 50 Hz) at the unblocked NMJ, in contrast, results in sustained contraction without fade. In the presence of a non-depolarizing block, a fade is noted at slower stimulation rates. In addition to inducing fatigue at the NMJ, high-frequency stimulation also increases local blood flow five- to six-fold, facilitating delivery of relaxant to the stimulated muscle. In the clinical setting, the stimulation frequency and the rate of block onset are directly proportional, such that an increase in stimulation frequency will result in a falsely elevated rate of onset. Induction of fatigue and an increase in blood flow also reduce the apparent (but not actual) dose requirements for all muscle relaxants. During a relatively steady and slowly recovering neuromuscular block, the interstimulus interval should be no less than 20 seconds, since at shorter stimulation intervals, the evoked responses become artificially decreased. The explanation for this may be the same as for the train-of-four fade; the first stimulation causes a muscle twitch and redistribution of antagonists on the end plate so that smaller and smaller numbers of muscle fiber responses follow consecutive nerve stimulations.

Patterns of Nerve Stimulation

The majority of nerve stimulators deliver a wide range of stimulating patterns, allowing for the differentiation between depolarizing and non-depolarizing block *(Figure 5)*.

Figure 5



Depolarizing - Nondepolarizing Block

The patterns include single-twitch, train-of-four, double burst, and tetanic stimulation, as well as a post-tetanic twitch count. The stimuli delivered should be square-wave, supramaximal, and most often 0.2 ms in duration. The modes of neurostimulation differ in the intervals and pattern of the delivered stimuli.

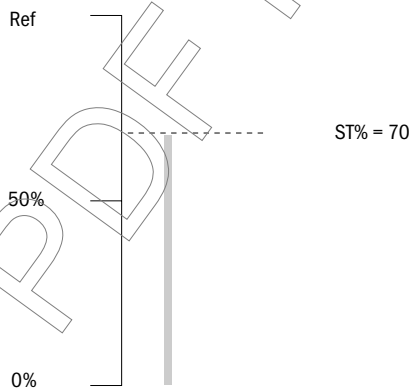
In the literature T often stands for twitch response. E means the response in EMG (electromyography) and M the response in MMG (mechanomyography). In this guide we therefore use R to represent response in general.

Single Twitch

If a single-twitch (ST) pattern is used, a baseline amplitude of the muscle response (R_{ref}) must be established prior to the administration of muscle relaxant *(Figure 6)*. The degree of block produced by the relaxant can be estimated by comparing a subsequent response to the baseline (R_1/R_{ref} x 100= ST%). In the presence of non-depolarizing muscle relaxants, high frequency stimulation can induce "fade" of the single twitch response. For instance, the ED_{95} (effective dose for 95% response suppression of the thumb adduction) of d-tubocurarine is decreased by a factor of three when the stimulus frequency is increased from 0.1 Hz to 1.0 Hz.

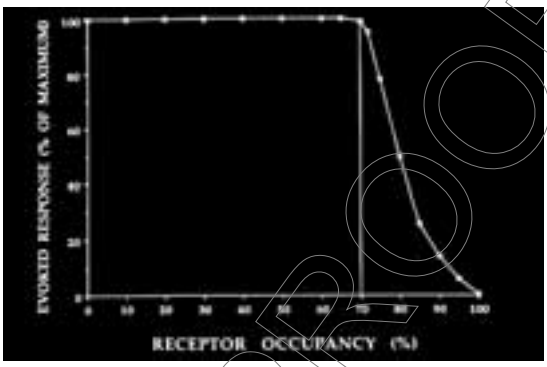
A supramaximal, 0.2-msec duration stimulus with a frequency of 0.1 Hz (10 s intervals or 6/min) is the most common single stimulation mode in many hand-held nerve stimulators. Other inter-stimulus intervals used in the clinical setting include a stimulus pattern every 12 seconds (0.08 Hz or 5 /min), 15 seconds (1/15 ~ 0.066 Hz or 4/min), 20 seconds (0.05 Hz or 3/min), or 60 seconds (1/60 ~ 0.0166 Hz).

Figure 6



The motor response to ST is not reduced until 70-75% of the receptors are occupied, and disappears once 90–95% receptor occupancy occurs *(Figure 7)*. Thus, the range of receptor block detected by ST stimulation (i.e., between 75% and 95% receptor occupancy) is narrow, limiting its clinical usefulness.

Figure 7



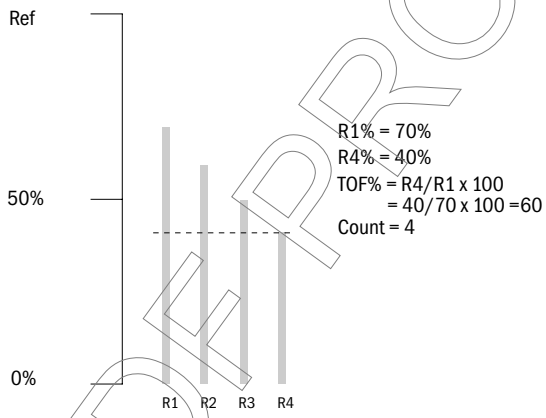
Receptor Occupancy

Other factors that limit the clinical usefulness of ST stimulation include the great variability of evoked responses to alterations in current, skin and muscle temperature, and resting muscle tension (preload). Therefore, careful documentation of baseline response is mandatory for comparison with subsequent stimulation responses. When the control height is evaluated by sight (visually) or by touch (tactile), as is the traditional clinical practice, the change in subsequent responses is difficult to assess and quantify accurately. Quantification of the evoked response by measuring force, EMG, acceleration, or movement greatly enhances the sensitivity of neuromuscular monitoring.

Train-of-Four

In the train-of-four (TOF) pattern, four individual stimuli are separated by 0.5 sec (2 Hz). The "train" can be repeated by chosen intervals but the optimal frequency is every 15 or 20 seconds. At this rate, TOF itself does not cause artificial fade. In the absence of block, the pattern induces four clearly defined muscle responses (R). In the presence of non-depolarizing block, TOF will exhibit fade *(Figure 8)*. The degree of fade is proportional to the extent of the neuromuscular block: the ratio of the amplitude of the fourth response (R_4) to that of the first response (R_1) estimates the extent of non-depolarizing block (i.e., the degree of receptor occupancy). This is known as the R_4/R_1 or TOF ratio.

Figure 8



Four responses to TOF stimulus

At the unblocked NMJ, the R_4/R_1 approximates 1.0. During a partial depolarizing block, the response height is reduced to the same extent in all four responses (no fade), and the R_4/R_1 ratio is 1.0. However, the ratio of R_1 to the control, or baseline twitch (R_1/R_{ref}) will be less than 1.0. If a phase 2 block develops after succinylcholine administration, the TOF responses will show "fade." During a non-depolarizing block, the R_4 begins to decrease

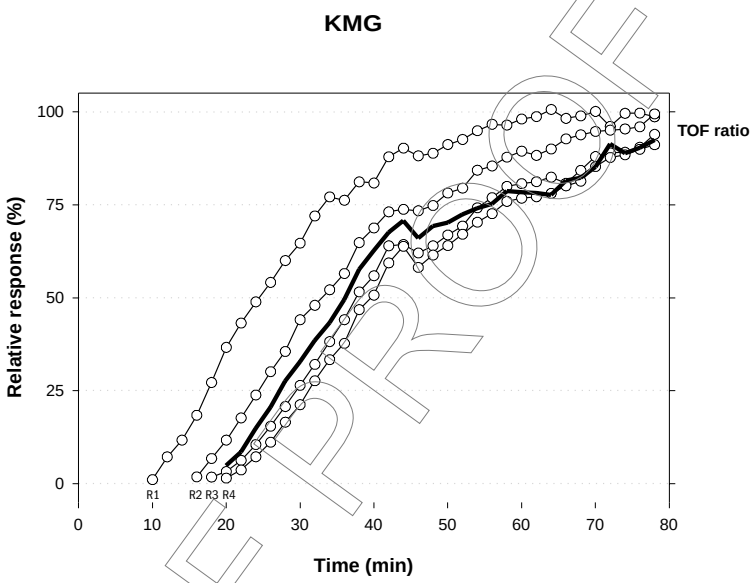
when 70–75% of the receptors are occupied (similar to when single twitch fade begins); the R_1 declines when the R_4/R_1 ratio falls below 0.7. The R_4 response is completely lost at approximately 80% receptor occupancy. The R_3 and R_2 responses are lost when approximately 85% and 85–90% of the receptors are occupied, respectively. When 90–95% of the receptors are blocked, R_1 disappears. During recovery of neuromuscular block, the responses appear in reverse order, R_1 first and R_4 last *(Figure 9)*. The recovery of TOF ratio is also depicted.

TOF stimulation has become the most popular method of assessing neuromuscular block in clinical practice. As long as all four responses are detectable, the TOF ratio remains consistent, regardless of the current intensity. This consistency is evident at current intensities that are at least 10 mA above threshold. TOF is less painful than tetanic stimulation, and thus is more comfortable for awake patients at risk for residual paralysis, as pain is directly related to the intensity of the stimulating current. Submaximal stimulation currents enable rather painless monitoring in intensive care patients requiring muscle relaxants as a part of their therapy.

TOF stimulation shows fade during a partial non-depolarizing block, but unlike tetanus, the TOF pattern does not induce changes in apparent onset or recovery. Unlike single twitch, TOF does not require a preblock control response, as the degree of block is proportional to R_4/R_1. A TOF ratio of 0.75 generally correlates with a sustained muscle response to 50 Hz for 5 seconds and with the first stimulation response having returned to baseline (see Figure 9). This degree of block also correlates with clinically adequate neuromuscular function, although a greater degree of recovery may be necessary for all cholinergic synapse .

It should be noted that the TOF ratio cannot be calculated before all four stimulations elicit a response, irrespective of the measurement method (if the R_4 response is not present, the ratio would be zero). This means that the minimum R_1% at the point where the ratio can be calculated is around 25-30 % *(see Figure 9)*.

Figure 9

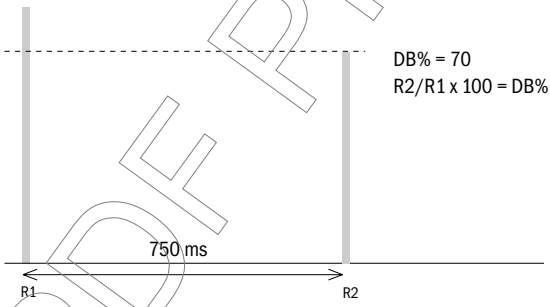


TOF recovery legend:
Recovery of four responses to train-of-four stimulation after neuromuscular block with vecuronium is shown. Train-of-four ratio (TOF%) is illustrated using solid line. Note, that the calculation of TOF% is possible first when all responses can be detected and that TOF% equals to R4% when R1% approaches 100%.

Double Burst Stimulation (DBS)

DBS was introduced in the late 1980s as an alternative method of monitoring neuromuscular block. It involves two bursts of 50-Hz stimuli separated by 750 ms *(Figure 10)*. While the duration of each individual stimulation is 0.2 ms, the number of impulses in each of the two bursts may vary. Patterns using three impulses in each burst ($DBS_{3,3}$) or only two impulses in the second burst ($DBS_{3,2}$) have gained wide use in clinical practice. When $DBS_{3,3}$ is applied to the unblocked NMJ, this pattern induces two short muscle contractions of equal strength. In a patient with a partial non-depolarizing block, $DBS_{3,3}$ and $DBS_{3,2}$ induce a weaker second response (i.e., the responses fade), analogous to the fade induced by TOF *(see Figure 8)*. The DBS and TOF ratios correlate closely over a wide range of stimulating currents and levels of neuromuscular block *(Figure 10)*.

Figure 10



When the TOF response is evaluated by visual and tactile means, degrees of neuromuscular block as low as R_4/R_1 ratio of 0.4 cannot be excluded with certainty. The main advantage of DBS in clinical practice is that a fade of two consecutive responses may be easier to evaluate by subjective means than the fade of the fourth response to the first in TOF stimulation. There is evidence that the first response of DB may appear earlier than R1.

Tetanic Stimulation

At the unblocked NMJ, high frequency (30-100 Hz) stimulation produces repetitive muscle action potentials and results in sustained muscle contraction. Initially, large quantities of ACh quanta are released from pre-synaptic stores. As the stimulus persists, the amount of ACh release decreases. Normally, greater quantities of ACh are released from pre-synaptic stores than necessary to elicit a response, and therefore, muscle contraction in response to tetanic stimulation persists despite decreasing ACh release. In clinical practice, a stimulus of 50 Hz for five seconds is usually selected, as the muscle tension evoked approximates that achieved during maximal voluntary effort. Supraphysiological rates of stimulation (70–200 Hz) are not commonly used in clinical practice, since even normal neuromuscular transmission may fatigue and fade may result.

During a partial depolarizing block, the peak muscle tension is reduced, but contraction is sustained for a 5-sec tetanic stimulation period, analogous to the maintenance of TOF ratio of 1.0, despite the decrease in the R_1/R_{ref} ratio. During non-depolarizing block (and phase 2 depolarizing block), the peak tension is decreased, and the tension "fades" if the stimulation is sustained. The degree of fade depends primarily on the extent of the neuromuscular block and may be used to quantify the depth of block. The degree of fade also varies proportionately with the frequency of stimulation. Higher stimulating frequencies result in a greater degree of fade. Tetanic stimulation results in an increased release of ACh with subsequent stimuli, a phenomenon known as post-tetanic potentiation (PTP) or post-tetanic facilitation (PTF) that persists for 2-5 minutes.

The duration and magnitude of PTP are a function of the degree of neuromuscular block, and may result in underestimation of block if the evoked responses are assessed during the period of potentiation. Alternatively, succinylcholine-induced phase 1

muscle block does not exhibit PTP. One limitation of tetanic stimulation is the pain associated with its use, it should be applied only to anesthetized patients. This limits 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 block is profound, TOF or ST stimulation evokes no response, and the extent of block cannot be assessed. However, the phenomenon of post-tetanic potentiation (PTP) may enable subsequent stimuli to induce a muscle response. The post-tetanic count (PTC) takes advantage of this period of PTP to assess the degree of neuromuscular block, even when ST, TOF, and DBS patterns evoke no response. PTC is generally used to ensure profound block during microsurgery, ophthalmic surgery, and when patient's coughing on the tracheal tube could have untoward consequences. PTC consists of a sequence of events, in which a tetanic stimulus (50 Hz for 5 seconds) is followed three seconds later by 20 single supramaximal stimuli at a frequency of 1 Hz *(Figure 11)*. The number of detected evoked responses is inversely proportional to the extent of block. In the presence of profound block, PTC allows clinicians to estimate the time to the appearance of the first stimulation responses, and to appropriately plan for reversal.

Figure 11

Sites of Stimulation

The site of neuromuscular stimulation depends on several factors. In the clinical setting, accessibility to a superficial nerve is the most important. For this reason, the ulnar nerve is most often chosen. The ulnar nerve primarily innervates the adductor pollicis muscle, abductor digiti minimi muscle (hypothenar), and the dorsal interosseous muscles. Monitoring this site usually does not interfere with the surgical field, and it is well suited for visual, tactile, and objective assessments. In addition, the adductor pollicis (AP) muscle is on the lateral side of the arm, whereas nerve stimulation occurs on the medial side. Thus there is little chance of direct muscle stimulation which could interfere with assessment. To stimulate the ulnar nerve, one electrode is placed on the radial side of the volar forearm about 1 cm (0.4") proximal to the wrist. The other electrode may be placed 3–4 cm (1.2-1.6") proximal to the first electrode (*Figure 12*) or over the ulnar groove at the elbow. In this configuration, however, the flexor carpi ulnaris muscle may be stimulated and result in augmented thumb adduction. Other clinical sites of nerve stimulation include the posterior tibial, the peroneal, and the facial nerves.

Muscle groups differ in their sensitivity to muscle relaxants. Therefore, the results obtained in monitoring one muscle group may not accurately reflect the state of relaxation at another muscle group. Proposed factors include differences in regional blood flow, muscle temperature, density, type of receptors and muscle fiber composition. 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 and higher receptor density. When compared to the adductor pollicis muscle, the diaphragm requires 1.5-2 times more relaxant to achieve paralysis. Differences in sensitivity to relaxants and in the onset times have clinical implications when peripheral sites are monitored. When high doses of relaxants are used (more than twice the ED_{95}), the faster onset time at the

diaphragm predominates, and block is achieved here before it is seen at the adductor pollicis muscle. However, if lower doses of relaxant are used, the adductor pollicis twitch may be ablated before maximal diaphragmatic relaxation is achieved.

The response of the orbicularis oculi muscle to facial nerve stimulation may be more accurate than peripheral muscles because it more closely reflects the sensitivity and time course of the airway musculature. However, direct muscle stimulation must be avoided, as it may result in an enhanced response and underestimation of the degree of overall block.

Monitoring of the Evoked Response

Clinicians monitor the evoked responses objectively or subjectively, or use both methods. In the clinical setting, most anesthesiologists rely on visual or tactile (i.e., subjective) means of assessment. These subjective means should be augmented by objective assessment tools (e.g., mechanic or electromyographic) and clinical evaluation (e.g., head lift, respiratory parameters, grip strength), especially in patients at risk for postoperative residual paralysis.

Subjective Means

Visual and Tactile Assessment

The most popular method of monitoring neuromuscular fade in response to TOF stimulation is visual and/or tactile assessment. For visual assessment, the clinician should be perpendicular to the plane of muscle movement. For tactile assessment, the thumb should be held in full abduction, and the evoked response should be evaluated at the distal thumb phalanx in the direction of AP contraction. It should be noted that TOF or single stimulation responses in the hand can not be used to decide when to proceed with laryngoscopy and tracheal intubation, as the hand muscles get relaxed later than those of the head and neck. Supramaximal ST stimulation at a frequency of 1.0 Hz may falsely overestimate the degree of block. Thus, a frequency lower than 1.0 Hz should be used. Continuous monitoring can optimally control the maintenance of a block. After the administration of succinylcholine, non-depolarizing muscle relaxants should not be administered until recovery of neuromuscular transmission is documented, so that pseudocholinesterase deficiency can be ruled out. In cases where a deep level of relaxation is necessary (e.g., neurological or ophthalmologic surgery), PTC can be used to assure a deep block.

It has been suggested that subjective assessments will not be consistent in detecting neuromuscular fade even when performed by experienced observers, regardless of the pattern of stimulation assessed. In some cases, the use of DBS has resulted in more accurate detection of neuromuscular fade, but its usefulness, as the only means of assessment, is limited. Neuromuscular testing may be performed using submaximal TOF stimulation without a loss of accuracy and with lessened patient discomfort. In most clinical settings, regardless of the pattern of neurostimulation or the current intensity delivered, there is no significant difference in the ability to detect fade between visual and tactile means.

Objective Means

Since tactile and visual means of evaluation are by definition subjective, more precise methods of evaluation of block are useful. There are basically two main principles. Either detection of muscle contraction or measurement of EMG after stimulation of a peripheral nerve.
Datex-Ohmeda provides state of the art solutions to both measurement types. For muscle contraction measurement we offer kinemyography (KMG). These methods will be explained in the two following paragraphs.
To complete the picture of different methods in measuring NMB we also explain here the more traditional methods such as mechanomyography and accelerography.

Kinemyography (KMG)

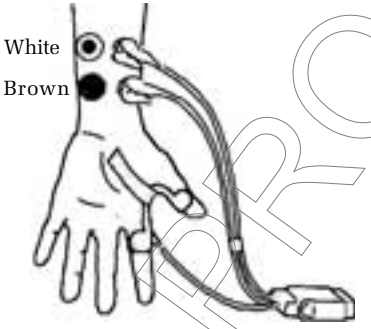
The Datex-Ohmeda MechanoSensor™ consists of two stimulating electrodes and a bending sensor, which is placed between the thumb and the forefinger to measure the muscle response to various stimulation modes (*Figure 12*).

The core of the MechanoSensor is a strip of piezoelectric polymer, which is housed inside the sensor. Piezoelectric material is used also in acceleration sensors, but here the characteristics of the

material are used to detect *movement* – the change in shape of the material when it is bent by the contraction of the adductor pollicis muscle. Therefore the method that Datex-Ohmeda uses is not accelerography.

When this piezoelectric material changes shape, the electrical charge in the material is redistributed and leads to an electron flow to balance the charges. This flow can be measured as a potential change, which is proportional to the amount of material bending (distortion).

Figure 12

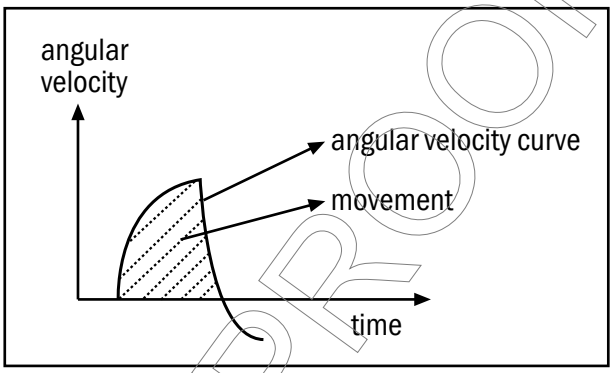


When the ulnar nerve is stimulated electrically, the thumb moves and bends the sensor and the piezoelectric foil inside. The signal is proportional to the angular velocity of the thumb movement. The area under the angular velocity curve *(Figure 13)* quantifies the thumb movement (bending) within a certain time interval. Angular velocity of the thumb depends on the force of the muscle contractions, which varies as a function of the level of neuromuscular block, but it is also dependent on the positioning of the sensor on the hand, and the temperature of the hand (and sensor). As the baseline may change during use, the ratio of the last to the first responses, and the absolute number of detected responses in deeper blocks, are used. The sensor should be fixed with a strip of narrow tape that does not prevent thumb

movement or bending of the sensor. Immobilization of the hand is not necessary, as the position and direction of the thumb do not affect the measurement, as long as the thumb is able to move freely.

A neonatal/pediatric version of the MechanoSensor (PediSensor™) has also been introduced for use in clinical settings.

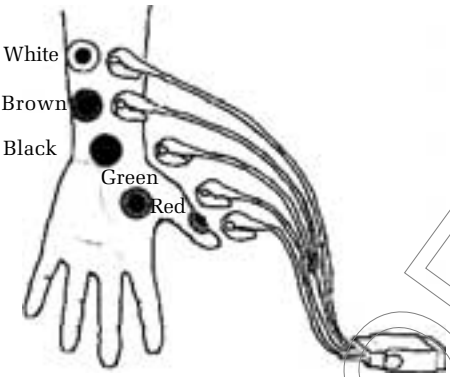
Figure 13



Electromyography (EMG)

Electromyography is the process of recording the electrical activity of a muscle in response to nerve stimulation *(Figure 14)*. The signal obtained depends on the location of the recording electrodes relative to the muscle. Most commonly, three recording electrodes are positioned to give the most consistent EMG signals: one electrode (green) is placed over the mid-portion of the muscle close to the neuromuscular junction and the other (red) is placed over the muscle tendon or finger. The placement of the third electrode (neutral, black) is variable. The innervating nerve is stimulated, and the recorded electrical activity of the muscle is inversely proportional to the degree of block at the NMJ. The evoked compound muscle action potential (cMAP) amplitude or area under the curve represents the sum of the individual muscle fiber potentials activated by the stimulus. The time between the application of the stimulus and the initial deflection of the evoked

Figure 14



response, which is known as the onset latency, represents the nerve conduction time and the time needed for neuromuscular transmission. The duration and shape of the cMAP depends upon the placement of the recording electrode on the muscle. Most EMG devices compute the area under the EMG curve, as this is a better representation of overall muscular activity than the waveform amplitude. This area is then numerically represented.

When the EMG signal is recorded from the thenar eminence, there is a good correlation between the EMG and the adductor pollicis force transducer at the thenar eminence. In this location, movement artifact makes EMG monitoring difficult. The hypothenar muscles are also used for the EMG, but these muscles are less sensitive than the adductor pollicis to non–depolarizing neuromuscular blocking drugs. The recording electrode can be placed over the first dorsal interosseal muscle. In this location, the EMG response correlates well with adductor pollicis force transduction.

The differences between EMG and mechanomyography (MMG) may be due to the sensitivity of the latter to factors affecting muscle contraction (e.g., mechanical). On the other hand, the EMG is influenced by factors involved in nerve conduction, neuromuscular transmission, and formation of the compound EMG wave, but is relatively independent of mechanical events.

Therefore, medications that influence excitation-contraction coupling (e.g., dantrolene) will not alter the EMG, but will modify the MMG response.

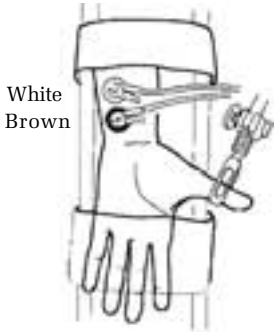
EMG has several advantages over MMG: it is more accurate and reliable, it is less bulky and time consuming than a force transducer, and that it is more practical for monitoring a number of muscle sites. It is, however, more expensive to use (electrodes) and electrical diathermy produces artifact. To date, most EMG monitors can record the response to single and train-of-four stimulation. The Datex-Ohmeda NMT module also measures the first EMG responses to the two burst stimulations. This module also counts the number of post-tetanic EMG responses (PTC).

Mechanomyography (MMG)

The isometric contraction of a muscle (usually the adductor pollicis muscle) in response to nerve stimulation (usually the ulnar nerve) is translated into an electrical signal via a force transducer *(Figure 15)*. The signal is displayed on a pressure monitor, and the amplitude of the electrical signal is proportional to the strength of muscle contraction. By measuring the TOF ratio, the depth of block can be determined accurately enough for clinical purposes.

For an accurate measurement of the evoked response, the hand must be fully immobilized to reduce movement artifact, while the movement of the thumb in the force transducer unit must be unencumbered. The thumb must always apply tension along the axis of the transducer. A preload of 200-300 g should be applied to the abducted thumb prior to ulnar nerve stimulation to ensure isometric contraction. The recording monitor must be able to display the full range of responses, since the tension developed during tetanic stimulation can be four times that achieved by single twitch. A transducer with a suitable tension range (0-5 kg) is adequate for monitoring a non-depolarizing block, but tetanus at the unblocked NMJ may generate even higher forces.

Figure 15



Accelerography (ACG)

The principle of accelerography is based on Newton's Law which states that force equals mass times acceleration (F = m • a). As mass is held constant, the force of thumb adduction in response to ulnar nerve stimulation is directly proportional to acceleration. A thin transducer (piezoelectric wafer) is attached to near the tip of the thumb. Whenever the thumb moves, a voltage is generated which is proportional to the degree of angular acceleration. The signal is amplified and displayed on a monitor screen. The monitor can also display the percent change of the evoked response from baseline, the calculated TOF ratio, and the PTC. Accelerography results are comparable to mechanomyographic TOF monitoring at varying current amplitudes. Accelerometers are less bulky and easier to use than force transducers, and because they measure isotonic contraction, they do not require a muscle preload. However, any interference of free thumb movement will reduce the accuracy of measurement. Accuracy may also be affected by thumb movement, or by failure of the thumb to return to its baseline position after a contraction, resulting in a TOF ratio greater than 1.0 in the unblocked state.

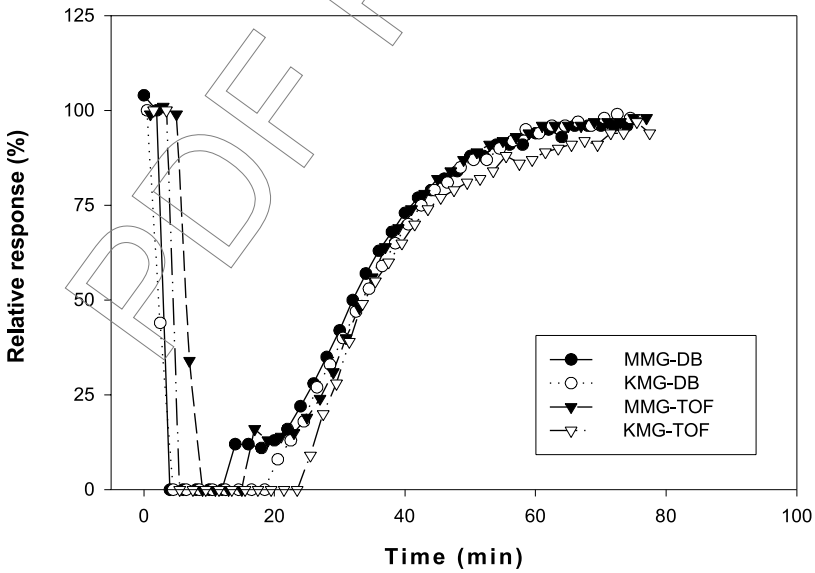
Clinical cases

Comparison of evoked KMG, MMG and EMG responses during recovery

MMG/KMG

The patient was anesthetized using fentanyl-isoflurane and nitrous oxide/oxygen. The *Figure 16* depicts monitored recovery from a rocuronium-induced neuromuscular block when using the Datex-Ohmeda kinemyographic (KMG) MechanoSensor between the third and fourth fingers in a hand placed into a mechano-myometric device (Stanec's board), which measures evoked isometric force in the thenar muscle. Electrically evoked responses to supramaximal ulnar train-of-four (TOF) or double burst ($DB_{3,3}$) stimulations were measured by alternating the NMT trunk cables in the Datex-Ohmeda S/5 Anesthesia Monitor (AM) with NMT module (M-NMT) every 30 seconds during relaxation and recovery from NMB.

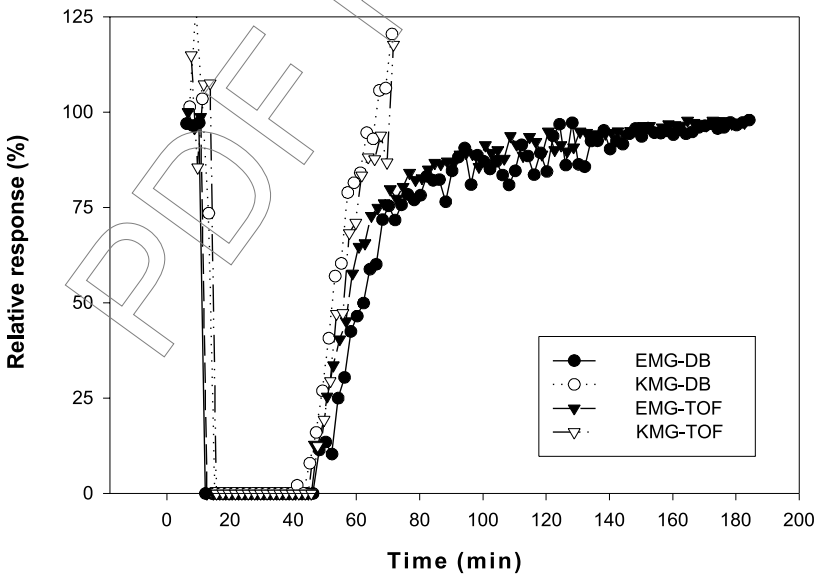
Figure 16



EMG/KMG

The patient was anesthetized using fentanyl-isoflurane and nitrous oxide/oxygen. The *Figure 17* depicts monitored recovery from a rocuronium-induced neuromuscular block when using the Datex-Ohmeda kinemyographic (KMG) MechanoSensor between the thumb and index finger and electro sensor on the first dorsal interosseal muscle and index finger. Electrically evoked responses to supramaximal ulnar train-of-four (TOF) or double burst ($DB_{3,3}$) stimulations were measured by alternating the NMT trunk cables in the monitor every 30 seconds. First EMG-responses to each burst (first and fourth of the whole sequence) are used to calculate the double-burst ratios.

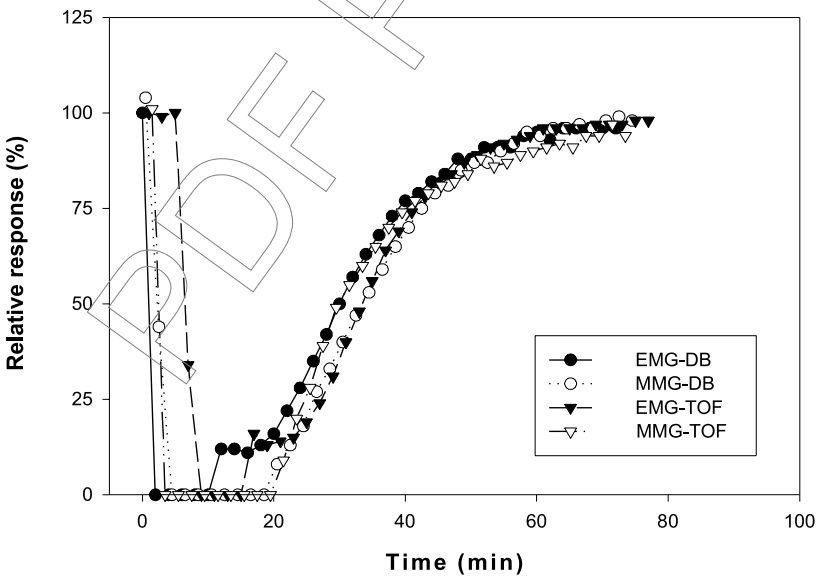
Figure 17



EMG/MMG

The patient was anesthetized using fentanyl-isoflurane and nitrous oxide/oxygen. The *Figure 18* depicts monitored recovery from a rocuronium-induced neuromuscular block when using Datex-Ohmeda Electrosensor on the first dorsal interosseos muscle and index finger in a hand placed into a mechano-myometric device (Stanec's board), which measures evoked isometric force in the thenar muscle. Electrically evoked responses to supramaximal ulnar train-of-four (TOF) or double burst ($DB_{3,3}$) stimulations were measured by alternating the NMT trunk cables in the monitor every 30 seconds. First EMG-responses to each burst (first and fourth of the whole sequence) are used to calculate the double-burst ratios.

Figure 18



Clinical Assessment of Neuromuscular Function

To estimate muscle strength and adequacy of reversal, a variety of clinical signs have been employed: the patients' ability to open their eyes, protrude their tongue, swallow, lift their head or leg, sustain a hand grip, or clench their teeth. Although useful in the clinical setting, clinical assessment has been shown to be inadequate in detecting all cases of residual block. These studies have found that between 2 % and 41 % of postoperative patients may have a TOF ratio less than 0.70, despite being able to meet clinical criteria of recovery. An initially strong muscle contraction that weakens with time is characteristic of residual paralysis. The patients' movements may appear jerky due to their inability to sustain muscular activity. While clinical tests of neuromuscular integrity are useful in assessing the degree of block, they require the patients' collaboration and cannot be performed with unconscious patients. The pattern of respiration and the adequacy of the tidal volume, vital capacity, and negative inspiratory pressure have been used as markers for neuromuscular integrity. In the presence of partial block, however, patients may have adequate ventilation, but their airway reflexes and ability to cough can be impaired. In addition, postoperative respiratory difficulties may be due to residual effects of anesthetic agents. High end-tidal CO_2 may be a sign of inadequate respiratory capacity. Residual block should always be excluded as a cause of respiratory depression by using a quantitative NMT monitor. The combination of clinical evaluation along with neuromuscular monitoring should be used.

When the TOF ratio is greater than 0.6, most patients are able to sustain head lift for three seconds or more, but this does not ensure normal muscle strength. When a TOF ratio exceeds 0.75, eye opening, cough and tongue protrusion may be clinically normal. Recently, it has been shown that the hypoxic breathing response is impaired at TOF ratios below 90 %. Furthermore, even despite the use of ultra-short acting muscle relaxants (mivacurium) and full reversal with anticholinesterases, some volunteers did not feel "street ready" and had residual abnormal

vision for up to 90 minutes after the return of the TOF ratio to a value of 1.0. Since neuromuscular monitoring provides objective evidence of the degree of block, it can be used in unconscious patients and in patients recovering from general anesthesia who are unable to fully cooperate with clinical examination. Monitors should complement clinical examination in the assessment of the status of neuromuscular transmission and adequacy of reversal.

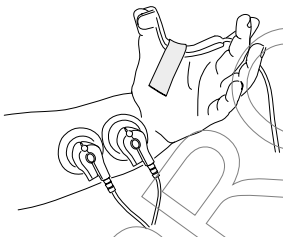
Pediatric Considerations

The indications for neuromuscular blocking agents (NMBAs) are in practice the both in children and adults. Children differ from adults in certain pharmacokinetic and pharmacodynamic characteristics. However, the dosing requirements do not vary significantly with age, because certain maturational differences counterbalance each other. Therefore most clinically available NMBAs can be administered to a pediatric patient according to their bodyweight.

The dose requirements of different NMBAs for an individual patient may vary significantly which promotes the use of neuromuscular monitoring.

In the OR, the purpose of neuromuscular monitoring in children is to optimize the dosage of the NMBA during maintenance of anesthesia and to exclude post-operative residual neuromuscular blockade (NMB). In the case of residual NMB, there will be an increased risk for postoperative respiratory complications which also cause delayed recovery times and increase costs due to waiting time. Therefore, the effects of NMBAs should always be monitored, preferably using an objective (quantitative) method.

In the ICU, the most common indications for neuromuscular blockade in children are to aid endotracheal intubation and to facilitate positive pressure ventilation. Additional indications (less frequent) include controlling shivering, intracranial hypertension (as one part of more complex management), controlling muscle activity/movement when such movement would be detrimental. Muscle relaxation is often used when a patient is agitated and unresponsive to aggressive sedation and analgesia.



Pediatric Mechanosensor

Summary

There are important reasons for monitoring the neuromuscular function:

- there is a wide variability in onset and recovery times with various relaxant regimens
- when clinical means of assessment are used, the incidence of residual curarization remains unacceptably high
- in clinical setting, infusion of both depolarizing and non-depolarizing agents is difficult to titrate accurately
- the development 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 assure steady intraoperative relaxation
- patient response and adequate recovery is difficult to predict accurately in certain disease states (myasthenia gravis, Eaton–Lambert Syndrome, hypothermia, and hypokalemia)
- the pharmacokinetic parameters of relaxants maybe altered in the elderly, those with renal or hepatic impairment, and in patients with atypical or reduced pseudocholinesterase levels
- drug interactions between neuromuscular agents and inhalational anesthetics, nitrous oxide, local anesthetics, anti-arrhythmics, aminoglycosides and calcium channel blockers can modify the response to both relaxants and reversal agents.

There is a wide variation in the response of patients to a "standard" dose of muscle relaxant. Thus, it seems prudent to monitor neuromuscular function whenever neuromuscular blocking drugs are employed. Objective assessment of neuromuscular function using quantitative nerve stimulators complements clinical assessment and improves detection of residual paralysis. The recent reports of significant morbidity (myopathy) associated with prolonged periods of muscle relaxation in the intensive care setting underscore the need for better monitoring of evoked responses. Better understanding and wider perioperative application of neuromuscular monitoring techniques will reduce patient morbidity and provide better anesthetic care.

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