

Neuromuscular Transmission Monitoring – Current Status

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INTRODUCTION:

Muscle relaxants are agents which have come into routine use and have become vital to the care and wellbeing of many patients undergoing anaesthesia and surgery. Evaluation of neuromuscular blockade and adequacy of reversal, using *clinical criteria, may at times be insufficient* and may be influenced by factors other than relaxants. In addition, patients vary widely in their response to relaxants. Therefore, *when careful titration of relaxants and precise information regarding the status of neuromuscular transmission is required, the response of muscle to nerve stimulation should be assessed.* Monitoring neuromuscular blockade is intended to balance adequate surgical relaxation with safe restoration of function at the end of the procedure.

PRINCIPLES OF NEUROMUSCULAR TRANSMISSION

MONITORING:

Neuromuscular transmission is monitored by evaluating the muscular response to supramaximal electrical stimulation of a peripheral motor nerve. The reaction of a single muscle fibre to a stimulus follows an all or none pattern. By contrast, the response of the whole muscle depends on the number of nerve fibers activated. If a nerve is stimulated with sufficient intensity, all the muscle fibers supplied by that nerve will react and the maximum response will be triggered. After administration of a neuromuscular blocking drug, the response of the muscle decreases in parallel with the number of fibers blocked. The *reduction in response to stimulation using constant current* reflects the degree of neuromuscular blockade.

The interaction of depolarising and nondepolarising muscle relaxants with nicotinic cholinergic receptors at the neuromuscular junction is obviously not the same. With the depolarisers, both the α subunits of the receptor channel undergo a conformational change

which initiates channel opening, resulting in depolarisation. Acetylcholine and the depolarising blocking drugs both interact with the recognition sites of the α subunits. Depolarising relaxants such as succinylcholine cause depolarisation of the endplate but the recovery period is much greater and extends to minutes rather than milliseconds. Prolonged depolarisation causes neuromuscular blockade. The production of the depolarising effect involves a summation of the actions of acetylcholine and the depolarising relaxants and the block may be intensified if additional acetylcholine is supplied.

The interaction of nondepolarising relaxants and acetylcholine with the recognition sites of the α subunits is truly competitive, in that, activation (or) blockade of the recognition sites depends upon the relative ambient concentration of agonist (acetylcholine) and blocking agent (nondepolarising relaxant). Hence blockade can be overcome by increasing the local concentration of transmitter.

The difference in the type of blockade produced, by the depolarising and nondepolarising relaxants, accounts for their differing response to nerve stimulation. This is the first fundamental concept, which is important to appreciate in the understanding of clinical monitoring (and reversal) of neuromuscular blockade.

The second is the ergonomics of acetylcholine synthesis, storage and release in the motor nerve terminal. The quantity of acetylcholine released per motor nerve action potential is inversely proportional to the demand placed upon the nerve terminal, i.e., inversely proportional to the stimulus frequency. For this reason small amounts of non-depolarising relaxants will block responses to peripheral nerve stimulation elicited at high frequency, whereas relatively high doses of relaxant will be required to abolish responses elicited at low frequencies of stimulation (e.g., 0.1 Hz.)

Stimulus frequency is therefore an important aspect of the measurement of nondepolarising blockade.

Thus stimuli of increasing frequency from single twitch (0.1 Hz) to tetanus may be used to detect the presence of increasingly subtle degrees of neuromuscular blockade. Peripheral responses will be decreased or abolished by smaller and smaller doses of nondepolarisers as stimuli of increased frequency are used.

In contrast, in the presence of depolarising block, stimuli of various frequencies from 0.1 Hz. to 50 Hz. show about the same degree of discrimination of the intensity of block. Therefore, there is no advantage in applying various stimulus patterns to detect increasingly subtle degree of depolarising block.

FEATURES OF THE ELECTRICAL IMPULSE:

Supramaximal stimulus: For the preceding principles to be in effect, the stimulus must be truly maximal throughout the period of monitoring. Therefore the electrical stimulus applied is usually at least 20 to 25% above that necessary for a maximal response. For this reason, the stimulus is said to be supramaximal.

Square waveform: The character of the waveform produced by the electrical impulse and the length of the stimulus are also important. The impulse should be monophasic and rectangular, that is, it should be a square waveform because a biphasic pulse may cause repetitive firing (a burst of action potentials in the nerve) thus increasing the response to the stimulation.

Duration of pulse: Optimal duration is 0.2 to 0.3 msec. A pulse exceeding 0.5 msec may stimulate the muscle directly or cause repetitive firing.

EQUIPMENT:

The neuromuscular monitoring equipment consists of

1. Stimulator
2. Stimulating electrodes
3. Electrodes to measure peripheral skin temperature.

Desirable features of a nerve stimulator:

Essential:

- Square wave impulse, 0.5 msec duration
- Ability to maintain selected current for duration of pulse (i.e., constant current, variable voltage)
- Battery power
- Multiple patterns of stimulation: Single twitch, TOF, Tetanus, PTC and DBS.

Optional:

- Rheostat for adjustable current output
- Polarity output indicator
- Ability to calculate and display fade ratio and/or % depression of single twitch from control values.
- High output (80-100 mA) and low output (5 mA) sockets.
- Audible signals with each stimulus delivered.
- Alarm for excessive impedance, lead disconnect, low battery etc.

Stimulating electrodes:

These can be of two types, surface electrodes or needle electrodes. Surface electrodes can be rubber electrodes or disposable pregelled silver or silver chloride electrodes (Fig. 1). Both types of electrodes can be used equally well provided the actual conducting area is small, approximately 7-8 mm in diameter. Otherwise, the current produced in the underlying nerve may not be adequate. Skin should always be cleaned properly and preferably rubbed with an abrasive before application of the electrodes. With needle electrodes, needles should be placed subcutaneously but never in a nerve.

Electrode to measure peripheral skin temperature:

This electrode measures the skin temperature. Cooling significantly increases skin resistance from a normal of 0 - 2.5 kilohm to 5 kilohm. This increase in skin resistance may cause the current delivered to the nerve to fall below the supramaximal level, leading to a decrease in the response to stimulation.

SITES OF NERVE STIMULATION

Peripheral nerve stimulation (PNS) can be accomplished at sites where motor nerve stimulation results in easily observed muscular contraction at a distal site.

The ulnar nerve / adductor pollicis brevis muscle response remains the most commonly observed and easily recorded response, upon which most clinical studies of NM blockade and / or its antagonism are based.

Sites:

Electrode	Nerve	Muscle	Response
Ulnar aspect of wrist (Fig. 2)	Ulnar Nerve	Adductor pollicis	Adduction of thumb
Behind ascending ramus of Mandible (Fig. 2)	Facial N	Superficial facial muscles	Movements of muscles of facial expression
Laterally above zygomatic Arch	Facial Nerve	Orbicularis Oculi	Eye blink
Beneath zygomatic arch, (+ ve Forehead)	Mandibular Nerve	Masseter	Jaw contraction
Head of fibula (Fig. 2)	Superficial peroneal nerve	Tibialis anterior	Dorsiflexion of foot
Behind medial malleolus (Fig. 2)	Post tibial Nerve	Flexor Hallucis	Plantarflexion of great toe

APPROPRIATE CONDITIONS FOR NERVE STIMULATION:

Recommendation	Comment
Able to deliver 50-60 mA currents across surface electrodes.	30 mA yields supramaximal stimulus in a majority of patients, but in a substantial minority, 50-60 mA are necessary.
Clean, dry, defatted, warm skin and moist, firmly placed electrodes.	It has been recently appreciated that decrease in peripheral temperature can lead to a substantial decrement in TOF ratio.
If ulnar nerve is used, abduct thumb (i.e., apply a preload) and feel twitch to assess fade.	It has been suggested fade can be manually detected at a TOF ratio approaching 0.6 if the thumb is abducted; otherwise the fade may be undetected at a TOF ratio of 0.4
If needle electrodes are used, (1) Do not insert into nerve, (2) Use current less than or equal to 10mA (3) Avoid unsuspected currents.	The conservative approach recommended by Cooper et al is to check each electrode relative to the other and relative to ground with a voltmeter to make sure there is no electrical potential whenever needle electrodes are used.
Negative electrode placed directly over nerve.	The nerve is more easily stimulated by the negative electrode, whereas if the negative electrode is over muscle, direct muscle stimulation is likely to result.

RECORDING OF EVOKED RESPONSES:

The methods for recording of the evoked responses are:

1. Visual and tactile measurement
2. Measurement of evoked mechanical responses (mechanomyography)
3. Measurement of evoked electrical responses (EMG)
4. Measurement of acceleration of the muscle response (Acceleromyography)

Visual and Tactile measurement:

The simplest and cheapest way of recording the response is to look and feel for it. With ulnar nerve stimulation, this is best accomplished by holding the patient's thumb with one's finger and feel for the response. Twitch count can be accomplished reliably with this method. However TOF fade is difficult to detect, when considerable degree of residual blockade is still present, corresponding to a TOF ratio as small as 0.3.

Force measurement:

An obvious solution to the lack of accuracy of tactile and visual assessment is to measure contractile force with a force transducer. A requirement for correct and reproducible measurements of evoked tension is that the muscle contraction be isometric. This is achieved by measuring thumb movement after application of a resting tension of 200 to 300 gm (a preload) to the thumb. When the ulnar nerve is stimulated, the thumb (adductor pollicis muscle) acts on a force displacement transducer. The force of contraction is converted into an electrical signal, which is amplified, displayed and recorded.

The arm and hand should be fixed rigidly. Care should be taken to prevent overloading the transducer. The transducer should be placed in correct relationship to the thumb (i.e., thumb should always apply tension precisely along the length of the transducer).

The problems with this method are:

- Bulky system
- Requires some skill to set up
- Expensive
- Can be adapted to only one, who is used to it.

EMG:

The electrical activity in the muscle can also be quantified by recording the electromyographic signal. The EMG is the electrical activity which spreads within muscle cells and precedes mechanical contraction. Stimulating electrodes are applied as in force measurement. The signal picked up by the analyzer is processed by an amplifier, a rectifier and an electronic integrator. The results are displayed either as a % of control or as a TOF ratio. When printed out, the results are given as “twitch heights”, the control value for the integrated EMG response being designated as 100%.

Evoked electrical and mechanical responses represent different physiologic events. Evoked EMG records changes in electrical activity of one or more muscles, whereas evoked mechanomyography records changes associated with excitation contraction coupling and the contraction of the muscle as well.

Advantages of EMG:

- Equipment is easier to set up
- Response reflects only those factors influencing neuromuscular transmission
- Response can be obtained from muscles not accessible to mechanical recording.

Difficulties with EMG:

- Improper placement of electrodes may result in inadequate pickup of the compound EMG signal.
- Changes in the position of electrodes in relation to the muscle may affect the EMG response. So fixation of the hand with a preload on the thumb may be more important.
- The evoked EMG response is very sensitive to electrical interference, such as that caused by diathermy.

Acceleromyography:

A new method for monitoring neuromuscular transmission consists of measuring acceleration of the thumb after stimulation of ulnar nerve. This technique is based on Newton's second law: force equals mass times acceleration. Thus if mass is constant, acceleration is directly proportional to force. Accordingly, after nerve stimulation, one can measure not only the evoked force but also the acceleration of the thumb.

Acceleromyography uses a piezoelectric ceramic wafer having electrodes on both sides. Exposure of the electrode to a force generates an electrical voltage proportional to the acceleration of the thumb in response to nerve stimulation. This signal is analyzed in a specially designed analyzer or perhaps displayed on a recording system.

Acceleromyography is a simple method of analyzing neuromuscular transmission. One requirement is that the muscle be able to move freely. Good correlation exists between TOF ratio measured by this method and TOF ratio measured with a force displacement transducer.

PATTERNS OF NERVE STIMULATION:

Traditionally, evaluation of neuromuscular function used three patterns of electrical stimulation: 1. Single twitch, 2. Train-of-four and 3. Tetanic nerve stimulation.

Two new patterns are also now available: 4. Post-tetanic count stimulation and 5. Double burst stimulation.

DESCRIPTION OF VARIOUS PATTERNS:

Single twitch stimulation:

Method:

In this, single supramaximal electrical stimuli are applied to a peripheral motor nerve at frequencies ranging from 1 Hz (1 per second) to 0.1 Hz (1 every 10 seconds). At frequencies greater than 0.15 Hz, evoked response will gradually decrease and settle at a lower level. As a result, a frequency of 0.1 Hz is generally used.

Interpretation:

The twitch height is suppressed with neuromuscular blockade, both depolarising and nondepolarising. (Fig. 3)

S.No.	Total receptors blocked (in %)	Twitch height (as % of normal)	Twitch suppression (in %)
1.	100	0	100
2.	90-95	0	100
3.	85-90	10-20	80-90
4.	80-85	25-95	5-75
5.	75	100	0

6.	50	100	0
7.	25	100	0

Train-of-four Stimulation (TOF):

Method:

In TOF, four supramaximal stimuli are given every 0.5 seconds, that is, at a frequency of 2 Hz. Each set (train) of stimuli is repeated every tenth to twelfth second, when used continuously.

Interpretation:

Each stimulus in the train causes the muscle to contract if neuromuscular transmission is normal. With nondepolarising neuromuscular blockade, there is a decrease in the amplitude of response. Also, there is a fade in the response, that is, the amplitude of the response decreases gradually from the first to the fourth response (Fig. 4). Dividing the amplitude of the fourth response by the amplitude of the first response provides the TOF ratio. The ratio is inversely proportional to the degree of neuromuscular blockade. However, subjective assessment of TOF fade is not reliable and is frequently missed at values as low as 0.4 to 0.5.

With a depolarising block, there is a decrease in the amplitude of all the four responses compared to the control (Fig. 5). No fade occurs in the TOF response and the ratio is one.

Uses:

1. To judge the onset of blockade (the response weakens, as does single twitch). Tracheal intubation may be begun when the response is noted to weaken visibly.
2. To judge the depth of block, during maintenance of relaxation, by noting sequential abolition of responses in the train.

Intense blockade –no response to TOF

Moderate or surgical blockade – response present to TOF

Number of responses	Degree of blockade
1	95
2	90
3	80
4	75

3. To judge the adequacy of recovery from block:

Reversal guidelines:

- a) In the absence of an evoked response to single twitch stimulation at 0.1 Hz ,or TOF, do not attempt to reverse the block because antagonism will be difficult to achieve; on the contrary, recovery may be prolonged.
- b) When there is only one response to TOF stimulation, adequate reversal may take as long as 30 minutes.
- c) At a TOF count of two to three responses, recovery may take upto 10 to 12 minutes with long acting relaxant and 4 to 5 minutes with intermediate acting drugs.
- d) When the fourth response to TOF stimulation appears, adequate recovery can be achieved within five minutes of drug administration with neostigmine or 2 to 3 minutes with edrophonium.

Criteria for recovery from block:

TOF ratio	Clinical tests, signs and symptoms
< 0.4	Patient is unable to lift the head or arm
= 0.6	Patient is able to lift the head for 3 seconds, can open eyes widely and stick out the tongue.
= 0.7 – 0.75	Patient can lift the head for atleast 5 seconds, cough sufficiently.
= 0.8	
= 0.9	

Because the TOF method relies on the decrease in transmitter release with more rapid rates of stimulation, it is necessary not to repeat TOF too frequently. Clinically, this has been determined to be no more often than once every 10 – 20 seconds. This rate of stimulation is fast enough to induce a reproducible decrement in transmitter release from the nerve terminal as a result of action of nondepolarising relaxants. This reproducibility of the decrement of the

fourth versus the first response (T4/T1) gives TOF a major advantage over single twitch stimulation.

Tetanic stimulation.

This consists of very rapid delivery of electrical stimuli, the most commonly used in clinical practice being 50 Hz stimulation given for five seconds.

Maximum voluntary muscle tension occurs at 30 to 50 motor nerve action potentials per second (30 to 50 Hz). Since motor nerve activation at rates higher than 50 Hz cannot be achieved voluntarily, external stimulation at 50 Hz is the highest rate of artificial stimulation compatible with normal physiology.

Interpretation: Tetanic stimulation is applied during recovery from non depolarising block. The absence of fade during tetanus, indicates recovery of normal functions. The most important aspect of clinical monitoring of tetanic responses is detection of fade. This fade of tetanus is called Wedensky inhibition and is difficult to detect clinically at TOF ratios > 0.3 . Because of possible antagonism of neuromuscular blockade in the hand, tetanic stimulation should not be given more often than every sixth minute. 50 Hz tetanic stimulation (in contrast to 100 Hz and 200 Hz) does not cause fatigue in non-paralysed muscle.

A considerable degree of fade may occur during the first fraction of a second during five second tetanus, after which the response may be sustained at a weaker level. This pattern may easily be misinterpreted as full recovery of functions, even when considerable weakness still exists. For this reason, and since the same information can be gained with greater precision using TOF, a less painful stimulus, tetanus is seldom indicated in current practice.

Post Tetanic Count (PTC).

During partial non-depolarising blockade, tetanic nerve stimulation is followed by a post tetanic increase in twitch tension (i.e. post tetanic facilitation of transmission). The degree and duration of PTF depends on the degree of neuromuscular blockade, PTF usually disappearing within 60 seconds of tetanic stimulation. With very intense neuromuscular blockade, there will be no response to TOF and single twitch stimulation and so these modes cannot be used to determine the degree of blockade. It is however possible to quantify intense neuromuscular blockade of the peripheral muscles by applying tetanic stimulation (50 Hz. For 5 seconds) and observing the Post tetanic response to single twitch stimulation given at 1 Hz., starting 3

seconds after the end of tetanic stimulation. During very intense blockade, there is no response to either tetanic or post-tetanic stimulation. However, when the very intense neuromuscular blockade dissipates and before the appearance of first response to TOF stimulation, the response to post-tetanic twitch stimulation occurs.

As the intense block dissipates, more and more responses to post tetanic twitch stimulation appear. For a given neuromuscular blocking drug, the time until return of the first response to TOF stimulation has a correlation to the number of post-tetanic twitch responses (post tetanic-count) present at a given time (Fig. 6).

For example, after injection of pancuronium, the response to post tetanic twitch stimulation appears 37 minutes before the first reaction to TOF stimulation. After vecuronium and atracurium it is seven to eight minutes.

Uses.

1. To evaluate the degree of neuromuscular blockade when there is no reaction to single twitch or TOF, as may be the case after injection of a large dose of a non-depolarising neuro-muscular blocking drug.
2. PTC can also be used whenever sudden movement must be eliminated. (As during ophthalmic surgery).

DBS:

Double Burst Stimulation initially was described by Engback et al and Drenk et al. It was devised in an attempt to increase manual perception of fade. DBS consists of two short bursts of three stimuli at a frequency of 50 Hz separated by 750 msec. The response to each burst is perceived as a single muscle contraction. These sets of stimuli are close enough together that, under conditions of partial blockade, fade will be elicited (Fig. 7). It is easier to manually detect fade with DBS than with TOF. The authors claim that with no manually detected fade of TOF response, there is only 50 % chance that the TOF ratio is greater than 0.6. They also indicate that in the absence of fade to DBS, there is a 90% chance that the TOF ratio measured mechanically is at least 0.6 and that of fade to DBS is detected, there is a 75% chance that the TOF ratio is less than 0.6 .

CLINICAL APPLICATION OF VARIOUS PATTERNS OF PNS:

In general, during nondepolarising block responses are evoked at low frequencies of stimulation (such as single twitch stimulation at 0.1 Hz) in order to assess levels of deep responses and to maintain excellent surgical relaxation.

High stimulus frequencies (e.g., Tetanus at 50 Hz.) are applied during spontaneous or induced recovery from non-depolarising block to exclude the presence of subtle degrees of block. Therefore, the demonstration of normally sustained tetanus at 50 Hz for 5 sec has historically been a commonly accepted proof of clinically adequate neuromuscular function in the unconscious patient.

Stimulus parameter	Stimulus rate	Clinical application
Single twitch	0.1 – 0.15 Hz repetitively	During onset and maintenance of block, to estimate deep levels of block. Tracheal intubation may be begun when the response is noted to weaken visibly. This occurs at about 70% twitch inhibition during onset of block.
TOF (train of four)	2 Hz for 2 sec, single or repetitively at 10-20 sec intervals	To judge onset of blockade (the response weakens as does single twitch) Tracheal intubation may be begun when response is noted to weaken visibly To judge the depth of block during maintenance of relaxation, by noting sequential abolition of responses in the train To judge adequacy of recovery from block
PTC (post tetanic count)	50 Hz for 5 sec followed 3 sec later by 1 Hz twitch stimulation	Applied during very deep block, when neither twitch nor TOF responses may be elicited.
Tetanus	50 Hz for 5 sec	To judge or predict adequacy of recovery to normal function. If a strong response is noted without fade, then adequacy of cough and head-lift may be present. Since it is difficult to see that no fade exists, tetanus has been replaced by TOF and DBS in the judgment of adequacy of recovery.
DBS (double burst stimulation)	50 Hz for 60 msec repeated 0.75 sec later	To judge or predict normal neuromuscular function when no recording facility is available. Detection of fade with DBS indicates a TOF ratio of < 0.6. A ratio of > 0.6, at which fade can no longer be seen, is usually compatible with head lift.

REPORTED COMPLICATIONS WHILE MONITORING NEUROMUSCULAR TRANSMISSION

S.No.	Event	Cause
1.	Underestimating the extent of blockade	Monitoring neuromuscular blockade in a paretic extremity, in which nicotinic receptors have been upregulated.
2.	Underestimating the extent of blockade	Monitoring neuromuscular blockade in the facial nerve, which is more difficult to block than the ulnar nerve.
3.	Unable to elicit a twitch by electrical stimulation	Severe diabetic polyneuropathy has been reported to prevent response to nerve stimulation
4.	Chemical burn from electrolysis caused by direct current via surface electrodes.	Contact of a nerve stimulator battery lead with the anesthesia machine chassis led to a current via ground and the grounding pad of the electrocautery; the direct current caused buildup of an alkaline pH beneath the electrodes.
5.	Burn with needle electrodes	Instrument failure in nerve stimulator leading to current across electrodes for a prolonged time.
6.	Pacemaker suppression with a nerve stimulator	VVI pacemaker inhibited by nerve stimulation of left facial nerve.
7.	Ulnar nerve palsy from pressure from a surface electrode	The nerve stimulator electrode was placed over the ulnar groove, and then substantial arm weight rested on the electrode.
8.	Surgical field movement	Spinal accessory root was stimulated in a patient who had substantially recovered from paralysis, causing a dramatic upper body jerk.

SITUATIONS WARRANTING THE USE OF A NERVE STIMULATOR:

1. Abnormal pharmacokinetics of muscle relaxants: Liver disease, kidney disease, severe illness and extremes of age.
2. Abnormal pharmacodynamics: Myasthenia gravis and myasthenic syndrome.
3. When one wishes to avoid drug induced reversal of neuromuscular blockade as in severe heart disease or bronchial asthma.
4. When it is imperative that post-op muscle power be maximal – as in severe pulmonary disease and marked obesity.
5. When surgery will be lengthy.
6. When neuromuscular blockade is produced by continuous infusion of a neuromuscular blocking drug.

CONCLUSION:

Residual paralysis after the use of neuromuscular blocking drugs during anaesthesia is common. It is anticipated that morbidity will decrease if the muscle relaxants and their reversal agents are titrated to effect, determined by neuromuscular monitoring. It is perhaps wisest to use this monitor as an adjunct and not a replacement for clinical criteria.

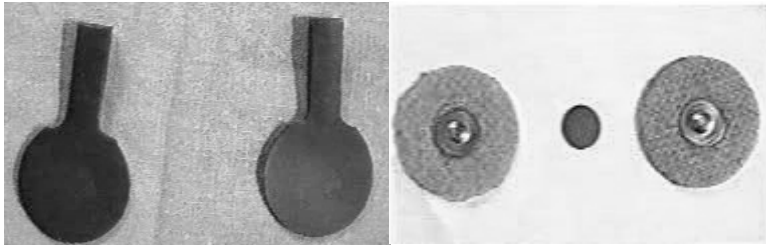


Fig. 1. Types of electrodes

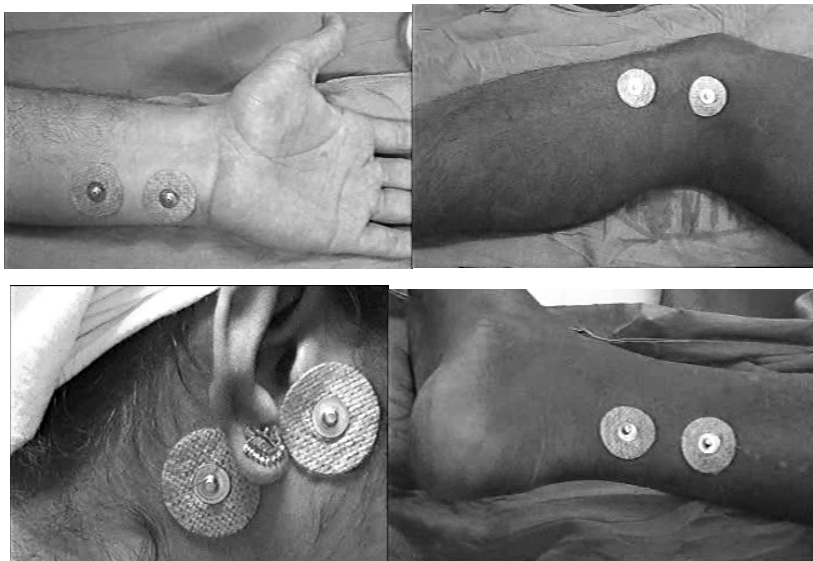


Fig. 2. Sites of electrode placement. a) Ulnar nerve, b) Common peroneal nerve, c) Facial nerve, d) Posterior tibial nerve

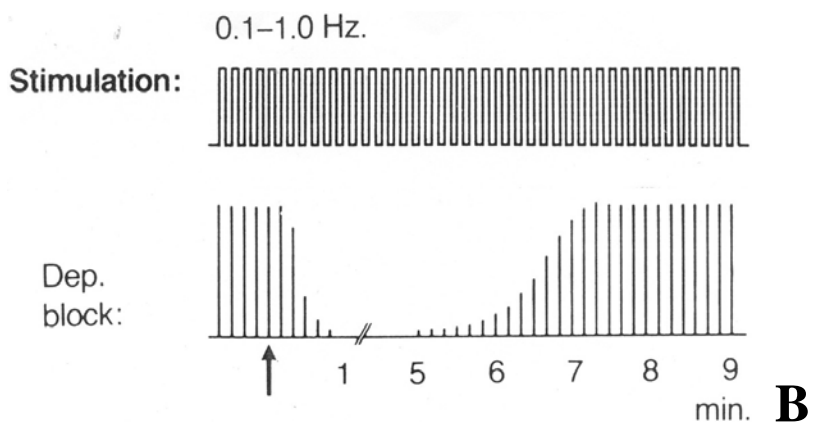
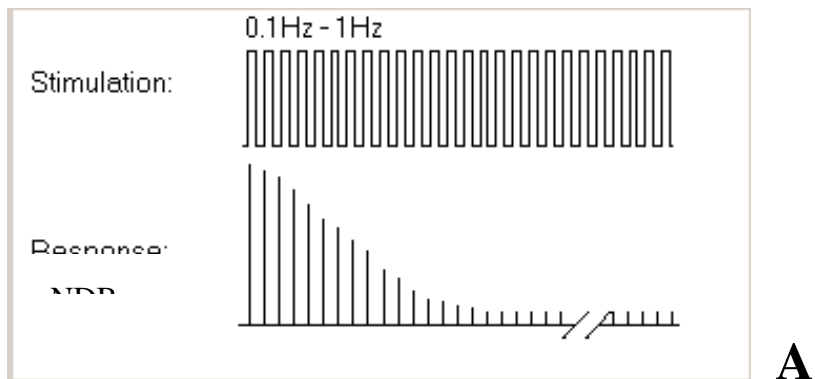


Fig. 3. Response to single twitch stimulus. A. Nondepolarising block. B. Depolarising block

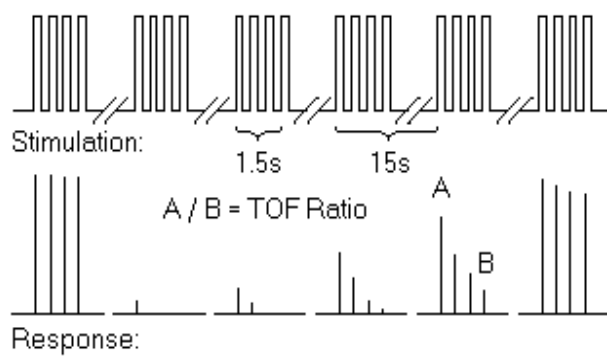


Fig. 4. Response to Train of Four (TOF) stimulation. Nondepolarising block

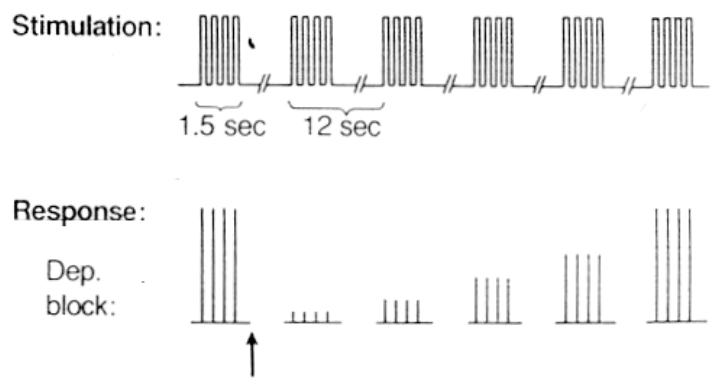


Fig. 5. Response to TOF stimulation. Depolarising block

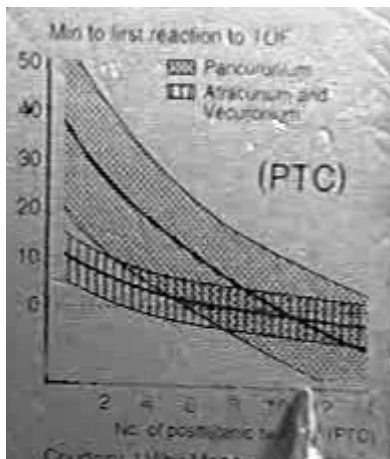


Fig. 6. Post tetanic count

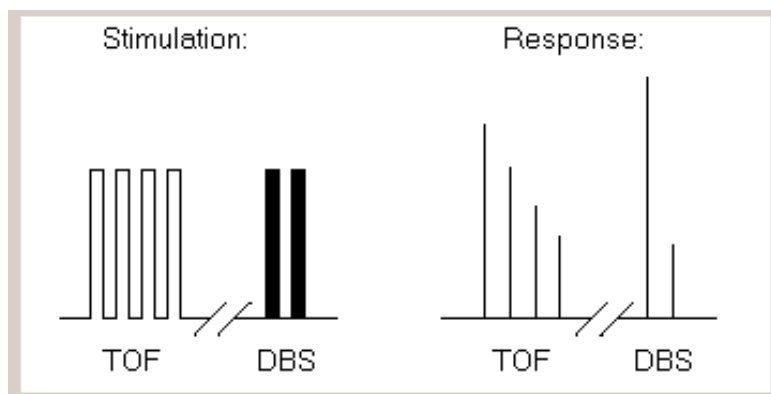


Fig. 7. Double burst stimulation