CME

# Neuromuscular Monitoring in the Perioperative Period

Glenn S. Murphy, MD

Neuromuscular monitoring devices were introduced into clinical practice in the 1970s. Qualitative neuromuscular monitors, or peripheral nerve stimulators, provide an electrical stimulus to a motor nerve and the response of corresponding muscle subjectively evaluated. A standard peripheral nerve stimulator provides several patterns of nerve stimulation, including train-of-four (TOF), double-burst, tetanic, and post-tetanic count. Qualitative (and quantitative) monitors are needed to determine onset of neuromuscular blockade, maintain the required depth of muscle relaxation during the surgical procedure, and assess an appropriate dose of reversal agent. However, absence of fade measured with a peripheral nerve stimulator does not exclude residual neuromuscular block; TOF ratios as low as 0.4-0.6 may be present when fade is no longer observed. In addition, the risk of incomplete neuromuscular recovery may be influenced by monitoring site. The adductor pollicis is more sensitive to the effects of neuromuscular blocking agents (compared to the muscles surrounding the eye), and monitoring at this site may more accurately reflect recovery of pharyngeal muscles (the last muscles to recover from the effects of neuromuscular blocking agents, in which dysfunction may persist even at a TOF ratio of 1.0). Quantitative monitors are devices that measure and quantify the degree of muscle weakness and display the results numerically. Several different technologies have been developed, including mechanomyography, electromyography, acceleromyography, kineograph, and phonomyography. Lower doses of anticholinesterases may be used to effectively reverse neuromuscular blockade at TOF ratios of 0.4-0.6; quantitative monitoring is required to determine that this level of neuromuscular recovery has occurred. As clinical tests of muscle strength, peripheral nerve stimulators are unable to determine whether full recovery of neuromuscular function is present at the end of the surgical procedure. The use of quantitative monitors is essential in excluding clinically important muscle weakness (TOF ratios <0.9 to 1.0) at the time of tracheal extubation. (Anesth Analg 2018;126:464–8)

In 1979, Viby-Mogensen et al[1] reported that 42% of patients administered a long-acting neuromuscular blocking agent (NMBA) in the operating room arrived in the postanesthesia care unit with objective evidence of postoperative residual neuromuscular block (defined at that time as a train-of-four [TOF] ratio of <0.7). Despite the introduction of intermediate-acting NMBAs, a large number of studies have described a high incidence (approximately 40%) of incomplete neuromuscular recovery during the early recovery period from anesthesia (now defined as a TOF ratio of <0.9 with quantitative neuromuscular monitoring).[2] Investigations in awake volunteers and surgical patients have demonstrated that small degrees of muscles weakness can have important clinical consequences. Subjects with TOF ratios <0.9 have an increased risk of pharyngeal dysfunction, airway obstruction, aspiration, impairment in pulmonary function tests, hypoxemic episodes, critical respiratory events, prolonged postanesthesia care unit length of stay, and unpleasant symptoms of muscle weakness.[2] Impaired upper airway integrity may persist in some subjects even after the TOF ratio has returned to unity.[3] Therefore, strategies to reduce the incidence of residual block and achieving a TOF ratio of >0.9 (or even 1.0) before tracheal extubation are essential in improving patient outcomes. The application of qualitative and quantitative neuromuscular monitoring in the operating room has been demonstrated to reduce the risk of postoperative neuromuscular blockade.[2] This review will discuss basic principles of neuromuscular monitoring, strategies for optimal use of qualitative monitors, and new developments in quantitative neuromuscular devices.

## BASIC PRINCIPLES OF NEUROMUSCULAR MONITORING

Two types of neuromuscular monitors have been developed for use in the perioperative period. Qualitative monitors (or peripheral nerve stimulators) are devices that deliver a stimulus to a peripheral nerve, and the subsequent muscular response is visually or tactilely observed. In contrast, quantitative monitors objectively measure the strength of muscle contraction and display the results on a screen (0-1.0 or 0%-100%).

Following electrical stimulation of a muscle, the strength of contraction is determined by the number of muscle fibers activated. Maximal contraction occurs when the electrical stimulation is sufficient to cause all muscle fibers to contract. In most patients, this threshold is approximately 40 to 50 mA for the ulnar nerve. To account for factors that can alter skin resistance, a current 10%-20% above this threshold should be applied (termed the supramaximal current). Quantitative monitors, such as the TOF-Watch-SX (Organon, Dublin, Ireland, no longer commercially available in the United States), can determine the supramaximal current using the calibration mode (typically 50–60 mA). In

From the Department of Anesthesiology, NorthShore University HealthSystem, University of Chicago, Pritzker School of Medicine, Chicago, Illinois.

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Address correspondence to Glenn S. Murphy, MD, Department of Anesthesiology, NorthShore University HealthSystem, 2650 Ridge Ave, Evanston, IL 60201. Address e-mail to dgmurphy2@yahoo.com.



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contrast, the supramaximal current must be set manually when using a peripheral nerve stimulator. Usually 50-60 mA is sufficient in the average surgical patient, although it is uncertain whether an actual supramaximal current has been delivered.

The 2 most common sites for neuromuscular monitoring are the ulnar nerve/adductor pollicis muscle and the facial nerve/orbicularis oculi or corrugator supercilii muscle. Clinicians must be aware that the evoked response to a particular muscle which is monitored may not reflect onset or recovery of strength of other muscle groups. This phenomenon is due the different sensitivities of muscles to NMBAs, with the diaphragm exhibiting the lowest sensitivity and pharyngeal muscles demonstrating the greatest sensitivity.[4] During many surgical procedures, the arms are tucked and the eye muscles are used as a monitoring site. Care must be taken to avoid direct muscle stimulation, since the facial nerve is in close proximity to the corrugator supercilii and orbicularis oculi muscles. A number of studies have demonstrated that eye muscles are relatively resistant to NMBAs and that recovery of neuromuscular function occurs significantly earlier in these muscles.[5] Thilen et al[5] documented that the risk of postoperative residual neuromuscular blockade (PRNB) was 5-fold higher if the monitoring site was the eye muscles compared to the adductor pollicis (a peripheral nerve stimulator was used and supramaximal current was not determined). In contrast, the adductor pollicis is more sensitive to the effects of NMBAs, and monitoring at this site may more accurately reflect recovery of pharyngeal muscles (the last muscles to recover from the effects of muscle relaxants). If an alternative monitoring location is used (facial, posterior tibial, or common peroneal nerve), the ulnar nerve/adductor pollicis should be assessed at the end of the procedure before the administration of reversal to properly determine the degree of neuromuscular blockade.

## QUALITATIVE NEUROMUSCULAR MONITORING (PERIPHERAL NERVE STIMULATOR)

A standard peripheral nerve stimulator provides several patterns of nerve stimulation. TOF stimulation is the most common mode used by clinicians. Four stimuli are provided at a 2-Hz frequency (every 0.5 seconds). A TOF count can be performed to assess the depth of neuromuscular blockade (the number of responses to 4 stimuli is determined). Tracheal intubation can be performed when all 4 responses have disappeared. During some surgical procedures, muscle relaxation can be provided by administering an adequate depth of anesthesia. For surgery requiring neuromuscular blockade, a TOF count of 1=2 usually provides sufficient relaxation. The TOF count can also be used to determine the appropriate time and dose of reversal agent (neostigmine should not be administered until the TOF count recovers to at least 2 or 3, while sugammadex is effective in reversing any level of neuromuscular blockade).

TOF monitoring should be used to assess recovery of neuromuscular function at the end of the surgical procedure. When nondepolarizing NMBAs are administered, fade will be observed as the TOF count recovers. The 2-Hz stimulation frequency used during TOF stimulation will reduce the intensity of each subsequent observed response. When the fourth response appears weaker than the first response, fade is present. However, the absence of fade (all 4 responses to TOF stimulation appear equal) does not assure the clinician that muscle strength has fully recovered and that tracheal extubation can be safely performed. A number of investigations have demonstrated that experienced anesthesiologists are unable to reliably detect fade when TOF ratios exceed 0.4.[6,7] Therefore, significant PRNB may still be present when no fade is visually or tactilely observed with TOF stimulation (TOF ratios between 0.4 and 0.9).

Double-burst stimulation (DBS) is another pattern of nerve stimulation available on most peripheral nerve stimulators. Two short (or 3) 50-Hz bursts are provided, separated by a 750-millisecond interval. The ability to detect fade with peripheral nerve stimulators may be improved with the DBS pattern compared to TOF stimulation. DBS relies on the direct comparison of 2 rapidly sequential, evoked stimuli (the muscle contraction in response to the 2 individual minitetanic bursts) rather than the indirect comparison of the fourth twitch with the first twitch in the series of 4 evoked responses of the TOF. Clinical trials have demonstrated that when using DBS monitoring, the threshold for subjective detection of fade is a TOF ratio of 0.6.[8,9] Although DBS allows more sensitive detection of PRNB than TOF fade, it is insufficient in documenting full recovery of neuromuscular function.

Tetanic stimulation involves the application of high-frequency impulses for 5 seconds. In clinical practice, 50-Hz and 100-Hz patterns are commonly used, and such high-frequency stimulation is perceived as one strong muscle contraction. Fade is observed after an initial muscle response during recovery from nondepolarizing NMBAs. Studies have suggested that the 50-Hz tetanic pattern is the least sensitive qualitative method of monitoring; fade can only be reliably detected when TOF ratios are below 0.3.[9] Although the threshold for detecting fade is increased using a 100-Hz stimulating current (up to a TOF ratio of 0.85), high tetanic stimulation rates may induce neuromuscular fade even in the absence of neuromuscular block because muscle may fatigue at high stimulation rates.[9]

Post-tetanic count (PTC) can be applied to assess the intensity of deep neuromuscular blockade when no responses are detected with TOF stimulation. A 5-second tetanic stimulus is provided, followed 3 seconds later by 10-20 single stimuli (1 Hz). The tetanic stimulus induces the release of acetylcholine at the neuromuscular junction, which allows the clinician to observe a muscle response when none was previously discernible. Deep block has been defined in studies as a PTC of 1-2, and this level of neuromuscular block may be beneficial in certain operative procedures (improved surgical conditions during laparoscopic, thoracoscopic, and laryngeal surgery; less postoperative pain).[10,11] The PTC can also be used to predict recovery from deep neuromuscular blockade. At a PTC of 10-12, the first response to TOF stimulation is typically observed (TOF count of 1). The introduction of sugammadex into clinical practice has expanded the ability of clinicians to maintain deep neuromuscular blockade in the operating room, with rapid recovery possible within 3-5 minutes after reversal (appropriate dosing of 4 mg/kg at a PTC of 1–2). In contrast, neostigmine is ineffective in antagonizing deep blockade.

## QUANTITATIVE NEUROMUSCULAR MONITORING

Quantitative neuromuscular monitors are devices which measure and quantify the degree of neuromuscular blockade and display the results numerically (0–1.0 or 0%–100%). Clinicians are unable to reliably detect PRNB with clinical tests and peripheral nerve stimulators unless TOF ratios are less than 0.4-0.6.[2] An investigation by Fuchs-Buder et al[12] demonstrated that lower doses of neostigmine (20–30 μg/kg) were effective in attaining full neuromuscular recovery within 10 minutes when administered at a TOF ratio of 0.4-0.6; however, quantitative monitoring was required to determine whether these thresholds had been achieved at reversal. To determine whether full recovery of neuromuscular function has occurred at the time of tracheal extubation in all patients, quantitative monitors are required. At the present time, only one stand-alone portable device is available in the United States, the STIMPOD (Xavant Technologies, Pretoria, South Africa; the TOF-Watch is no longer commercially manufactured). In addition, the Datex-Ohmeda Neuromuscular Transmission Module (M-NMT, GE Healthcare, Helsinki, Finland) is available as a monitor that can be used with the anesthesia machine.

### Mechanomyography

Mechanomyography (MMG) measures isometric force of contraction of the adductor pollicis in response to ulnar nerve stimulation. A 200-300 g preload is attached to the thumb to improve consistency of the evoked responses. The force of contraction is converted to an electrical signal, and the amplitude of the signal is proportional to the strength of the muscle contraction. TOF data obtained from MMG are precise and reproducible, and this monitor is considered the "gold standard" to which all new technologies should be compared. However, MMG requires an elaborate setup and was developed primarily for research purposes. In addition, MMG monitors are no longer commercially manufactured.

### Electromyography

Electromyography (EMG) measures the electrical response (compound muscle action potentials) of a muscle following nerve stimulation. The electrical activity of the muscle is proportional to the force of contraction. The EMG response can be determined as the peak amplitude of the signal or the total area under the EMG curve. To obtain appropriate signals, 3 surface electrodes must be placed over the muscle to be interrogated. There are important advantages of EMG monitors. Several different muscle groups can be assessed (adductor pollicis, abductor digiti minimi [foot], laryngeal, orbicularis oculi, diaphragm). Since electrical activity is measured instead of force, free movement and immobilization of the muscle are not required (the hand can be tucked beside the patient instead of being placed on an arm board). In addition, studies suggest that results obtained from EMG are comparable to those observed with MMG.[13] Limitations of EMG monitors include potential electrical interference from devices in the operating room (such as electrocautery, which can affect data obtained from other neuromuscular monitoring technologies) and the effect of temperature on the measured response (a reduction in temperature in the assessed muscle will amplify the EMG response). At the present time, only one EMG monitor is commercially manufactured, the Datex-Ohmeda Neuromuscular Transmission Module. A small, stand-alone EMG monitor is currently in development for routine clinical use (the TetraGraph, Senzime AB [publ], Uppsala, Sweden; www.senzime.com; personal communication).

### Acceleromyography

Acceleromyography (AMG) utilizes a piezoelectric sensor to measure acceleration of a stimulated muscle. Movement generates a voltage in the piezoelectric crystal that is proportional to the force of contraction (based on Newton's second law, force = mass × acceleration). The signal is analyzed and displayed on a monitor. Any free-moving muscle can be monitored, including the adductor pollicis, orbicularis oculi, corrugator supercilii, and the flexor hallucis brevis (foot). The accuracy of TOF responses during neuromuscular recovery can be improved if the device is appropriately set up prior to NMBA administration. When monitoring the adductor pollicis, the application of a preload (TOF-Watch hand adapter; Organon) has been demonstrated to increase the precision of AMG by returning the thumb to its original position after each stimulation.[14] The hand should be secured to the armboard of the operating room table, and movement of the thumb must occur in a strictly horizontal direction. In addition, calibration should be performed before administration of NMBAs. Calibration detects the supramaximal stimulating current and adjusts the $T_1$ (single twitch) response to 100%. Performance of AMG to detect PRNB has been demonstrated to be improved if calibration is used in the clinical setting.[15] Furthermore, baseline TOF ratios obtained with AMG often exceed 100% (typically 105%–115%). This phenomenon complicates interpretation of neuromuscular recovery. If a baseline TOF ratio is 115% (1.15), then a TOF ratio at the end of surgery of 90% (0.9) may actually represent a corrected TOF ratio of 78% (0.78). Therefore, to exclude PRNB, TOF values obtained during neuromuscular recovery should be calculated as a percentage of the TOF ratio measured at baseline (process termed normalization). Normalization of TOF ratios should be performed when using AMG in the clinical setting; otherwise the degree of recovery will be overrepresented at the end of a surgical procedure.

Several different stand-alone AMG devices have been developed. The TOF-Watch, the TOF-Watch S, and the TOF-Watch SX have now become standard monitors for clinical use and research, but are no longer commercially manufactured. The STIMPOD (Xavant Technologies) and the TOFscan (Drager Technologies, Mississauga, ON, Canada, available in the European Union) use a 3D AMG transducer to measure movement of the stimulated muscle. An important disadvantage of first-generation AMG monitors, such as the TOF-Watch-SX, is that acceleration of a muscle following nerve stimulation is only measured in a single direction (perpendicular to the face of the transducer). However, stimulation of the ulnar nerve results in isotonic contractions of the adductor pollicis that are often in 3 dimensions, involving 3 joints, frictional forces, and deformation of tissues. The complex nature of the movement of the thumb following nerve stimulation may account for the lack of precision and accuracy reported in some studies with first-generation AMG devices.[16] The TOFscan transducer is encased

in a thumb splint that is designed for optimal positioning and applies a preload. According to the manufacturer, no initial calibration of the device is required. Since movement of the thumb often occurs in more than one plane, these devices may provide more accurate TOF information, although studies demonstrating these data are limited.[17]

## Kinemyography

Kinemyography (KMG) was developed as a 1 of 2 quantitative monitors available with the neuromuscular transmission module (M-NMT) for the Datex-Ohmeda (Helsinki, Finland) anesthesia machine. The module includes an integrated piezoelectric motion sensor that quantifies neuromuscular function by measuring the electrical signal generated by the deformation of the sensor strip that is placed on the thumb (plastic device positioned between the index finger and the thumb). As with AMG, KMG is based on the piezoelectric effect; bending of the sensor with thumb contraction generates an electrical signal. This signal is processed and analyzed to display TOF ratios, single twitch height, PTC, and DBS data. Studies comparing data obtained from KMG to EMG and MMG during onset and recovery of neuromuscular function have suggested that this information cannot be used interchangeably because the bias can be large and limits of agreement may be wide.[18,19] Despite this limitation, advantages of KMG monitoring include ease of use (minimal setup time, no requirement for an additional standalone monitor), minimal reverse fade and drift, and ability to provide quantitative data that are superior to the information made available from a standard qualitative monitor.

## Phonomyography

Phonomyography (PMG) is based on the principle that muscle contraction evokes low-frequency sounds emitted by lateral movement of muscle fibrils that can be detected using special microphones. The condenser microphone is attached to the skin surface, and the intensity of sounds generated is proportional to the force of contraction. A special circuit is used to filter out the noise and amplify the signal and a software subsystem developed that analyses the acquired signal. PMG can be applied to a variety of muscle groups, including the adductor pollicis, vastus medialis, laryngeal, and corrugator supercilii. PMG is easy to apply and does not require special fixation of muscles. In addition, good agreement has been demonstrated between measurements obtained with PMG and MMG ("gold standard").[20] However, at the present time, PMG monitors have not been developed for clinical use and have only been evaluated in the research setting.

In conclusion, qualitative and quantitative monitors should be used whenever NMBAs have been administered. Studies have demonstrated that the risk of residual neuromuscular block can be reduced if a PNS is routinely applied.[2] In addition, a PNS can be used to determine when to administer additional NMBAs and the appropriate dose of reversal agent at the end of the procedure. However, surveys have established that the majority of clinicians do not routinely use PNSs during general anesthesia cases.[21] The risk of PRNB can be nearly eliminated at the time of tracheal extubation if quantitative monitors are used perioperatively. Unfortunately, quantitative monitors are not available in most anesthesia departments in the United States.[21] The development of second-generation EMG and 3D AMG quantitative monitors (TOFscan and STIMPOD), that are small, portable, and require minimal setup times, may increase the acceptability of these types of devices in clinical practices. When sugammadex is used to reverse neuromuscular blockade, the need for quantitative monitoring may be reduced, since the risk of PRNB is minimal (1%–2%). However, quantitative monitoring may still be required to determine that all patients (morbidly obese, elderly) have fully recovered from neuromuscular blockade at the time of tracheal extubation. In addition, a PNS is always needed to determine suitable depth of neuromuscular blockade during the procedure and the appropriate dose of sugammadex to antagonize the NMBA.

## DISCLOSURES

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**Contribution:** This author prepared and wrote the manuscript.
**Conflicts of Interest:** Glenn S. Murphy has served as a Speaker and on the Advisory Board for Merck.
**This manuscript was handled by:** Maxime Cannesson, MD, PhD.

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