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NEUROMUSCULAR BLOCKADE (GS MURPHY, SECTION EDITOR)

Quantitative Neuromuscular Monitoring: Current Devices, New Technological Advances, and Use in Clinical Practice

Hajime Iwasaki[1] · Reka Nemes[2] · Sorin J. Brull[2] · J. Ross Renew[2]

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Abstract

Purpose of Review The purpose of this review is to summarize various quantitative neuromuscular monitoring modalities and describe strategies to implement them into routine practice. We will contrast these objective modalities with unreliable clinical tests and subjective techniques that expose patients to unnecessary risk associated with postoperative residual weakness.

Recent Findings As major specialty societies publish guidelines and consensus statements urging anesthesiologists to utilize quantitative monitors, clinicians must familiarize themselves with this equipment. Furthermore, new monitors are emerging as the industry tries to address the need for user-friendly, reliable monitors.

Summary Clinical assessment is an unacceptable technique to guide neuromuscular blockade management in patients receiving neuromuscular blocking agents. The use of a peripheral nerve stimulator can provide some information regarding the level of neuromuscular blockade in patients; however, it cannot reliably confirm adequate recovery. The use of objective, quantitative monitoring is an essential practice that helps guide the administration of neuromuscular blocking agents and excludes deleterious postoperative residual weakness.

Keywords Quantitative monitoring · Residual muscle weakness · Neuromuscular blockade · Patient safety

Introduction

Postoperative residual weakness remains a significant and underappreciated threat to patient safety. Multiple studies have demonstrated a high incidence (~40%) of insufficient recovery from neuromuscular blockade in the postoperative period [1]. Postoperative residual neuromuscular weakness exposes patients to unnecessary risk and is associated with subjective symptoms of weakness, critical respiratory events, and prolonged length of stay in the postanesthetic care unit (PACU) [1]. Several strategies have emerged to combat this issue, with varying degrees of success. The use of shorter acting neuromuscular blocking agents (NMBAs) [2] and reversal agents such as neostigmine and sugammadex that antagonize the effects of NMBAs decreases the incidence of postoperative residual weakness [1, 3]. The routine use of quantitative neuromuscular monitors reduces complications from postoperative residual weakness [4, 5]. In fact, the implementation of appropriate quantitative neuromuscular monitoring eliminated instances of reintubation in the PACU related to postoperative residual weakness over a 4-year period in one large academic center [4, 6•].

Despite an abundance of evidence that postoperative residual weakness is prevalent and exposes patients to significant risk, many anesthesiologists fail to employ adequate neuromonitoring when utilizing NMBAs. A large international survey found almost 10% of the American anesthesiologists and almost 20% of the European anesthesiologists never use any form neuromuscular monitors in patients receiving NMBAs [7]! Barriers to employing quantitative neuromuscular monitoring include anesthesiologists not recognizing the scope of the problems associated with postoperative residual weakness as well as lack of familiarity with quantitative neuromuscular monitors. Major anesthesia societies have recently submitted consensus statements and guidelines mandating the use of neuromuscular monitoring, in particular quantitative monitoring, when NMBAs are administered in an effort to address this persistent patient safety issue [8••, 9••]. As

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✉ J. Ross Renew
renew.johnathan@mayo.edu

[1] Asahikawa Medical University, Hokkaido, Japan

[2] Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA

momentum builds towards utilizing quantitative neuromuscular monitoring in an effort to enhance patient safety, anesthesiologists may have to familiarize themselves with novel devices.

In this review article, we will discuss the limitations of subjective techniques to confirm recovery from neuromuscular blockade, patterns of neurostimulation that anesthesiologists can use to determine the level of neuromuscular blockade, the varying sensitivities different muscle groups have in response to neuromuscular blockade, and various quantitative neuromuscular monitoring modalities that can be used to minimize the risk of postoperative residual weakness (Table 1).

Clinical Assessment and Peripheral Nerve Stimulation

Clinical Assessment

Head and Leg Lift

In 1961, Dam et al. first demonstrated that the head-lift test (flexing the neck and lifting the head from the pillow) was a useful sign to detect residual muscle weakness [10]. This was based on the fact that conscious patients were often unable to lift the head when small doses of curare were administered, despite the lack of respiratory impairment. In 1971, Ali et al. reported that at least 3 s of head lift was associated with recovery of the train-of-four ratio (TOFR) to 0.6 [11]. In 1997, Kopman et al. reported that the lowest TOFR to achieve 5-s head lift was 0.75 (range 0.48–0.75) [12]. Eikermann et al. found that despite a sustained 5-s head lift, the volunteers still had significant decline in various respiratory parameters [13]. Furthermore, Russel et al demonstrated that patients who received NMBA had a mean of 29% of the initial grip strength when they could sustain 5 s head lift [14]. In short, the 5-s head-lift test is neither sensitive nor specific at excluding postoperative residual weakness, and its use is not recommended.

Grip Strength

Kopman et al. reported that grip strength was decreased (averaged 57% of the control) in all subjects at a TOFR of 0.7 [12]. This recovered to 83% of the control at a TOFR = 0.9. In this study, however, patients who received only general anesthetics (without NMBA) also showed a mild depression (77% of the control) in grip strength [14]. Hence, grip strength fails as a sensitive and specific means of determining recovery from NMBA.

Tongue Depressor Test

During the tongue depressor test, subjects have to hold a wooden tongue depressor with their incisor teeth while the investigator tries to pull it out of their mouth. In a study in awake volunteers, Kopman et al. demonstrated the average of the lowest TOFR at return of this ability was 0.86 (range 0.68–0.95) [12]. Since none of the subjects could pass this test at TOFR < 0.68, they concluded that it may be more useful than head-lift test when the patient is cooperative. As this test cannot be performed in an intubated patient, there is no role for this test in excluding residual weakness in the perioperative period.

Peripheral Nerve Stimulation

A peripheral nerve stimulator (PNS) is typically a handheld battery-operated device with two stimulating electrodes that can deliver various patterns of neurostimulation. When utilizing a PNS to guide management of NMBA, clinicians can either perform visual or tactile assessment of the muscle response to neurostimulation. However, a PNS is not a monitor. Rather it is a means of delivering neurostimulation with the clinician subjectively evaluating the response. To visually assess the response to neurostimulation using a PNS, the observer should be at an angle of 90° to the plane of muscle movement [15]. For tactile assessment, the observer should hold the subject's thumb in full abduction so as to produce a preload and feel the response [15, 16]. Viby-Mogensen et al. demonstrated that even very experienced anesthesiologists could not always tactilely detect fade when TOFR was > 0.4 [16]. This group also reported that tactile evaluation was slightly (but not significantly) superior to visual evaluation [16]. Drenck et al reported that, in contrast to train-of-four (TOF) stimulation, tactile evaluation allows for detection of TOFR < 0.6 when double-burst stimulation was performed [17]; however, the differences between tactile and visual means of subjective assessment are relatively small, and neither technique is adequate to ensure full recovery and patient safety [18]. Visual and tactile assessment using a PNS may be useful to judge the depth of block during surgery; however, it is clear that postoperative residual neuromuscular blockade and complete recovery of the neuromuscular function cannot be detected with these methods.

Patterns of Neurostimulation

Single Twitch

With single twitch stimulation, the muscle twitch height following supramaximal stimulation is obtained (Fig. 1a). The effect of NMBA can be evaluated by comparing subsequent twitch height to the baseline (before the administration of NMBAs). Investigators have utilized varying frequencies when studying

Table 1 Practical comparison of neuromuscular monitoring modalities

Modality	Principle	Pros	Cons	Monitoring site	Current availability
MMG	Directly measures isometric muscle contraction force.	- Measures muscle force directly. - The "reference" modality.	Cumbersome and time-consuming setup. Not suitable for clinical practice.	- Ulnar nerve—adductor pollicis muscle; - Posterior tibial nerve—flexor hallucis brevis muscle	Commercially not available
EMG	Measures compound muscle action potentials evoked by neurostimulation.	- Many muscles can be examined. - Does not require freely moving limbs. - Easy and fast setup and short calibration.	Possible interference from other electrical equipment (electrocautery). Currently available in modular form only.	- Ulnar nerve—adductor pollicis, abductor digiti minimi, and first dorsal interosseous muscles; - Posterior tibial nerve—flexor hallucis brevis muscle; - Phrenic nerve—diaphragm	E-NMT (GE Datex-Ohmeda NMT, Waukesha, WI, USA)
AMG	Measures the acceleration of the thumb or any freely moving muscle. The acceleration is directly proportional to the force according to Newton's second law.	- Current NMB management guidelines are based on AMG measurements. - Most widely used technique.	Requires the use of hand adapter, fixation of arm and fingers, free movement of thumb, normalization of recovery TOF ratios.	- Ulnar nerve—adductor pollicis muscle; - Facial nerve—orbicularis oculi, corrugator supercilii muscles; - Posterior tibial nerve—flexor hallucis brevis muscle	-Infinity Trident NMT SmartPod (Dräger, Lübeck, Germany) -IntelliVue NMT (Philips, Amsterdam, the Netherlands) -TOF-Scan (IDMed, Marseille, France) -Stimpod NMS450 (Xavant Technology, Pretoria, South Africa)
KMG	Measures the distortion of a piezoelectric film sensor. The level of distortion is proportional to the force of thumb contraction.	Easy to apply.	Available only in modular form.	- Ulnar nerve—adductor pollicis muscle	M-NMT (GE Datex-Ohmeda NMT, Waukesha, WI, USA)
PMG	Measures the emitted low frequency sound of sliding muscle fibers.	Many muscles can be examined.	Relatively expensive microphones. Commercially not available.	- Ulnar nerve—adductor pollicis, abductor digiti minimi, and first dorsal interosseous muscles; - Facial nerve—orbicularis oculi, corrugator supercilii muscles; - Posterior tibial nerve—flexor hallucis brevis muscle; - Recurrent laryngeal nerve - Posterior cricoarytenoid and lateral arytenoid muscles	Implemented in an anesthesia robot system (McSleepy) but commercially unavailable at the moment
CMG	Measures the pressure change in an air-filled balloon due to the hand muscles' contraction in response to ulnar nerve stimulation	Seemed to be a reliable technique.	Commercially not available.	- Ulnar nerve—all hand muscles innervated by ulnar nerve	Not available
Cuff pressure modality	Measures the pressure change in a modified non-invasive blood pressure cuff due upper arm muscles' contraction evoked by brachial plexus stimulation	Easy to apply.	Needs further validation.	- Brachial plexus—muscles of upper arm	TOF-Cuff (RGB Medical, Madrid, Spain)

MMG mechanomyography, *EMG* electromyography, *AMG* acceleromyography, *KMG* kinemyography, *PMG* phonomyography, *CMG* compressomyography, *NMB* neuromuscular blockade, *TOF* train-of-four

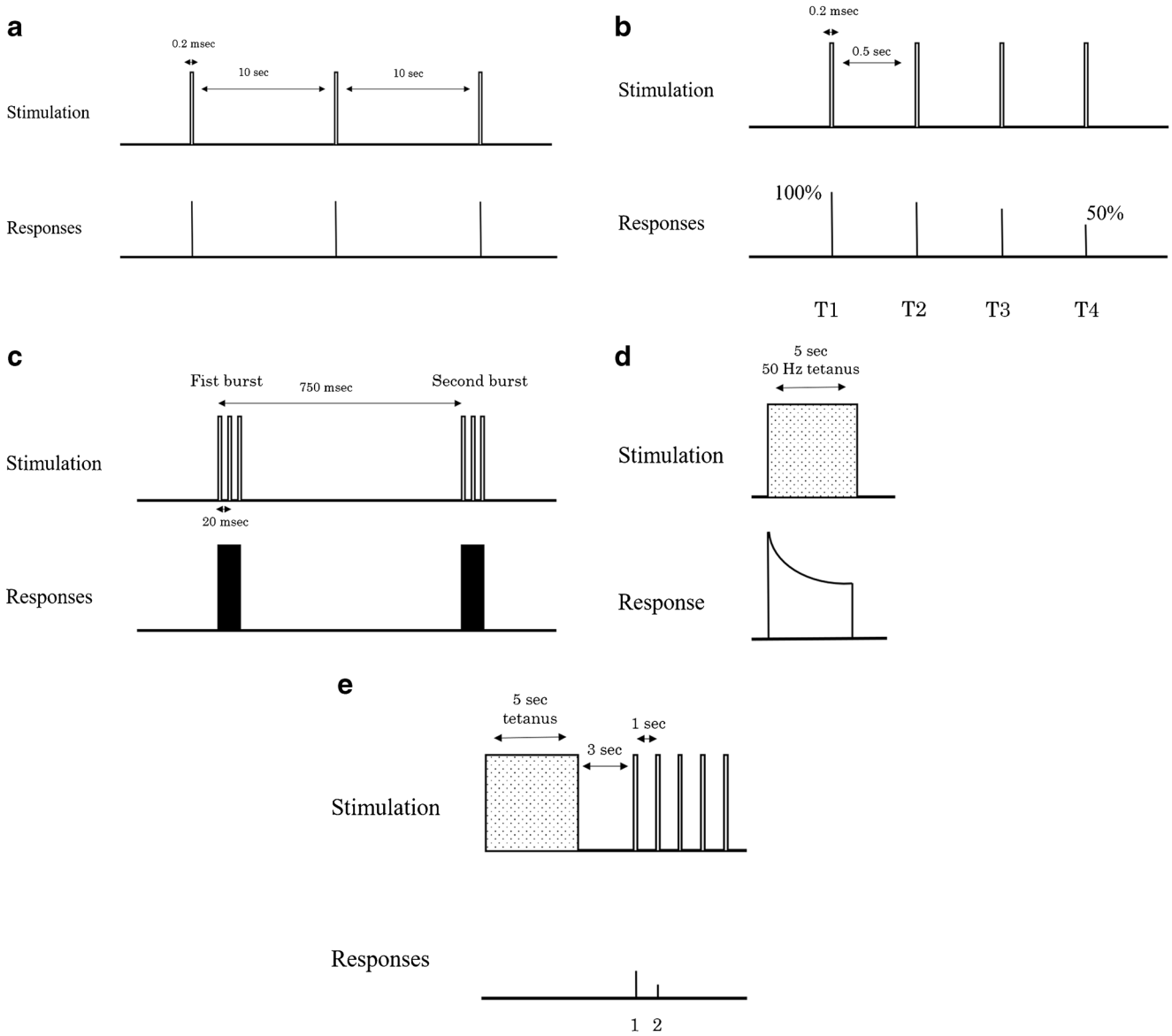

Fig. 1 **a** Single twitch. This figure indicates 0.1 Hz (one stimulation per 10 s) single twitch stimulation during no neuromuscular blockade. **b** Train-of-four (TOF). This figure indicates TOF stimulation and responses during partial non-depolarizing blockade. A TOF consists of four equal 0.2 ms stimuli at a frequency of 2 Hz (0.5 s interval between each of the four stimuli). The TOF ratio is a ratio of the fourth twitch height and the first twitch height (T4/T1). TOF ratio in this figure is 50%. T1 first evoked response, T2 second evoked response, T3 third evoked response, T4 fourth evoked response. **c** Double-burst stimulation (DBS). DBS consists of two 50 Hz tetanic burst at an interval of 750 ms. $DBS_{3,3}$ which is shown in this figure consists three stimuli of 0.2 ms duration in each burst. Two equal responses in this figure can be seen during no neuromuscular blockade. **d** Tetanic stimulation. This figure indicates a tetanic stimulus of 50 Hz for 5 s. The response to this stimulus in this figure can be seen during neuromuscular blockade. **e** Post-tetanic count (PTC). With this mode, 1 Hz single twitch will be applied 3 s after tetanus stimulation (50 Hz, 5 s). The responses in this figure (PTC = 2) indicates profound neuromuscular blockade

single twitch neurostimulation, as frequency affects the twitch response following administration of NMBAs [19, 20]. Ali et al. demonstrated that increasing the frequency of neurostimulation from 0.1 to 1.0 Hz significantly decreased the effective dose of D-tubocurarine [21]. In other words, the degree of neuromuscular blockade may be overestimated when single twitch stimulation is performed at higher frequencies. When utilizing single twitch neurostimulation to determine the onset of neuromuscular blockade, Eikermann et al. found variability at different frequencies and ultimately recommended 0.1 Hz stimulation to detect the onset time of NMBA [22].

Train-of-Four

Train-of-four stimulation was first introduced by Ali and Gray in 1970 [20] and is now the most common mode of neurostimulation in clinical practice. With this mode, four supramaximal stimuli occur at a frequency of 2 Hz, with the

sequence repeated every 10–20 s (Fig. 1b). The degree of neuromuscular blockade can be assessed by TOFR and TOF count (TOFC). TOFR is the ratio of the fourth twitch height (T4) and the first twitch height (T1). A TOFR < 1.0 indicates "fade" and is characteristic of either non-depolarizing blockade or a phase 2 depolarizing blockade. Fade cannot be observed during phase 1 depolarizing blockade with succinylcholine [23]. Experienced clinicians are unable to detect fade at TOFR between 0.4 and 0.9 when utilizing a peripheral nerve stimulator [16], leaving objective, quantitative neuromuscular monitoring as the only means of confirming recovery and excluding postoperative residual weakness. Indeed, objectively derived TOFR has been shown to be superior to tactile assessment with TOF, double-burst, and tetanic stimulation at excluding residual weakness [24]. As such, experts recommend confirming recovery from neuromuscular blockade by demonstrating a TOFR ≥ 0.9 measured at the adductor pollicis muscle after stimulating the ulnar nerve [9••, 25]. TOF stimulation is less painful than tetanic stimulation and can be used in awake patients to detect postoperative residual weakness. Brull et al. reported that TOFR is consistent at submaximal and supramaximal current and, therefore, a low-current (i.e., 20–30 mA) TOF stimulation is suitable for awake patients in detecting residual weakness [26].

Once T4 disappears following TOF stimulation, the TOFR is zero and clinicians can utilize TOFC to monitor moderate levels of neuromuscular blockade. Once T1 disappears following TOF stimulation (TOFC = 0), post-tetanic count (PTC) can be utilized to monitor deep levels of neuromuscular blockade (discussed in the following section). Some experts have advocated maintaining a TOFC < 2 to establish maximal relaxation and facilitate abdominal surgery [27], although this recommendation has been questioned [28]. It should be noted that the monitoring site impacts the determination of level of blockade, as significant variability exists between muscles groups following neurostimulation [29]. Such caveats are also addressed in the following section.

Double-Burst Stimulation

Double-burst stimulation (DBS) was first introduced by Viby-Mogensen and his colleagues in 1989 [30]. This pattern of stimulation was developed in an effort to improve the ability of clinicians to determine fade by tactile evaluation. DBS consists of two 50-Hz tetanic bursts at an interval of 750 ms. $DBS_{3,3}$ consists of two bursts of three stimuli, each 0.2 ms in duration (Fig. 1c), while $DBS_{3,2}$ consists of three stimuli of 0.2 ms duration in the first burst, but only two stimuli in the second burst. $DBS_{3,2}$ is superior to $DBS_{3,3}$ in detecting fade subjectively at higher TOFR [31]. With $DBS_{3,2}$, fade could be felt in 83% of the cases at TOFRs between 0.71 and 0.8 [31]. However, $DBS_{3,2}$ yields more false positives in detecting fade than $DBS_{3,3}$ when TOFR is 0.81 to 1.0 [31].

When utilizing a peripheral nerve stimulator, tactile evaluation of the muscle response to $DBS_{3,3}$ and TOF allows for detection of TOFR < 0.6 and TOFR < 0.4, respectively [17]. Samet et al. reported that the sensitivity and negative predictive value of DBS to detect residual weakness were both 29%, while specificity and positive predictive value were both 100% [32]. In other words, fade after DBS indicates the presence of residual weakness; however, lack of fade does not exclude residual weakness. Therefore, DBS cannot reliably exclude residual neuromuscular blockade [24, 32].

Tetanic Stimulation

Tetanic stimulation was first introduced by Tassonyi in 1975 [33]. Similar to DBS, this method was developed in an effort to improve the clinicians' ability to determine fade subjectively. The higher the frequency of tetanic stimulation, the greater fade will appear [15]. A stimulus of 50 or 100 Hz for 5 s is commonly used in clinical practice (Fig. 1d). During stimulation, the observer only detects one strong, sustained muscle contraction. Tetanic stimulation with 50 Hz has a low sensitivity in detecting fade, as 43% of the patients do not show any fade at TOFR 0.13–0.4 [24]. Although fade to 100 Hz tetanus is detectable up to a mechanomyographic TOFR = 0.9, the specificity is poor (55%) [32]. In other words, 100 Hz tetanic fade can be present even when there is no residual paralysis. Tetanic stimulation should only be applied to anesthetized patients, as it is painful.

Post-Tetanic Count

Post-tetanic count (PTC) was first described in 1981 [34] and utilizes a series of single twitches at 1 Hz twitch applied 3 s after tetanus stimulation (50 Hz, 5 s) (Fig. 1e). This method is based on the phenomenon of post-tetanic potentiation. Acetylcholine concentrations increase in the synaptic cleft following high-frequency (tetanic) stimulation, and subsequent muscle stimulation results in a potentiated (amplified) muscle contraction. PTC can be used to monitor deep levels of neuromuscular blockade when TOFC = 0. Post-tetanic potentiation can affect the degree of the recovery, and repetitive PTC stimulation within 3 min is not recommended [35, 36]. However, Hakim et al. found that although first twitch height of TOF slightly increases for 10 min after PTC, TOFR remains reliable [37]. There is a correlation between PTC and TOF recovery [38]. For each non-depolarizing NMBA, the first response to TOF (T1) occurs when PTC has reached a certain value. In case of rocuronium, T1 reappears when PTC is 10 or more [38].

Differing Muscle Group Sensitivities

The response and recovery from NMBA are variable among different muscle groups. The differences in the onset of

neuromuscular blockade are largely affected by the blood perfusion of muscles. Peripheral muscles receive proportionately less blood than central muscle groups and thus develop slower onset of blockade. The differences in spontaneous recovery and reversal times are partially explained by different fiber compositions of muscles. Muscles composed of more type I slow fibers are more sensitive to NMBAs and have a slower recovery compared to those which contain more type II fast fibers [39]. Beside muscle fiber composition, the density of junctional nicotinic acetylcholine receptors, the cross-sectional area of muscle fibers, and the area of the motor end plate seem to be determining factors in the muscles' sensitivity to NMBAs [40].

While it is difficult to describe the precise order of muscles sensitivities as pertinent research has utilized fairly heterogeneous methods, several themes emerge [41]. It is well established that the two endpoints of this scale are set by the diaphragm/laryngeal adductor muscles (most resistant to NMBAs) and the pharyngeal muscles (most sensitive to NMBAs). The most commonly used muscle for monitoring, the adductor pollicis muscle (mAP), is located between the two endpoints of the sensitivity scale, closer to the pharyngeal muscles. This makes it a useful representative of overall neuromuscular function.

A TOFR > 0.7 measured at the mAP was once considered to be adequate for safe extubation [42]. However, more recent data suggest the upper esophageal sphincter and pharyngeal dilator muscles remain weak at TOFR between 0.7 and 0.9; this level of recovery is associated with aspiration and upper airway obstruction, particularly in at-risk populations [43, 44]. Therefore, current recommendations define recovery as a normalized TOFR > 0.9 as measured at the mAP [9••].

Besides the mAP, two other muscles also innervated by the ulnar nerve have been used to monitor level of neuromuscular blockade. The first dorsal interosseous has a similar response to NMBAs as mAP; therefore, it is a good alternative for electromyography (EMG) and phonomyography (PMG) monitoring [45, 46]. The abductor digiti minimi (mADM) muscle has shown slightly higher resistance, faster recovery than the mAP [45–47], but the repeatability of EMG measurements at the hypothenar (mADM) is better than at the thenar (mAP) muscles [45].

The big toe is another reasonable alternative for neuromuscular monitoring when the hands are inaccessible. The flexor hallucis brevis muscle (mFHB) produces flexion of the big toe following posterior tibial nerve stimulation. In previous investigations, the onset of neuromuscular blockade appeared slower at the mFHB than at the mAP [48–50], which is possibly a result of slower circulation to the lower extremities [49]. However, the mFHB proved to be more resistant to NMBAs than mAP as its recovery was significantly faster in the majority of investigations [31, 48–51].

When the arms are tucked under surgical drapes, quite often the only accessible site for monitoring is the head. The orbicularis oculi (mOO) and corrugator supercilii muscles (mCS) are easily accessible; however, clinicians must be cautious when using these muscles for making clinical decisions. The recovery curve of mCS is similar to the diaphragm and the laryngeal adductors. The mOO is closer to mAP, yet remains more resistant to NMBAs. As a result of its higher perfusion, the facial muscles show faster onset than mAP following NMBA administration [52–55]. Although these muscles are a good indicator of vocal cord relaxation [52, 56], they are not necessarily better indicators of ideal intubating conditions than the mAP [52, 55, 57]. The authors strongly discourage the use of facial muscles to make a decision regarding the appropriateness of tracheal extubation, as such a practice has been associated with significant postoperative residual weakness [58]. Rather, the site of monitoring should be changed to the mAP at the end of operation when the hand becomes accessible in order to confirm recovery [9••, 59].

Monitoring Modalities

Mechanomyography

Mechanomyography (MMG), historically considered the gold standard method of neuromuscular monitoring, measures the isometric force of muscle contraction via a force transducer and converts it to an electrical signal. Typically, the ulnar nerve is stimulated and the force of the mAP contraction is measured. Mechanomyography requires the use of a preload, which is usually a 200 to 300-g resting tension applied to the thumb. Although the preload improves the consistency of the measurements, it makes the setup of the system unsuitable for routine clinical use. MMG requires a sophisticated calibration process, is sensitive to temperature changes, and requires a stable baseline. These obstacles have relegated this modality to research purposes only.

Electromyography

Electromyography (EMG) measures the compound muscle action potentials (CMAPs) evoked by neurostimulation. The amplitude of the CMAPs is directly related to the number of activated muscle fibers, and thus, the force of muscle contraction. EMG has several advantageous features: it has a good correlation with MMG [60–67], it is applicable to several muscle-nerve units (not just the mAP), it does not require the immobilization of the hand or the use of a preload, and the calibration is simpler and faster compared to acceleromyography and MMG. Temperature changes affect EMG measurements to a lesser extent than they do MMG measurements, with every 1 °C decrease in skin temperature increasing the CMAP amplitudes by 2–3% [68]. In a comparative investigation, Hänzi et al. found EMG more reliable for

use in daily practice as it was less influenced by external disturbances than acceleromyography [69]. However, EMG is susceptible to direct muscle stimulation or interference from surgical cautery. Nonetheless, EMG is considered by many to be the most user-friendly modality and could potentially become the next standard for qualitative monitoring.

Currently, there is only one EMG-based monitor available (GE Datex-Ohmeda NMT, Waukesha, WI, USA). While this monitor is incorporated into the anesthesia workstation, a portable EMG-based monitor, TetraGraph (Senzime B.V., Uppsala, Sweden), is under development with the first clinical trials in progress (personal communication).

Acceleromyography

Acceleromyography (AMG) uses Newton's second law (force = mass × acceleration) to indirectly measure neuromuscular transmission. As the mass of the monitored muscle is constant, the force of muscle contraction is directly proportional to its acceleration. The acceleration is measured and converted to an electrical signal by a piezoelectric transducer. The most frequently monitored muscle with AMG is the mAP, as thumb contraction is measured in response to ulnar neurostimulation. The piezoelectric transducer has also been attached to the corrugator supercilii and orbicularis oculi muscles [54, 55, 70], the big toe [48, 50], or the trapezius muscle [71]. However, the data obtained from these monitoring sites show a high level of uncertainty, therefore cannot be recommended for routine monitoring [9••].

AMG has shown good correlation with MMG [72] and EMG [73, 74]; yet, it is not interchangeable with these techniques. To ensure a good repeatability of the measurements, the user has to address several precautions. First, the user must ensure that the thumb always returns to the same position after each contraction by fixing the forearm and the fingers [75]. A hand adapter can aid with this process, as it stabilizes the hand as the thumb moves and eliminates motion artifacts, decreasing the variability of the measurements [76, 77]. Some authors advocate the use of a special cast to further improve repeatability [78]; however, this has not yet gained wide acceptance. In some patients, the pre-relaxation TOFRs can exceed 100%, termed the "reverse fade" phenomenon. In this instance, a TOFR > 0.9 at the end of surgery is insufficient to confirm recovery, as the minimum recovery threshold has to be compared with the baseline TOFR, not to the ideal 100%. Therefore, recovery data must be normalized to pre-relaxation baseline values prior to tracheal extubation [79•].

AMG was developed by Viby-Mogensen et al. in the late 1980s [80] and has become one of the most popular quantitative monitoring techniques over the years. The first AMG-based devices [72] were soon followed by the more user friendly, portable TOF-Watch series (Schering-Plough Corp., Kenilworth, NJ) which were suitable for both clinical and research investigations. Unfortunately, these monitors were withdrawn from the market in the USA in 2016. Similar AMG technology is now available in several integrated forms that incorporate this monitor into the anesthesia work station (Table 1). In addition, two portable AMG monitors have been recently introduced to market: the Stimpod NMS450 (Xavant Technology Ltd., Pretoria, South Africa) and TOF-Scan (IDMed, Marseille, France). These new monitors have modified, three-dimensional piezoelectric transducers, which sense the motion of the thumb in all directions, not just in one plane. This modification will hopefully further improve the precision of the AMG technology, but further clinical studies are needed.

Kinemyography

Kinemyography (KMG) can be considered a variant of AMG. It uses a piezoelectric film embedded in a flexible molded strip. In contrast to AMG, the electrical signal is generated by the bending of the piezoelectric sensor instead of acceleration [81]. The probe of KMG is placed in the groove between the thumb and the index finger. The electrical signal is directly proportional to the extent of bending of the piezoelectric probe in response to ulnar nerve stimulation. The technique was introduced in 1994 [81], and the first KMG device was the ParaGraph (Vital Signs Inc, Totowa, NJ) [82]. The presently available KMG device, M-NMT integrated neuromuscular transmission module (Datex-Ohmeda, Helsinki, Finland; now GE HealthCare), was introduced in 2002 [83]. The disadvantages of KMG are similar to those of AMG: it requires a freely moving thumb, and it is highly susceptible to baseline drift unless the arm is immobilized. Because the mechanosensor strip can guide the movement of the thumb, KMG is less susceptible to the reverse fade phenomenon than AMG without use of a preload device [83]. However, in comparative investigations, KMG TOFRs overestimated the MMG- [81, 84, 85] and EMG-derived TOFRs [86, 87]. Furthermore, the repeatability of KMG measurements was lower and the limits of agreement were wide [87]. Therefore, these modalities cannot be used interchangeably, and a TOFR of 1.0 should be achieved at the end of an operation to provide safe extubation conditions [87].

Compressomyography

Based on a single publication in 2008 [88], compressomyography (CMG) seemed to be a promising technique. Similar to AMG, CMG monitors neuromuscular function indirectly. An air-filled balloon is placed in the palm of patients with the fingers closed and secured around the balloon with a flexible strap. Muscle contraction is evoked with superficial ulnar nerve stimulation. The force of muscle contraction of the hand muscles is transmitted to the balloon via two plastic strips, which ensured the even distribution of force

and uniform deformation of the spherical balloon with each hand contraction. A pressure transducer was connected to the balloon and a pressure monitoring unit. The pressure change in the balloon is measured, and it is directly proportional to the force of muscle contraction.

CMG was free of the pre-relaxation reverse fade phenomenon, allowing for faster and easier calibration. It had a low bias regarding T1% and TOFRs when compared to MMG. Additionally, CMG showed 80% sensitivity and 86% specificity in predicting MMG TOFR > 0.9 during recovery. In spite of these promising results, this technique has not been further developed, and it is not available for clinical use.

Phonomyography

The lateral movement of muscle fibrils produces low frequency sounds which can be detected with special low-frequency microphones [89]. The first devices used large, air-filled chamber microphones, which were unsuitable for daily anesthesia practice. Over time, the microphones have decreased in size considerably. These condensed microphone systems are easy to set up and correlate very well with MMG-derived data [46, 90]. PMG can be applied to any superficial muscle, not just the mAP. It has been successfully used to monitor the neuromuscular blockade at the laryngeal muscles [91] and the corrugator supercilii muscle [46, 53]. Unfortunately, PMG-based monitors are not currently commercially available. PMG has recently been integrated into a closed-loop anesthesia management system [92], although further investigation is needed to determine this system's usability and reliability.

Cuff Pressure Modality

A new quantitative monitor recently has been introduced: TOF-Cuff (RGB Medical Devices, Madrid, Spain). The cuff modality relies on a specially modified non-invasive blood pressure monitor; although the exact technology employed is not disclosed by the manufacturer, it likely detects changes in pressure due to muscle contraction (similar to compressomyography). Stimulating electrodes integrated into the inner surface of the blood pressure cuff are intended to stimulate the brachial plexus at the humeral level [93]. The bulk contraction of the upper arm muscles evoked by neurostimulation generates a pressure change in the slightly inflated blood pressure cuff which is sensed and analyzed by the monitor [94]. The pressure change is directly correlated to the force of muscle contraction. In the first clinical trial, the agreement between TOF-Cuff and MMG was similar to other modalities compared to MMG (at TOF ratios > 0.1 the bias was − 0.03 with the limits of agreement between − 0.32 and 0.38 (95% CI − 0.02 to − 0.04)) [94]. In a recently published clinical trial, the TOF-Cuff seemed to overestimate the MMG-derived TOFR by 20% in the last phase of recovery. A TOF-Cuff-derived TOFR of 0.9 had a specificity of 91% and a positive predictive value of 84% to predict a MMG TOFR of 0.7 [93]. Further clinical investigations are needed to prove the reliability and reproducibility of this new monitoring modality.

Conclusion

Postoperative residual weakness remains a significant threat to patients receiving NMBAs during the perioperative period. In numerous studies, the use of quantitative neuromuscular monitoring persists as an essential strategy to combat this problem. Unfortunately, many anesthesiologists do not routinely utilize such monitors and their patients inevitably experience unpleasant and dangerous, unrecognized postoperative residual weakness. The pressure to employ quantitative monitoring is increasing as new guidelines, expert opinions, and consensus statements emerge from major anesthesia societies. It is hoped that the scientific data that continue to be published and review articles such as the present one will prompt clinicians to consider the limitations of subjective evaluation and clinical signs in determining the adequacy of neuromuscular recovery and convince them that the use of objective monitoring is optimal for ensuring the safety of our patients.

Compliance with Ethical Standards

Conflict of Interest Hajime Iwasaki declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors..

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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