Anaesthesia 2017, 72 (Suppl. 1), 16–37 doi:10.1111/anae.13738

Review Article

Conceptual and technical insights into the basis of neuromuscular monitoring

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Summary

Unrecognised postoperative residual neuromuscular block remains a frequent occurrence in recovery rooms. Evidence indicates that current practice continues to perpetuate the status quo, in which 10–40% of patients experience postoperative residual weakness. A departure from the current practice requires small efforts on the clinicians' part. This review addresses several selected core questions regarding neuromuscular blockade monitoring and provides a framework to rationally discuss and develop basic guidelines for the use of neuromuscular blocking agents in patient care.

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Accepted: 29 September 2016
Keywords: monitoring neuromuscular function; neuromuscular blocking drugs; tetanic stimulation; train-of-four (TOF); twitch height

Introduction

In the mid-1950s, inadequate recovery of neuromuscular function at the end of surgery was a common occurrence. It was termed 'neostigmine-resistant curarisation' [1] and was attributed to mechanisms such as depression of the acetylcholine cholinesterase system rather than the failure of neostigmine to antagonise a profound block induced by d-tubocurarine [2]. Therefore, it is not surprising that the use of neuromuscular blockers during this time was associated with a mortality rate that was six times greater (1:370 anaesthetics) than when neuromuscular blockers were avoided (1:2100 anaesthetics) [3]. Noticeably, 63% of deaths that involved the use of a neuromuscular blocker were caused by respiratory failure.

In 1958, the use of a peripheral nerve stimulator (PNS) was suggested for the diagnosis of prolonged apnoea after the use of neuromuscular blockers [4]. In 1965, Churchill-Davison [5] opined, 'The only satisfactory method of determining the degree of neuromuscular block is to stimulate a motor nerve with an electric current and observe the contraction of the muscles innervated by that nerve.' Although the ability to monitor neuromuscular blockade has been available for decades, clinical management of neuromuscular blocking drugs remains suboptimal because the use of intra-operative neuromuscular monitoring devices is not routine [6] and patients still suffer from potentially serious morbidity due to the residual effects of neuromuscular blocking drugs [7, 8]. This review addresses

Table 1 Core questions about neuromuscular blockade and neuromuscular monitoring.

- What are the stages of neuromuscular blockade? How long does each last?
- How is residual neuromuscular blockade defined?
- What is the incidence of residual neuromuscular blockade?
- What is the incidence of adverse events associated with residual neuromuscular blockade?
- What is the definition of monitoring, and how are peripheral nerve stimulators different from neuromuscular monitors?
- What is the clinical purpose of stimulation modes available on a peripheral nerve stimulator (single twitch, train-of-four, tetanic stimulation with 50 vs. 100 Hz and post-tetanic twitch count)?
- What are the clinical utility and limitations of peripheral nerve stimulation in assessing neuromuscular blockade?
- What are the clinical advantages of monitoring the train-of-four ratio with a quantitative monitor?
- How is the information obtained from neuromuscular blockade monitoring used to rationally select reversal agents and calculate their doses?
- When interpreting data obtained from neuromuscular blockade monitors, does the location of electrode placement matter (adductor pollicis muscle vs. facial muscles)?
- How does the time course of neuromuscular blockade effect measured at the adductor pollicis or facial muscles compare with the time course of effect measured at the airway musculature and diaphragm?

several selected core questions regarding neuromuscular blockade monitoring (Table 1) and provides a framework to rationally discuss and develop basic guidelines for use in patient care.

Postoperative residual neuromuscular weakness: how frequent is it and does it matter?

The currently accepted definition for 'adequate recovery' from neuromuscular block is the return of the train-of-four (TOF) ratio to ≥ 0.9. It is believed that this level of recovery restores the functional integrity of the muscles involved in airway protection [9, 10]. Naguib et al. [11] conducted a meta-analysis of 24 trials (3375 patients) that were published between 1979 and 2005 and noted that the incidence of postoperative residual neuromuscular weakness (defined as a TOF < 0.9) following the use of intermediate-acting neuromuscular blocking drugs was ~41%. Table 2 depicts the various studies that document the incidence of residual neuromuscular block in the past 10 years. The incidence of short-term critical respiratory events in the postoperative care unit is approximately 0.8% [12]. Thus, it is possible that > 100,000 patients annually in the USA alone are at risk of adverse events associated with undetected residual neuromuscular blockade [13]. Residual neuromuscular block is inherently associated with increased risk of morbidity and patient discomfort [7, 8], and increased length of stay in postoperative care units/recovery [14]. Monitoring the effects of neuromuscular blocking drugs ensures their appropriate intra-operative use [15], guides effective antagonism and helps prevent residual neuromuscular weakness.

Why is there such a reluctance to use a monitoring device routinely whenever a non-depolarising neuromuscular blocker is administered? In a survey of anaesthesia providers, Naguib et al. [6] found that 19.3% of European and 9.4% of American anaesthetists never use a device to guide management of intra-operative non-depolarising neuromuscular blockers. These anaesthetists believe that they can safely manage neuromuscular blockade without using a conventional PNS (which requires the clinician to evaluate the evoked response visually or tactilely; see Nomenclature and definitions, below) or a quantitative monitor (that measures and displays the TOF ratio in real-time) [16]. A substantial proportion of anaesthetists in the USA and Europe believe that their patients never experienced clinically significant adverse outcomes related to residual neuromuscular block [6]. Evidence, however, contradicts these beliefs [16–19].

The 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia has concluded that the use of neuromuscular blocking drugs has been associated with a substantially high incidence of unintended awareness during surgery in paralysed patients [20]. In 2016, the Association of Anaesthetists of Great Britain and Ireland (AAGBI) *Standards of Monitoring* recommended the use of a monitoring device whenever neuromuscular blocking drugs are used [21]. There is a growing interest in establishing similar practice guidelines in different European countries [22]. We need to recognise, however, that the impact of guidelines can be negligible [23] unless they are supported by implementation strategies [24, 25].

Table 2 Selected reports of postoperative residual paralysis, 2006–2016.

Study	Intermediate-acting NMBA	Reversal	TOF Threshold	Monitoring modality	Residual paralysis	Comments
Cammu et al. [26]	Atrac/Cis/Miv/Roc		0.9	Clinical		One of 320 inpatients
	Outpatients	In 26%		(49% of cases)	38%	required re-intubation
	Inpatients	In 25%			47%	in PACU; Subjective assessment did not decrease incidence of residual paralysis
Maybauer et al. [88]	Cis	None	0.9	AMG	57%	Variability in duration
	Roc		0.9	AMG	44%	of action of Roc greater than Cisatrac
Murphy et al. [89]	Roc	Yes	0.9	AMG	5%	AMG lowers RNMB risk
				Subjective	30%	
Butterly et al. [14]	Vec/Cis	Yes	0.9	Subjective	22%	Less RNMB with Cis
Yip et al. [90]	Atrac/Vec/Roc	In 65%	0.9	Not reported	31%	21% of patients with RNMB required airway support
Murphy et al. [7]	Roc	Yes	0.9	AMG	15%	AMG monitoring lowers
			0.9	Subjective	50%	RNMB
Cammu et al. [91]	Atrac/Roc/Miv		0.9	Subjective		Body mass index we an
		None		(38% of cases)	15%	independent predictor
		Neo			15%	of desaturation in PACU
		SGX			2%	
Kumar et al. [92]		Yes in 100%	0.9	Not performed		RNMB resulted in
	Vec				66%	reductions in forced
	Atrac				60%	vital capacity and peak
	Roc				46%	expiratory flow
Norton et al. [93]			0.9		30%	CRE present in 51% with RNMB
Esteves et al. [94]	Atrac/Cis/Roc/Vec	Yes (67% of patients)	0.9	Subjective	26%	Incomplete recovery more frequent after reversal than no reversal (31% vs. 17%)
Kotake et al. [17]	Roc		0.9	Clinical		RNMB as high as 9%
		None			13%	with SGX without
		Neo			24%	monitoring
		SGX			4%	
Pietraszewski et al. [95]	Roc	None	0.9	Not used	44%	Incidence of RNMB was 44% in elderly and 20% in young patients
Fortier et al. [96]	Roc	Yes	0.9	Optional	64%	Incidence of RNMB was 56% on PACU arrival
Xara et al. [97]	NMBAs used in 66% of patients	Yes	0.9	Optional	18%	CRE more common (46%) in patients with RNMB
Ledowski et al. [98]	Atrac/Roc/Vec	Yes (48% of patients)	0.9	Optional (used in 23% of patients)	28%	RNMB after neo reversal was twice as high as no reversal in paediatric patients
Brueckmann et al. [99]	Roc			Subjective		OR discharge shorter in
		Yes-Neo	0.9		43%	SGX-treated patients
		Yes-SGX	0.9		0%	
Batistaki et al. [18]	Roc/Cis			Clinical		Female gender and
		Yes-Neo	0.9		14.6%	co-morbidities increased
		Yes-SGX	0.9		9.5%	incidence of RNMB

NMBA, neuromuscular blocking agent; TOF, train-of-four; RNMB, residual neuromuscular block; Atrac, atracurium; Cis, cisatracurium; Vec, vecuronium; Roc, rocuronium; Miv, mivacurium; PACU, post-anaesthesia care unit; AMG, acceleromyography; CRE, critical respiratory events; SGX, sugammadex; OR, operating room.

Nomenclature and definitions

Monitoring can be broadly defined as undertaking and analysing routine measurements aimed at detecting a change in the environment or health status of a person (population). It is clear from the voluminous literature that the term 'monitoring' is misused. Therefore, a brief discussion of the correct terminology is warranted. Most of the published clinical and research reports describe clinicians as 'monitoring' peri-operative neuromuscular function. In fact, in the vast majority of publications, clinicians evaluate neuromuscular function either by subjective means (i.e. clinicians guess or estimate the strength of muscle contractions in response to train-of-four stimulation by visual or tactile means), or they infer adequate return of neuromuscular function by assessing clinical signs, such as 5s head-lift, tidal volume, grip strength or 5s leg lift. Such evaluations are inaccurate and rarely protect patients from residual weakness [26]. These evaluations should not be termed 'monitoring' since they do not involve actual measurement of function or analysis of evoked responses. Objective assessment (i.e. measurement of response and analysis) is the only type of monitoring that will assure adequate return of neuromuscular function and patient safety, and should be used in appropriate context [25, 26]. Similarly, there is an important difference between peripheral nerve stimulators (PNS) that clinicians use to stimulate a nerve (and guess the adequacy of muscular responses), and neuromuscular monitors (such as mechanomyographic, acceleromyographic, electromyographic and kinemyographic devices) that measure and analyse muscle responses (see below). From the preceding, it should be clear that neuromuscular monitoring can only be performed with objective monitors. Any other assessment of muscle function (whether determined by visual or tactile estimation or by clinical tests) has very limited reliability and cannot assure patient safety.

Why monitor?

Monitoring neuromuscular function guides the clinical management of neuromuscular blockade and helps to minimise the incidence of postoperative residual weakness. This can be achieved easily by using of a quantitative monitor. If these devices are unavailable, the use of a PNS, which requires the clinician to evaluate the evoked response visually or tactilely, is strongly recommended. The use of a monitoring device in all patients who receive neuromuscular blocking drugs should not be optional (and in the UK at least, no longer is). Evidence indicates that residual neuromuscular block is common [11] and that all clinical signs of recovery such as the ability of a patient to lift his/her head or sustain a hand grip for 5 s, are inaccurate and insensitive (Fig. 1), and should not be relied upon to exclude the presence of residual neuromuscular block [26, 27]. Tidal volume and vital capacity have returned to normal when the TOF ratio is between 0.4 and 0.6 [28], and in a patient whose trachea is still intubated, vital capacity and $PaCO_2$ can be normal despite considerable muscle weakness. In such patients, tracheal extubation can lead to airway obstruction and serious morbidity and mortality.

A number of factors can complicate a patient's clinical reaction to neuromuscular blockers. First, most patients appear to tolerate substantial and variable degrees of residual block because of the existence of a substantial margin of safety in respiratory muscles [29, 30]. For instance, in one study, none of the 12 volunteers experienced any airway obstruction or arterial oxygen desaturation at a TOF ratio < 0.4 [28]. In another study [12] that investigated the clinical consequences of residual neuromuscular block, only a small fraction of patients developed clinical manifestations of residual weakness. The authors noted that the majority of patients (91%) with evidence of residual block (TOF ratio between 0.7 and 0.9) did not experience adverse respiratory events [31]. The question remains, however: what happens to patients at risk, such as those suffering from chronic obstructive airway disease or sleep apnoea?

In addition, the variability in the duration of effect for a specific dose among patients is a well-recognised phenomenon (Fig. 1). The clinical duration of a typical dose of rocuronium (0.6 $mg.kg^{-1}$) during propofol–opioid–nitrous oxide–oxygen anaesthesia has a median duration of effect of 31 min in adults, but the duration can substantially vary from patient to patient and range from 15 min to 85 min [32, 33]. In another study, 10% and 37% of patients 2 h after administration of an intermediate neuromuscular blocker still had a TOF ratio < 0.7 and < 0.9, respectively [34]. Recovery times after

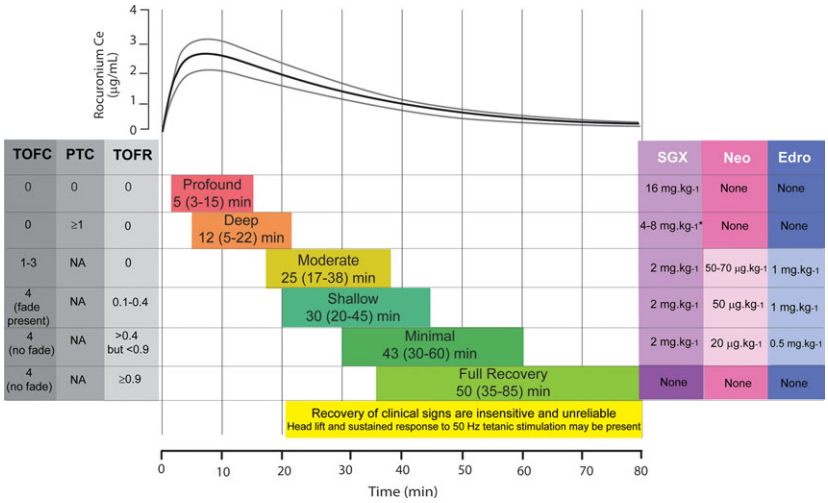

Figure 1 Rocuronium recovery chart. Simulations of predicted effect site concentrations, depth of block and duration of block, various modes of monitoring neuromuscular block (TOFC, PTC, TOFR); and the recommended doses of the three most common pharmacological neuromuscular reversal agents [sugammadex (SGX), neostigmine (Neo) and edrophonium (Edro)]. The top graph represents the predicted effect site concentrations over time for a 0.6 $mg.kg^{-1}$ rocuronium bolus (black line) based on published pharmacokinetic parameters [100, 101]. The grey lines represent estimated 10% variability in effect site concentrations. The duration in minutes (median and range) in each predicted state of neuromuscular blockade (coloured boxes) was adapted from published data [32, 33]. Estimates assume maintenance of anaesthesia with propofol, fentanyl and 66% nitrous oxide. TOFC, train-of-four count; PTC, post-tetanic count; TOFR, train-of-four ratio. TOFC and PTC can be assessed by subjective (tactile or visual) means using a peripheral nerve stimulator (PNS). In addition to TOFC and PTC, a quantitative monitor measures TOFR. The time range of recovery of clinical signs (e.g. head lift) and sustained response to 50 Hz tetanic stimulation is presented in the yellow box. It is important to note that all the clinical signs of recovery from neuromuscular blockade are insensitive and unreliable [26]. *At the deeper level, a higher dose of sugammadex (8 $mg.kg^{-1}$) may be required 'off-label'.

the administration of neostigmine are also variable. The median time from the administration of 70 $\mu g.kg^{-1}$of neostigmine upon reappearance of the third tactile TOF response until TOF recovered to 0.9 was 17.1 min (range of 8.3–46.2 min) [35].

Genetic factors also contribute to the variability in response to these drugs. For example, recovery of the first twitch height to 90% of the baseline following the administration of 1 $mg.kg^{-1}$ succinylcholine ranges from 6 min to 13 min in patients with genotypically normal butyrylcholinesterase activity, vs. 9 min to 21 min in patients with low enzymatic activity [36]. In patients with mutations in the butyrylcholinesterase gene (*BCHE*), the duration of succinylcholine-induced neuromuscular blockade can be several hours [37]. Patients with underlying disease (such as hepatic or renal dysfunction) also show marked variability in their response to drugs [38, 39]. In order to capture the aforementioned variability in individual responses to neuromuscular blocking drugs and hence, ensure patient safety, the significance of using a monitoring device becomes self-evident.

Peripheral nerve stimulation: technological principles

Proper evaluation of neuromuscular response to peripheral nerve stimulation requires that minimal basic criteria are met. This section provides an outline for the desired characteristics for peripheral nerve stimulation (Table 3).

Supramaximal stimulation. Why?

An action potential can be elicited when an electrical stimulation of sufficient magnitude is applied to a nerve. Every nerve is composed of many fibres that vary in size, each with its own critical stimulating threshold [40]. In order for a muscle to contract, a certain minimum number of muscle fibres must to be depolarised. As the current amplitude (in milliamperes, mA) increases, progressively more muscle fibres are

Table 3 Essential features of some of the patterns of neurostimulation.

Pattern	Characteristics
Single twitch (ST)	• A 'control' ST is established by determining maximal response to increasing stimulus current (in mA) • An increase in maximal current by 20–30% assures 'supramaximal' current and consistent muscle response over time • Pulse width of 0.2–0.3 ms • A single, supramaximal stimulus at a frequency of 1/s (1 Hz) or 1/10 s (0.1 Hz) • Stimulating frequencies > 1 Hz potentiate subsequent muscle contractions • Range of receptor occupancy (~75–95%) detected by ST is narrow • Cannot differentiate depolarising from non-depolarising block
Train-of-four (TOF)	• Four ST stimuli at a frequency of 2 Hz • No control muscle response is needed • Ratio of 4th to 1st response is T4/T1 or TOF ratio • 'Fade' defined as a weaker fourth contraction (T4) than the first (T1) – TOF ratio < 1.0 • TOF delivered at 15–20 s intervals to prevent potentiation of subsequent TOF ratio • TOF ratios > 0.40 cannot be detected subjectively • Differentiates depolarising from non-depolarising block • More comfortable to assess in awake patients than tetanic (or DBS) stimulation • Helps determine degree of block in the range of surgical relaxation, ~70–100% receptor occupancy
Double burst stimulation (DBS)	• Two mini-tetanic bursts (2 or 3 impulses at 50 Hz in each burst) separated by 750 ms • DBS delivered at 20-s intervals to avoid potentiation of subsequent muscle responses • No control muscle response needed • Ratio of 2nd to 1st muscle response is D2/D1 or DBS ratio • 'Fade' is defined as a weaker second response (D2) than the first (D1) – DBS ratio < 1.0 • Fade of TOF is identical to fade of $DBS_{3,3}$ • TOF ratios > 0.60 cannot be detected subjectively • Differentiates depolarising from non-depolarising block • Less painful to measure in awake patients than tetanic stimulation, but more painful than TOF • Subjective assessment of DBS fade is superior to TOF fade
Train-of-four count (TOFC)	• When all 4 responses of TOF stimulation are present, the TOFC = 4 • When T4 disappears, the TOFC = 3 • When T3 disappears, the TOFC = 2 • When T2 disappears, the TOFC = 1 • When T1 disappears, the TOFC = 0 • There is an established relationship between TOFC and receptor occupancy (depth of block)
Tetanic stimulation (TET)	• Common frequency is 50 Hz for 5 s • Alternative more demanding (but supraphysiologic) TET is 100 Hz for 5 s • The 100 Hz TET can induce fatigue in normal controls • Differentiates depolarising from non-depolarising block • May induce direct muscle stimulation • More painful to awake patients than DBS, TOF • TET fade over the 5 s is equivalent to TOF fade • TET at intervals < 3 min may potentiate subsequent muscle contractions
Post-tetanic count (PTC)	• TET at 50 Hz for 5 s followed 3 s later by a series of 20 ST at frequency of 1 Hz • More post-tetanic ST responses indicate less block • Allows assessment of profound block (TOFC = 0) • When PTC = 0, further NMBA administration not recommended • PTC at intervals < 3 min may potentiate subsequent muscle responses

depolarised, and the current at which sufficient muscle fibres are activated to result in a detectable muscle contraction is termed 'threshold' current. As the current increases, more muscle fibres are depolarised – the last ones being those with the highest threshold for stimulation. Once all fibres in a certain muscle are depolarised, any further increase in stimulating current will no longer be able to recruit additional fibres. This current intensity is termed, 'maximal' current. To ensure that all fibres in a muscle will be depolarised by

the stimulus despite changes in skin resistance over time, the stimulating current is increased by 20–30%. The resultant 'supramaximal' current will then assure that all muscle fibres will continue to be depolarised, and any subsequent decreases in the force of muscle contraction (if any) are due to the effects of neuromuscular blocking drugs, and not changes in skin resistance.

How strong should the stimulating current be to achieve supramaximal stimulation?

In practice, stimulation should be increased gradually, starting from 10 mA to 20 mA towards a level that achieves the strongest repeatable muscle contraction. This level should then be exceeded by 20–30% to ensure the delivery of a supramaximal stimulation. A current of 40–70 mA is usually sufficient to provide supramaximal stimulation in anaesthetised patients, although in some patients, higher current amplitudes may be necessary [41, 42]. According to Ohm's Law, the current (I) is directly related to the voltage (V) and inversely related to the 'resistance' or impedance (R) (I = V/R). In the presence of oedema [43] or in morbidly obese patients, the impedance is substantially increased, and higher currents may be required in order to ensure the delivery of supramaximal stimuli. In fact, what is delivered to the nerve is the charge (in microcoulombs, μC), which is the product of current intensity (in milliamperes, mA) and stimulus duration (in milliseconds, ms) [42].

A nerve stimulator that generates a constant current is recommended because the stimulus intensity will not be affected by variations in tissue impedance. In other words, the stimulus current remains constant, with the output voltage varying automatically as skin resistance changes over time. In contrast, stimulators that are designed to regulate voltage (constant-voltage devices) will not guarantee the delivery of supramaximal stimuli because the current delivered decreases as the skin impedance increases (Ohm's Law) during anaesthesia [44] or when the batteries start to deplete. In such instances, the clinician may overestimate the depth of neuromuscular blockade.

Duration of the stimulus

The stimulus must be applied for a minimum duration (should not exceed 0.3 ms) in order to elicit a response but to avoid direct muscle stimulation. After the nerve is depolarised there is a brief period during which it is completely unresponsive to further stimuli (refractory period). This is followed by a longer period when only a stronger stimulus produces a response. If the initial stimulus duration outlasts the refractory period of the nerve, it may re-depolarise the nerve so that a second action potential is generated.

There is an inverse relation between the current required to obtain a supramaximal response and the stimulus pulse duration. A current intensity of 30 mA generated by a stimulator that delivers a pulse duration of 0.2 ms will result in a charge of 6 μC. In general, charges of 12–15 μC are required for a maximal muscle response, although some muscles have even higher requirements [42]. Reducing pulse duration to a briefer time (e.g. 0.1 ms) will require substantially higher currents (> 120 mA) to elicit a supramaximal response [42], but such current intensities cannot be delivered by any of the current nerve stimulators; their maximal current output is 70–80 mA.

Characteristics of the stimulus

Ideally, the stimulus should be monophasic and have a square waveform with an amplitude that rises and decays rapidly. These characteristics reduce the possibility of accommodation, when the activation threshold of the nerve rises with a slowly generated stimulus. It is also important that the stimulator produces only a single monophasic pulse. Biphasic waveforms consist of a repeating current pulse that has a negative phase followed by a positive phase, and are not used for monitoring neuromuscular function.

Frequency of stimulation

Higher frequencies of nerve stimulation generally produce a stronger mechanical response. Because there is no refractory period for the mechanical event of muscle contraction, a subsequent contraction can start before any relaxation has occurred. The effect of repeated stimuli within a brief period on muscle contraction is known as 'temporal summation.' If the frequency of stimulation exceeds 30 Hz, fusion of the individual muscle contractions occurs, and such a response is called a tetanic response, which is characterised by a sustained muscular contraction. Although

a tetanic contraction can produce a tension that is four to five times greater than that produced by a single maximal stimulus, tetanic contraction is associated with muscle fatigue.

Patterns of nerve stimulation

For a summary of the most important characteristics of the various neurostimulation patterns used in the clinical setting, please refer to Table 3.

Single twitch (ST) stimulation

In unparalysed subjects, when supramaximal single electrical pulses are applied to a peripheral nerve at rates of 0.1 or 0.15 Hz (1 twitch every 10 s or 6.7 s, respectively), they evoke single contractions (Fig. 2). The proper use of ST stimulations requires standardisation and calibration of the ST amplitude before the administration of a neuromuscular blocker in order to have a valid comparison ('baseline' or 'control') with subsequent responses. This pattern of stimulation is primarily used for determining the potency (dose–response) of neuromuscular blocking drugs. Higher frequencies of stimulation (e.g. 1 Hz) will induce muscle fatigue and may result in the overestimation of the potency of non-depolarising neuromuscular blocking drugs [45]. This stimulus pattern cannot differentiate between depolarising and non-depolarising neuromuscular blockade. Subjective evaluation of ST has little clinical application except as part of a post-tetanic twitch count (PTC) sequence (see below).

Train-of-four (TOF) stimulation

This pattern of stimulation is composed of four stimuli each separated by 0.5 s (a frequency of 2 Hz) delivered to a peripheral nerve that will elicit four successive muscular contractions in unparalysed subjects [46–48]. Train-of-four is usually repeated every 10–15 s and the TOF ratio (TOFR) or 'fade' ratio is calculated by dividing the amplitude of the fourth response (T4) by the amplitude of the first response (T1); T4/T1. Unlike ST, no control value needs to be determined for TOF stimulation because TOF sequence measures the relationship between the fourth and the first twitches, thus serving as its own control.

In the unparalysed individual, the TOF ratio is 1.0 (Fig. 3a) (when measured by mechanomyography or electromyography only) and in the presence of a shallow block induced by a depolarising block (Fig. 3b). During block induced by a non-depolarising neuromuscular blocking drug, TOF fade (the amplitude of T4 is less than T1) can be detected (Fig. 3c); thus, the TOF becomes < 1.0. After the administration of a non-depolarising neuromuscular blocking drug, a progressive reduction in the amplitude of four twitches is noticed (Fig. 3d) with the fourth twitch being most affected. As the block progresses, the first response to disappear is the fourth twitch, followed by the third, second and finally the first twitch. This order of reappearance is reversed during the recovery phase (T1 is the first twitch to recover) (Fig. 3e). The TOF count (TOFC) is defined as the number of evoked responses that can be detected (0–4).

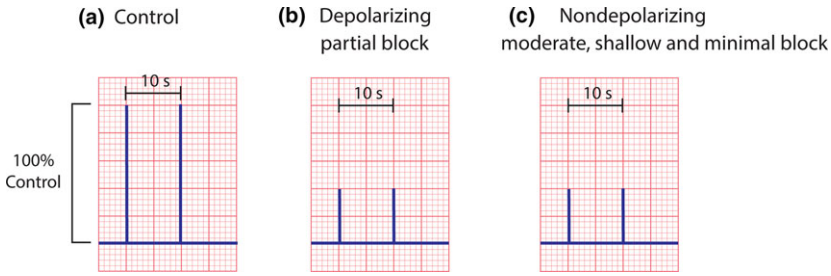

Figure 2 Single twitch stimulation. Depiction of muscle contractions in response to single twitch (ST) stimuli delivered at a frequency of 0.1 Hz during normal conduction (Control, a); partial depolarising block (b); and moderate, shallow or minimal non-depolarising block (c). Note the lack of fade between the first ST and subsequent ST evoked responses during both depolarising and non-depolarising block when stimuli are delivered at this slow, 0.1 Hz frequency. For this and other figures, the control value is that of the evoked mechanical response of the adductor pollicis muscle (in N) to a supramaximal stimulation of the ulnar nerve.

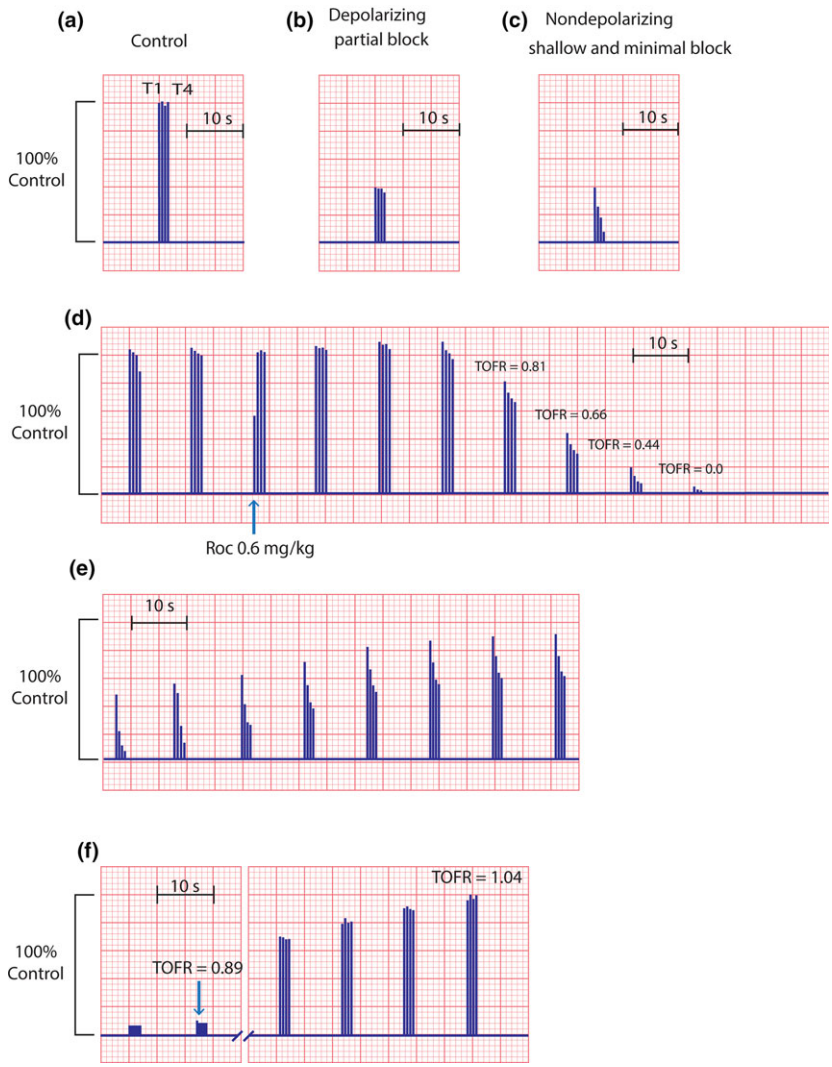

Figure 3 Train-of-four (TOF) stimulation. Train-of-four (TOF) pattern in the absence of neuromuscular block (a, Control). The TOF ratio (TOFR) is calculated as the ratio between the fourth twitch of the TOF sequence (T4) and the first (T1). In the unblocked muscle, the TOF ratio is 1.0. During a partial depolarising block, there is minimal, if any, fade such that the TOF ratio remains close to 1.0 (b). During a partial non-depolarising block, T4 decreases preferentially, followed by T3, then T2 and lastly, T1. The decrease in TOF ratio from the normal ratio of 1.0 is called 'fade' (c). In panel d, a set of two TOF stimuli are recorded, followed by administration of rocuronium. Over the ensuing three sets of TOF stimuli, the TOF ratio remains at baseline (1.0), followed by progressive increase in fade (decrease in TOF ratio) from 0.81 to 0.0 during neuromuscular block onset. During recovery of block (e), the TOF ratio increases progressively towards 1.0. During recovery from 1.0 $mg.kg^{-1}$ succinylcholine (f), there is no significant fade in the train-of-four (TOF) response during recovery. At 8% recovery of T1 (the first twitch in the train-of-four), the TOF ratio was 0.89 and at 96% recovery of T1, the TOF ratio was 1.04. Roc, rocuronium.

In contrast with non-depolarising neuromuscular blocking agents, succinylcholine, a depolarising neuromuscular blocker, causes a progressive reduction in the amplitude of all four twitches of more or less the same magnitude with virtually no fade (i.e. TOF ratio is maintained around unity) until all twitches disappear. The recovery phase follows the same pattern (Fig. 3f). Train-of-four fade is only seen if phase 2 block develops when succinylcholine is administered in large doses (usually > 3 $mg.kg^{-1}$) [49].

The determination of the actual TOF ratio requires the use of a quantitative monitor that

measures and displays the TOF ratio in real time. With the use of a quantitative monitoring device, one can also discriminate between a non-depolarising (TOF fade present) and phase 1 depolarising (virtually no TOF fade) neuromuscular blockade (Fig. 3). A TOF of 0.9 or more should be achieved before tracheal extubation following the administration of non-depolarising neuromuscular blocking drugs. Subjective evaluation of TOF stimulation with the use of a PNS requires the observer to determine (i) the number of twitches (TOFC), and (ii) the strength of the first response in the train and compare it with the fourth evoked response by tactile or visual means. TOFC of 1, 2, 3 and 4 corresponds approximately to 10%, 20%, 30% and 40% of ST control twitch height [50, 51]. The limitation of TOF ratio is that once it approaches 0.40, most clinicians cannot detect the presence of fade by subjective assessments, and may therefore not administer a reversal drug to ensure adequate recovery of neuromuscular function before tracheal extubation.

Train-of-four is the most appropriate mode of neuromuscular assessment in clinical practice, and it can be tolerated by awake patients in recovery and the ITU the post-anaesthesia and intensive care units. Brull et al. [52] reported that TOF stimulation can be performed accurately using a submaximal current in awake individuals once all four evoked responses are present.

Tetanic stimulation (TET) and post-tetanic twitch count (PTC)

A 5-s tetanic stimulation (TET) at 50 Hz is the most common high-frequency stimulation pattern used in the clinical setting. Post-tetanic twitch count (PTC) is assessed by counting the number of responses when a sequence of ST stimulation at 1 Hz is applied for 20 s following a 5-s, 50-Hz tetanus [53]. In the unparalysed subject, the mechanical response to a 50-Hz tetanic stimulation is characterised by a sustained and intensified contraction with no fade or post-tetanic potentiation (Fig. 4a). Tetanic stimuli of higher frequencies (100–200 Hz) are unphysiological as they may induce muscle contraction fade even in the absence of neuromuscular blocking drugs, and should not be used clinically [54–56]. Tetanic fade (muscle fatigue) and post-tetanic potentiation (increased muscle contractility) are characteristics of non-depolarising block and phase 2 depolarising block. Figure 4b–d illustrates that as the recovery from deep non-depolarising neuromuscular blockade progresses, the number and amplitude of PTC increases. Tetanic stimulation results in an apparent acceleration of recovery during the period of post-tetanic potentiation (Fig. 5). This may have significant and important clinical implications. Brull and Silverman [57] stated that tetanic stimulation '. . .may lead to unnecessary repeated administration of neuromuscular blocking agents, or at the other extreme, to false estimation that adequate neuromuscular function exists.' Therefore, tetanic

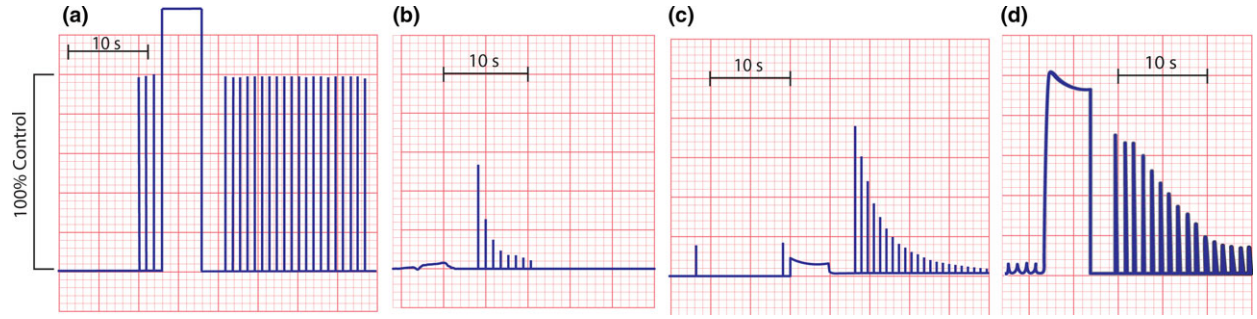

Figure 4 Tetanic stimulation and post-tetanic count (PTC). (a) In the unblocked muscle, the mechanical response to a 50 Hz tetanic stimulation is characterised by a sustained contraction with no fade or post-tetanic potentiation. (b) Application of tetanus during deep block resulted in a faint contraction for 5 s, and post-tetanic potentiation that results in eight progressively weaker contractions (PTC = 8). Note that when measuring the PTC one always uses 1 Hz stimulation. (c) Single twitch is repeated every 12 s, followed by a 5-s tetanus, then decay to an amplitude lower than the pre-tetanic single twitch amplitude. The pre-tetanic stimulus twitch amplitude is 16% of the control value and the first post-tetanic twitch amplitude increased to 76% of the control value. (d) With further spontaneous recovery of neuromuscular blockade, the tetanic and post-tetanic twitch amplitudes increase.

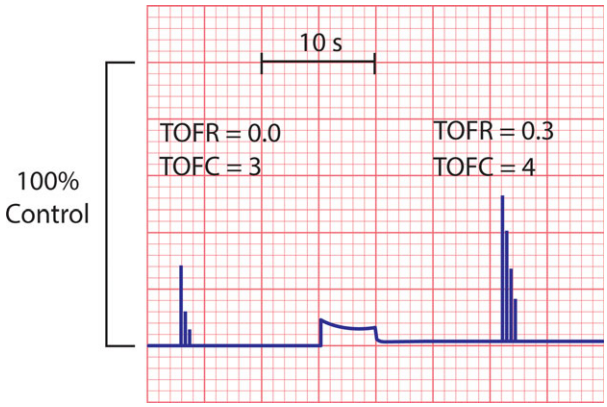

Figure 5 Tetanic stimulation results in apparent acceleration of recovery during the period of post-tetanic potentiation. Train-of-Four count (TOFC) is 3 before the tetanus and the recovery is falsely accelerated to a TOFR of 0.30 due to post-tetanic facilitation.

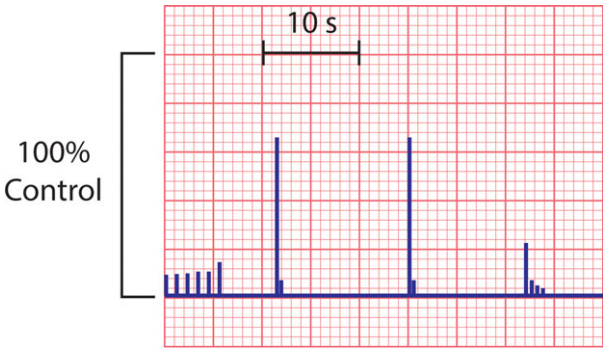

Figure 6 Different patterns of stimulation (single twitch at 1 Hz, double burst stimulation ($DBS_{3,2}$) and train-of-four). The pre-DBS twitch height was 14% of the control value. The amplitude of the first stimulus of DBS (D1) reaches 66% of Control amplitude. The train of four ratio is 0.18.

stimulation should not be repeated for a period of 2–3 min [57]. Train-of-four stimulation every 15 s, unlike tetanic stimulation, does not potentiate subsequent neuromuscular responses after its application [58]. Tetanic stimulation is painful and should never be applied to awake subjects.

In the clinical settings, PTC is used to monitor the depth of neuromuscular blockade when a deep block (a PTC = 1 or greater; but a TOFC of zero) is required until the end of a surgical procedure, as in open-globe ophthalmic surgery under general anaesthesia or intracranial surgery [59, 60]. Post-tetanic twitch count can also be utilised to roughly estimate the time needed for the first twitch of TOF to recover from a deep block [61]. Once the PTC approximates 10–12, a TOFC of 1 appears when intermediate-duration non-depolarising neuromuscular blocking agents are used.

Mechanisms

Post-tetanic potentiation: A tetanic stimulus is associated with an increase in intraterminal calcium concentration, which induces an increase in the mobilisation of acetylcholine vesicles and fusion between vesicles at the motor nerve presynpatic area [62, 63]. Exocytosis of these fused vesicles increases quantal size [64]. The net result is a transient increase in subsequent end-plate potentials and temporary increase in the strength of muscle contractions.

Fade: The mechanism of fade seen with repetitive nerve stimulations as in TOF and tetanic stimulations is poorly understood. It was proposed that twitch depression and fade are a separate and independent phenomena – twitch depression results from the block of postsynaptic $\alpha 2\beta\delta\varepsilon$ nicotinic receptors, while fade results from the block of presynaptic $\alpha 3\beta 2$ nicotinic receptors [65, 66]. It has been suggested that the presynaptic nicotinic receptors act in a positive feedback mechanism to maintain acetylcholine release during repetitive nerve stimulation. The blockade of the presynaptic receptors by neuromuscular blockers prevents acetylcholine from being made available to sustain muscle contraction during high-frequency (tetanic or train-of-four) stimulation. Because the released acetylcholine does not match the demand, fatigue occurs and fade is observed in response to stimulation. This mechanism, however, has been questioned, as fade also appears to occur after the block of postsynaptic receptors alone [67].

Double burst stimulation (DBS)

Double burst stimulation has been introduced as an alternative to TOF stimulation in an attempt to improve the ability to detect residual neuromuscular blockade by subjective means [68]. The two commonly used patterns are $DBS_{3,3}$ and $DBS_{3,2}$. The pattern

$DBS_{3,3}$ consists of a mini-tetanic sequence of three stimuli at 50 Hz, followed 750 ms later by an identical sequence. The pattern $DBS_{3,2}$ consists of brief three 50 Hz tetanic stimuli, followed 750 ms later by two short 50 Hz stimuli (Fig. 6). The evoked responses following DBS are higher in amplitude than those elicited by TOF, and because the subjective evaluation consists of direct comparison of two sequential contractions (as opposed to comparing the fourth and first responses in a train of four rapid contractions), the subjective evaluation of DBS-induced fade is marginally improved: this sequence generally can be used to detect fade until the TOF ratio reaches 0.60 [69]. It must be noted, however, that even this pattern of stimulation is inadequate to ensure adequate recovery (TOF > 0.90) by subjective means.

Is there a difference between the various muscle groups in their response to the administration of a muscle relaxant?

Different groups of skeletal muscles perform different functions and exhibit marked fibre heterogeneity at the cellular and subcellular structures that reflect an adaptation to the different patterns of activity. For example, the myosin composition of the muscle fibres of the diaphragm is substantially different from that in leg muscles [70]. Neuromuscular blockers are used as adjuvants to anaesthetic drugs to achieve adequate relaxation of the upper airway, vocal cords and diaphragm in order to facilitate tracheal intubation and surgery. The depth of neuromuscular blockade is typically assessed by stimulating the ulnar nerve and monitoring the response of

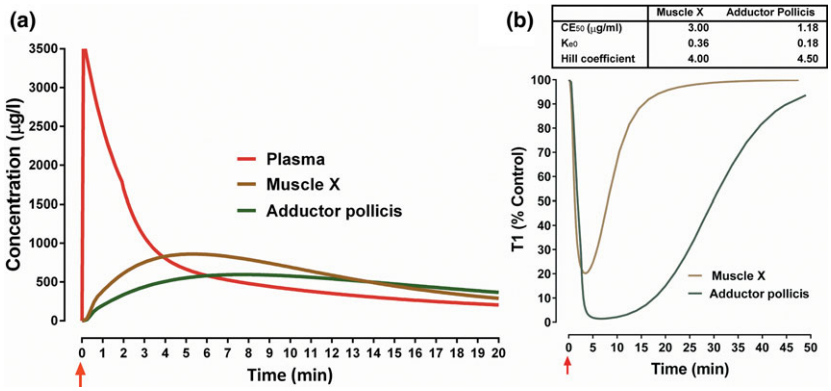

Figure 7 Recovery characteristics of different muscles. Neuromuscular blockade develops faster, lasts a shorter time and recovers faster at the laryngeal and diaphragmatic muscles than the adductor pollicis muscle, although the laryngeal and diaphragmatic muscles are more resistant to neuromuscular blocking drugs. This figure depicts a computer simulation based on Sheiner's model [102] and data reported by Wierda et al.[103]. Concentrations (panel A) and effect (panel B) over time for a 0.45 $mg.kg^{-1}$ rocuronium i.v. bolus. The ED_{95} of rocuronium at the adductor pollicis from this model is 0.33 $mg.kg^{-1}$. Rocuronium 0.45 $mg.kg^{-1}$ is given as a bolus at time zero. Muscle X represents a muscle (such as the diaphragm, the laryngeal adductors, or corrugator supercilii muscle), which is less sensitive to the effects of non-depolarising relaxants than the adductor pollicis muscle but has greater blood flow. Panel A presents the predicted rocuronium plasma and effect site concentrations at the adductor pollicis muscle and muscle X. Note that that concentration of rocuronium reaches higher levels at a faster rate in muscle X than in the adductor pollicis muscle. Panel B presents the predicted T1% as a percentage of control at muscle X and the adductor pollicis muscle. The CE_{50} represents the effect site concentration at which there is a 50% probability of effect. The k_{e0} represents the micro rate constant for drug leaving the effect site compartment. The Hill coefficient represents the slope of the effect site concentration vs. effect curve (not shown). In this example, the concentration of rocuronium producing 50% block (EC_{50}) of muscle X is 2.5 times that of the adductor pollicis muscle, but the half-life of transport between the plasma and effect compartment ($t_{½}k_{e0}$) of muscle X is only half as long. The rapid equilibration between plasma concentrations of rocuronium and muscle X results in the more rapid onset of blockade at muscle X than at the adductor pollicis muscle. The greater EC_{50} at muscle X explains the faster recovery of this muscle from neuromuscular block (faster rocuronium wash-out) than at the adductor pollicis muscle.

the adductor pollicis (thumb) muscle. Nevertheless, the sensitivity of the diaphragm and airway muscles to neuromuscular blocking drugs is different from that of the adductor pollicis muscle (Fig. 7). Therefore, the onset and speed of recovery following the administration of neuromuscular blocking drugs is dependent on which muscle is being monitored [71, 72].

Airway muscles

Compared with peripheral muscles, the laryngeal and diaphragmatic muscles are more resistant to the effects of neuromuscular blocking drugs [71, 72]. Neuromuscular blockade develops faster, lasts a shorter time and recovers faster at the laryngeal and diaphragm muscles compared with the peripheral, thumb muscle. These observations may seem contradictory because there is also convincing evidence that the effective plasma concentration of the drug necessary to achieve 50% of the intended effect (EC_{50}) for almost all drugs studied is between 50% and 100% higher at the diaphragm or larynx than it is at the adductor pollicis (i.e. the diaphragm and the larynx are more resistant to the effects of drugs than the muscles of the hand). This apparent contradiction can be explained by the rapid equilibration (shorter mean equilibration half-life, $t_{½}k_{e0}$) between plasma and the effect compartment at these muscles [73]. The greater total blood flow per gram of muscle at the diaphragm or larynx results in a higher peak plasma concentration of drug than at the adductor pollicis in the brief period before rapid redistribution is well under way (Fig 7).

Facial muscles

Stimulation of the facial nerve will evoke contraction of the orbicularis oculi muscle (the eyelid) as well as of corrugator supercilii muscle (the eyebrow). The corrugator supercilii muscles follow the time course of paralysis and recovery of the laryngeal adductor muscles, while the orbicularis oculi muscles follow those of peripheral muscles such as the adductor pollicis muscle [74]. Monitoring of facial muscles is a poor substitute for monitoring the adductor pollicis muscle. A recent report showed a 52% incidence of residual paralysis in the recovery room using subjectively assessed eyebrow responses, compared with 22% incidence of residual paralysis with hand muscle monitoring [75].

Where should we monitor?

Stimulation of the ulnar nerve and measuring the elicited response at the adductor pollicis muscle is the preferred site of monitoring neuromuscular function. The ulnar nerve innervates the adductor pollicis, abductor digiti quinti and first dorsal interosseous muscles. Electrical activation of peripheral motor nerves requires two electrodes to produce a current flow, which are typically arranged in a monopolar configuration. The stimulating electrode creates a localised electric field that depolarises the membrane of a nearby nerve. In the monopolar configuration, the depolarising (negative) electrode is placed distally 1 cm proximal to the wrist crease on the radial side of the flexor carpi ulnaris, while another is placed proximally on the volar forearm as shown in Fig. 8 [42, 76]. This orientation ensures maximal neuronal stimulation and muscular response (Fig. 9) [42]. The evoked contraction of the adductor pollicis muscle can be assessed by tactile (Fig. 10) or visual means (subjectively) or recorded and measured with the use of an appropriate transducer and monitoring device, as described below.

If the hand is not accessible, stimulation of the facial nerve may be used as long as the limitations of facial muscle monitoring and potential confounding variables associated with this monitoring site are followed [75, 77]. The electrodes should be placed near the stylomastoid foramen (just below and anterior to the mastoid bone) (Fig. 11a) or just anterior to the ear lobe (Fig. 11b) to evoke contraction of the orbicularis oculi or the corrugator supercilii muscles. The evoked response can be assessed tactilely (not recommended) (Fig. 12) or quantified using an acceleromyography transducer (Fig. 13). The stimulator electrodes should

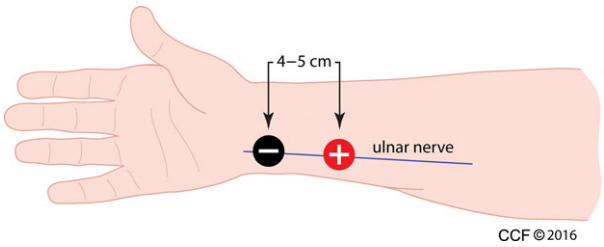

Figure 8 Representation of correct placement of the stimulating electrodes for ulnar nerve stimulation. Note that the black (negative) electrode is distal to the proximal, red (positive) electrode.

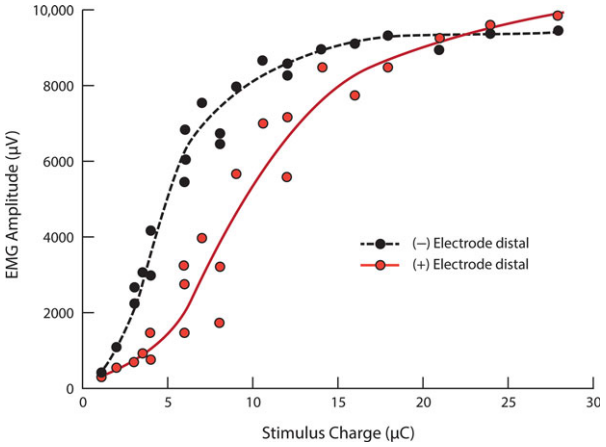

Figure 9 Relationship between stimulus charge (in μ Coulombs, μC) and the evoked response amplitude (electromyographic action potential) in two electrode position orientations: negative electrode placed distally and positive electrode placed distally. Data obtained from a series of 24 combinations of current intensity (mA) and pulse duration (ms) in volunteers. Reproduced from Brull and Silverman [42] with permission.

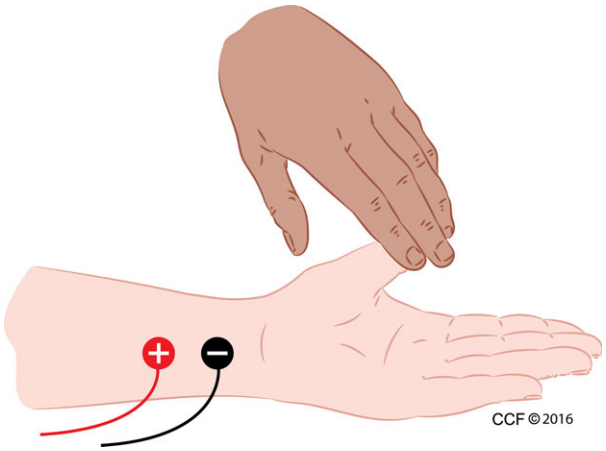

Figure 10 Subjective (tactile) evaluation of neuromuscular responses at the adductor pollicis (thumb) muscle in response to ulnar nerve stimulation. Note the negative (black) electrode is placed distally.

be placed along the ulnar nerve at the end of the surgical procedure (once the patient's hand becomes available) to ensure adequate recovery of neuromuscular function before tracheal extubation.

An alternative site for monitoring when the hand is not available is the posterior tibial nerve behind the medial malleolus (Fig. 14); the response of the flexor hallucis brevis is assessed by subjective (plantar flexion of the foot, not recommended) or objective means such as acceleromyography (Fig. 15) [78].

Quantitative modalities

Having described the key differences between peripheral nerve stimulators (PNS) and neuromuscular monitors, we will concentrate on describing the various types of technologies that can be used to stimulate, analyse, record and display ('monitor') neuromuscular function.

Acceleromyography (AMG)

Acceleromyography has been in clinical use for three decades, and it is based on Newton's Second Law (Force = mass × acceleration): the force of muscle contraction is proportional to acceleration, as mass remains constant. Acceleromyography involves measurement of the acceleration of a muscle (usually the adductor pollicis) in response to nerve (usually the ulnar) stimulation (Fig. 16). If the hand is not available for monitoring the adductor pollicis muscle, other sites can be used. The flexor hallucis longus (toe) muscle in response to posterior tibial nerve innervation can be measured (Fig. 15), or the orbicularis oculi or corrugator supercilii muscles can be measured in response to facial nerve stimulation (Fig. 13).

Although acceleromyography has de facto become the 'standard' of clinical care, it has significant limitations that continue to prevent the technology from achieving wide clinical adoption [79]. In addition to the need for pre-use calibration, AMG monitors cannot be used clinically when unencumbered movement of the thumb is not assured, such as surgical procedures in which the arms are placed at the patient's side under surgical drapes. A work-around may be to protect the monitored arm and thumb inside a TOF-tube, but the limits of agreement between mechanomyography (see below) and AMG were in the range of -19% to +24% when the TOF ratio was 0.9 [80]. Furthermore, the use of the recommended Hand Adapter that maintains a preload to improve precision [81] also increases the average control TOF ratios from 1.07 (no pre-load) to 1.13 (with a significant range between TOF = 1.01–1.23). This significant overshoot of the baseline TOF measured with AMG, the so-called 'reverse fade' [82, 83] prompted the recommendation to

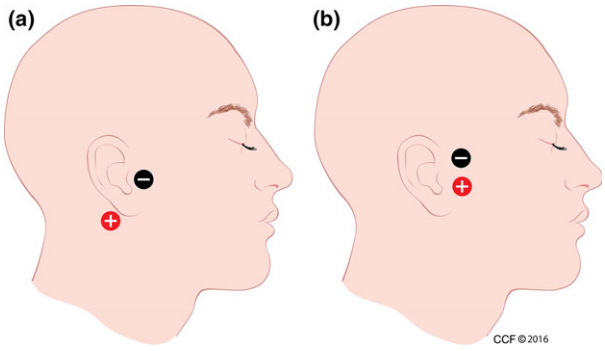

Figure 11 Suggested placement of stimulating electrodes for monitoring of the eye (orbicularis oculi, corrugator supercilii) muscles. Given the course of the facial nerve, note that the positive (red) electrode is always proximal and the negative (black) electrode always distal.

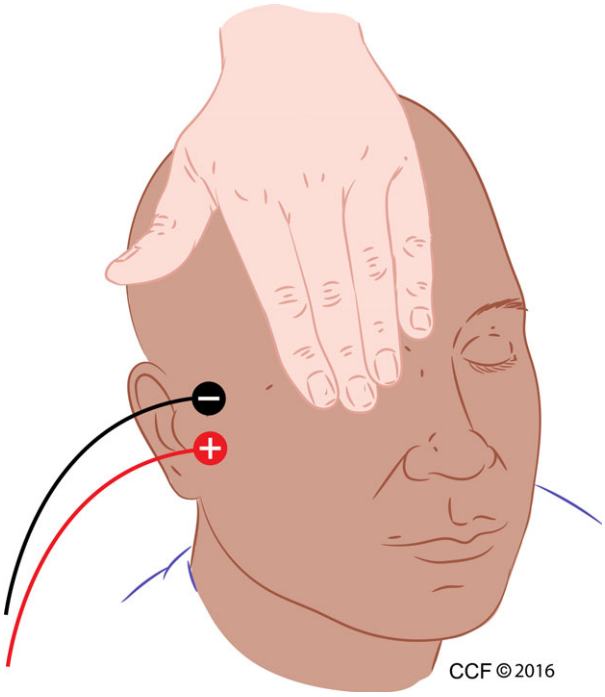

Figure 12 Subjective (tactile) evaluation of neuromuscular responses at the orbicularis oculi (eye) muscle in response to facial nerve stimulation. Note the negative (black) electrode is placed distally.

consider a TOF > 1.0 as minimum recovery threshold when a calibrated AMG is used [79]. Similarly, when comparing AMG obtained evoked responses to those obtained with EMG, the AMG TOF ratio is significantly higher than the EMG TOF [82] (Fig. 17).

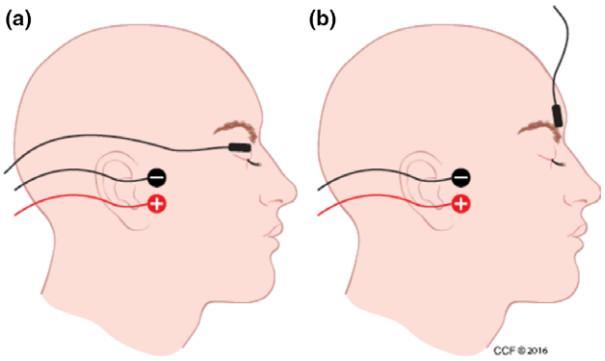

Figure 13 Apparatus for objective monitoring of the orbicularis oculi (a) and the corrugator supercilii (b) muscle contraction using acceleromyography. An accelerometer is attached to the eyelid (a) or the eyebrow (b). Facial nerve stimulation (note that the negative electrode is distal to the positive electrode) will result in contraction of the eye muscles, which is measured by the accelerometer. The results are displayed on the monitor's screen.

Despite its limitations, the strength of AMG is that it can continuously record, analyse and display important parameters, such as ST and TOF, making it usable for the clinician and facilitating a rational approach to administration of neuromuscular blocking agents and their antagonists (Fig. 18).

Mechanomyography (MMG)

Mechanomyography is based on the measurement of the force of muscular contraction in response to nerve activation. Most commonly, the thumb is placed in a holder that is attached to a force transducer (Fig. 19), and the force of thumb adduction resulting from ulnar nerve stimulation is recorded and measured. Although it has long been considered the standard of neuromuscular monitoring, the MMG set-up is cumbersome to use, bulky, and similar to AMG, it requires unencumbered thumb movement [84]. Additionally, MMG requires stringent preparation and maintenance of a constant preload; it is very sensitive to repetitive stimulation and MMG-measured force of contraction increases as much as 35–50% in the first few minutes of stimulation [85]. For these reasons, MMG as a method of measurement of neuromuscular function in the clinical setting has been abandoned.

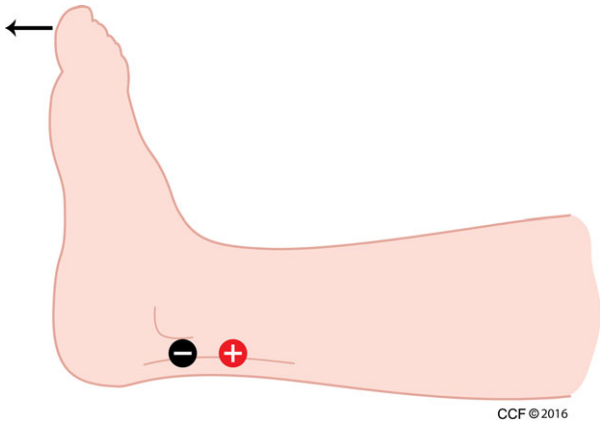

Figure 14 Suggested location of stimulating electrodes along the posterior tibial nerve (posterior to the medial malleolus). Stimulation causes plantar flexion of the toes. Note the negative (black) electrode is placed distally.

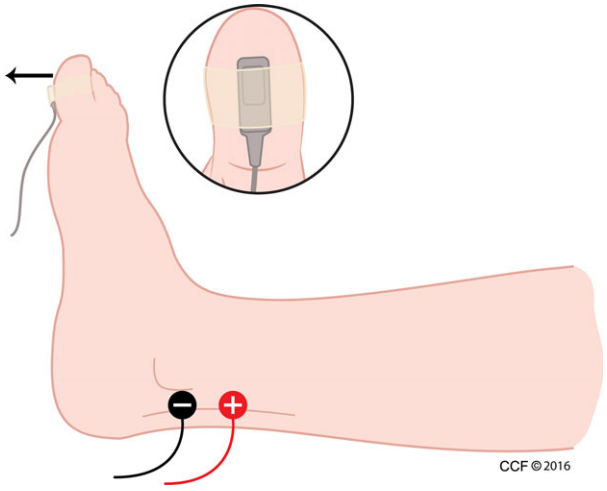

Figure 15 Apparatus for objective monitoring of the flexor hallucis longus (toe) muscle contraction using acceleromyography. An accelerometer is attached to the plantar surface of the large toe. The stimulating electrodes are placed along the posterior tibial nerve (posterior to the medial malleolus). Stimulation causes plantar flexion of the toes. Note the negative (black) electrode is placed distally.

Kinemyography (KMG)

Kinemyography is based on a mechanosensor strip that contains a piezoelectric polymer. The strip is placed between the base of the thumb and the base of the index finger (Fig. 20), and when the thumb adducts in response to ulnar nerve stimulation, the

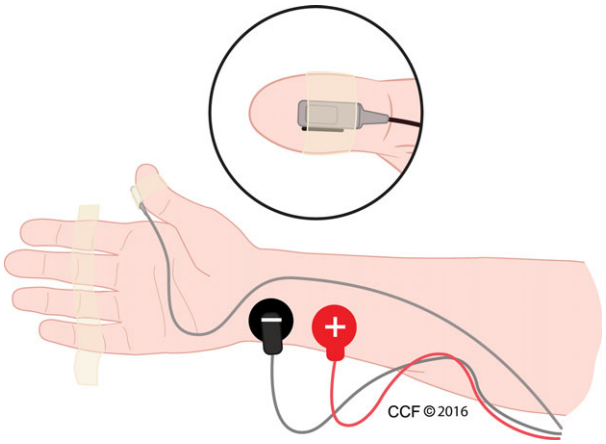

Figure 16 Apparatus for objective monitoring of the adductor pollicis (thumb) muscle contraction using acceleromyography. An accelerometer is attached to the thumb and the fingers and secured to prevent movement during nerve stimulation. Ulnar nerve stimulation (note that the negative electrode is distal to the positive electrode) will result in contraction of the adductor pollicis muscle, and the thumb acceleration is measured. The results are displayed on the monitor's screen.

polymer strip generates an electrical current that is proportional to the degree of bending. The KMG is simple to use clinically, but the results obtained are not interchangeable with other monitoring technologies. For instance, the TOF ratio of 0.90 obtained with KMG is equivalent with an EMG TOF of 0.80 (with TOF limits of agreement of 0.65–1.0) [86]. With repeated use, the mechanosensor strip may slide out of its intended location, and clinicians may tape the strip in place. Although this procedure maintains the strip in its intended location, the tape may actually also interfere with accurate measurement of responses. Despite this limitation, KMG is an easy to use technology that will give the clinician much more reliable information than that obtained subjectively, and its use is recommended.

Electromyography (EMG)

Electromyography is one of the oldest technologies used for monitoring the neuromuscular function. Like the other technologies, it involves stimulation of a peripheral nerve and measurement of the muscle action potential (MAP) that is generated by the contraction of the innervated muscle (Fig. 21).

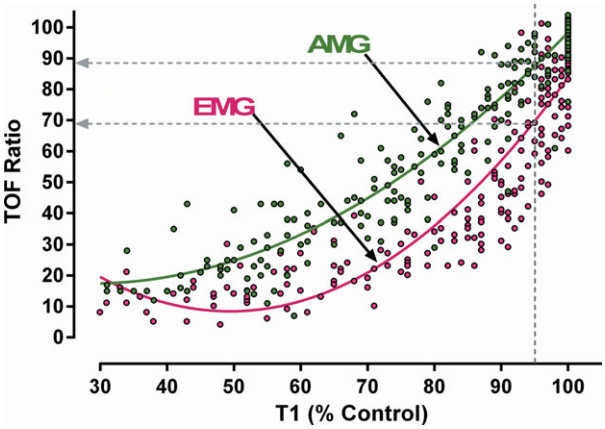

Figure 17 Electromyographic (EMG) and acceleromyographic (AMG) twitch height (T1) as a function of the train-of-four (TOF) fade ratio. Note that at 95% recovery of T1, TOF ratio is higher as measured by AMG than by EMG (~0.88 vs. ~0.68, respectively) because acceleromyographic TOF values tend to overestimate the extent of EMG recovery. Adapted from Kopman et al. [82] with permission.

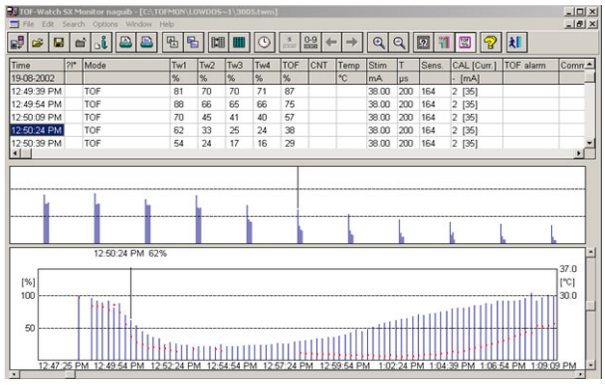

Figure 18 Computer 'screenshot' from TOF-Watch™ Monitor software. Time course of 0.3 mg.kg^{-1} rocuronium dose is shown on the lower panel. The control acceleromyographic TOF response is at the extreme left of the lower panel (the train-of-four ratio, TOFR, is shown as red dots as 100%). In the upper panel, the highlighted time (in blue) indicates that the TOFR at that time is 0.38 (or 38%, where T4/T1 = 24/62). The actual recordings corresponding to this time are indicated by the black markers on both the middle and lower panels. Please note that the single twitch returns to baseline before the TOF ratio.

Electromyography measures an electrical event that occurs at the neuromuscular junction: the activation of postsynaptic receptors by acetylcholine (a chemical process) that converts it to a mechanical response (excitation–contraction coupling that results in muscle contraction). For this reason, EMG is less prone to interference from presynaptic or postsynaptic events, and is likely a better indicator of pure neuromuscular function.

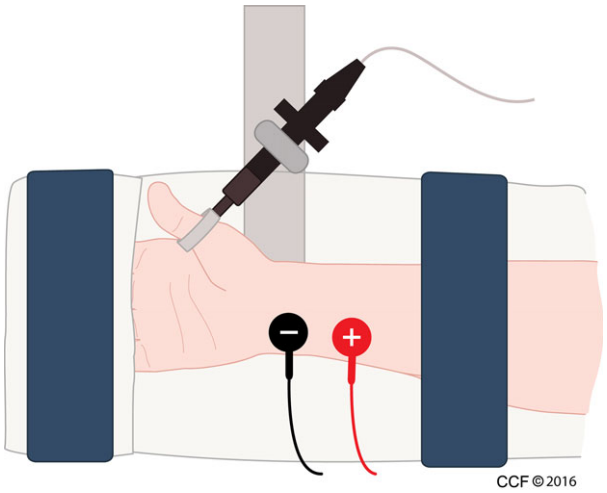

Figure 19 Apparatus for objective monitoring of the adductor pollicis (thumb) muscle using mechanomyography. A force transducer ring is attached to the thumb, and the fingers are secured to prevent movement during nerve stimulation. Ulnar nerve stimulation (note that the negative electrode is distal to the positive electrode) will result in the contraction of the adductor pollicis muscle, and the force of contraction is measured by the force transducer. The results are displayed on an interfaced screen.

In contrast with monitoring of MMG, in which repetitive stimulation may induce an amplification of responses, EMG amplitude is stable over time, decreasing less than 2% per hour during constant stimulation [85]. Similarly, temperature affects the EMG amplitude to a much lesser extent than it affects MMG: EMG amplitude increases by 2–3% for every 1°C temperature decrease [85]. Much like the subtle differences in TOF ratios measured with KMG compared with EMG there is also a difference between responses obtained with EMG and MMG, although this difference may be clinically insignificant [87].

What are the specifications of the ideal monitor?

The ideal neuromuscular monitor would not have the current limitations. It would be portable so it could be

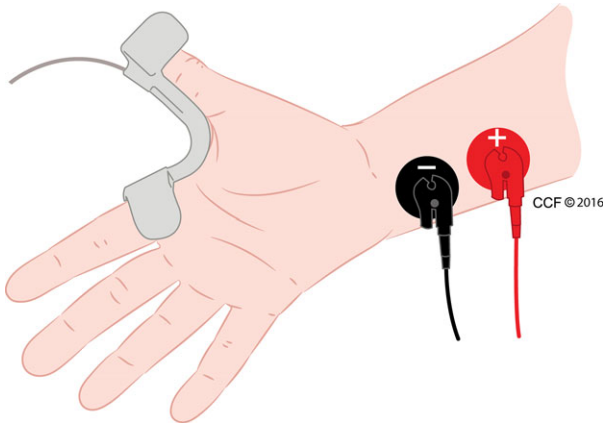

Figure 20 Apparatus for objective monitoring of the adductor pollicis (thumb) muscle contraction using kinemyography. A mechanosensor (metallic strip) is placed in the groove between the thumb and index finger; ulnar nerve stimulation produces adductor pollicis muscle contraction that bends the strip, generating a current, which is proportional to the strength of muscle contraction. The results are displayed on the monitor's screen.

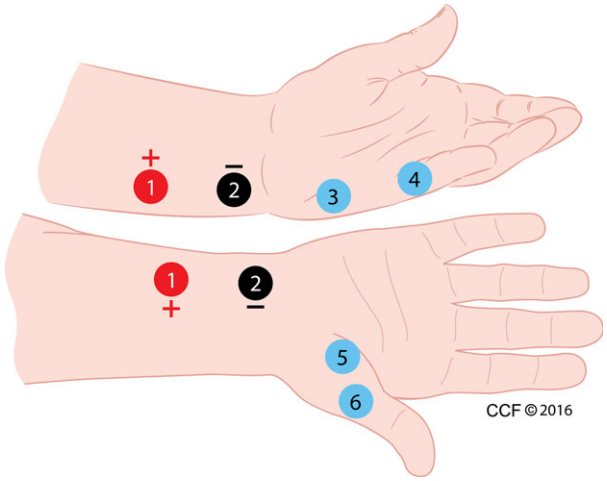

Figure 21 Placement of the stimulating electrodes (1 and 2) along the ulnar nerve; and of the recording electrodes for monitoring the abductor digiti minimi (3 and 4) or the adductor pollicis (5 and 6) muscles by electromyography.

used in remote locations away from the anaesthesia workstations (cardiac catheterisation units, radiology suites, endoscopy units, etc.), yet be easily integrated into the workstation and the electronic medical record; it would display graphically the ST as a percent of control (T_1/T_C) and the TOF; it would have the ability to provide a graphical display of the block onset and recovery history, so the clinician would be able to make projections and plan optimal management; and ideally, be integrated into neuromuscular monitoring feedback loops that will guide administration of neuromuscular blocking agents and optimise the timing of pharmacologic antagonism.

What are the most common mistakes clinicians make in monitoring?

(1) *Not using a neuromuscular monitor*. As presented above, subjective evaluation of responses and clinical testing of patients have not decreased the incidence of postoperative residual weakness. Best practice is to use objective monitors whenever possible; if monitors are not available, do not administer anticholinesterase reversal until spontaneous recovery indicates at a minimum a TOF count of 3, and wait at least 15 min after reversal before extubating the trachea.

(2) *Use of facial muscles for subjective monitoring*. This practice usually leads to overdosing of neuromuscular blocking agents, because the facial muscles are much more resistant to muscle relaxants, and because of the potential for direct muscle stimulation. Best practice is to always establish a baseline TOF response at the adductor pollicis muscle (hand) before moving the site of monitoring to the face, if hands are not available intraoperatively. Before tracheal extubation, always recheck for adequate reversal at the adductor pollicis muscle.

(3) *Using 5-s TET for less than 5 s*.: All of the studies that describe the effects of tetanic stimulation on subsequent responses have employed a 5-s duration, so any information obtained following lesser tetanic durations is likely wrong. Best practice is always to use the appropriate duration (5 s); tetanic stimulation should only be administered to anaesthetised patients, and it will not harm them. Conversely, obtaining false information about the degree of neuromuscular recovery may do so.

(4) *Using subjective evaluation of TOF count*. Studies have documented that subjective evaluation of TOF count most often *overestimates* (rather that underestimates) the degree of recovery, such that

the dosing and/or the timing of antagonism will likely be inadequate. Best practice is when pharmacological reversal with both anticholinesterase drug (neostigmine) and selective relaxant-binding agents (sugammadex) is based on the degree of recovery indicated by TOF count obtained objectively (i.e. measured).

(5) *Determining the onset of neuromuscular block by ST at 1 Hz.* The relatively high frequency of stimulation (one stimulus per second) will increase the local blood flow and speed delivery of neuromuscular blocking agent to the monitored muscle, falsely indicating a faster onset of block than at the laryngeal muscles. This may make tracheal intubation more difficult and increase the potential for vocal cord injury. Best practice is always to monitor TOF rather than ST for assessment of neuromuscular block onset.

(6) *Assessing neuromuscular function < 3 min after TET.* High frequency stimulation (TET) will lead to a 2–3-min period in which subsequent evoked responses are potentiated (period of post-tetanic potentiation). Best practice is only to use TET when the TOF = 0 and the TOC count = 0, and wait at least 3 min between TET and a subsequent TET, ST or TOF stimulation.

(7) *Not maintaining monitored muscle normothermia.* Particularly when the patient's arms are away from the body, the hand may become exposed to the cold operating room environment. The resultant hypothermia of the monitored muscle (adductor pollicis) will significantly affect neuromuscular transmission and give erroneous information about the depth of block or degree of recovery. Best practice is to maintain the peripheral muscle normothermia with the use of heat warmers.

(8) *Not ensuring good skin contact.* Best practice is to decrease skin resistance by cleaning and degreasing the skin with an abrasive paste before placing the electrodes, and use fresh wet-gel electrodes to decrease the impedance at the electrode-skin interface and prevent skin burns.

Conclusions

Drugs that provide neuromuscular blockade and its reversal have enjoyed widespread use among anaesthesiologists for many decades. Although perhaps not viewed as an essential tool to administering these types of drugs, neuromuscular blockade monitoring should not be difficult to interpret and should always be used. The intent of this review was to clarify key elements of neuromuscular monitoring. In conclusion, the authors encourage consistent use of a neuromuscular monitoring device any time a neuromuscular blocking drug is used, whether depolarising or non-depolarising, and recommend the development of educational activities that make anaesthesia practitioners aware of important misunderstandings in the management of neuromuscular block that directly and frequently impact patient safety.

Competing interests

MN has had no commercial affiliations of any kind since 2014. SB had research funded by Merck & Co., Inc., and is a shareholder and member of the Board of Directors for Senzime AB. KJ holds an equity position in Applied Medical Visualizations, LLC.

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