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Acceleromyography for Use in Scientific and Clinical Practice

A Systematic Review of the Evidence

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This systematic review describes the evidence on the use of acceleromyography for perioperative neuromuscular monitoring in clinical practice and research. The review documents that although acceleromyography is widely used in research, it cannot be used interchangeably with mechanomyography and electromyography for construction of dose–response curves or for recording different pharmacodynamic variables after injection of a neuromuscular blocking agent. Some studies indicate that it may be beneficial to use a preload to increase the precision of acceleromyography, and to "normalize" the train-of-four ratio to decrease the bias in relation to mechanomyography and electromyography. However, currently the evidence is insufficient to support the routine clinical use of preload and "normalization." In contrast, there is good evidence that acceleromyography improves detection of postoperative residual paralysis. A train-of-four ratio of 1.0 predicts with a high predictive value recovery of pulmonary and upper airway function from neuromuscular blockade.

Introduction

Historical Background

ACCELEROMYOGRAPHY for clinical use in anesthesia was introduced in 1988.[1,2] Evidence indicated that postoperative residual curarization (PORC) was a problem[3] and that there was a need for a simple and user-friendly method of neuromuscular monitoring for use in the clinical setting. In contrast to the more cumbersome methods of electromyography and mechanomyography, acceleromyography might fulfill these criteria. Contrary to mechanomyography, which is based on isometric measurements, and electromyography, which is based on measurement of the compound action potential, acceleromyography in its original form was based on isotonic measurements (freely moving thumb). The theory behind acceleromyography is based on Newton's second law of motion, force = mass × acceleration. When mass is constant, acceleration is directly proportional to force. For measurement of acceleration, an acceleration transducer is normally used, consisting of a piezoelectric ceramic wafer embedded within a suitable housing (fig. 1). Whenever the piezoelectric wafer is moved (accelerates), a voltage is generated, and if the transducer is fixed to a digit or muscle, any movement generates an electric signal. The signal is subsequently conditioned, analyzed, and recorded in a monitoring unit. The first prototype used a modified Myograph 2000® (Biometer International A/S, Odense, Denmark) as the recording unit,[1] but it was soon replaced by a commercially available acceleromyograph, the Accelograph® (Biometer International A/S).[2] Later came the Mini-Accelograph® in combination with Myotest® (Biometer International A/S)[4] and the TOF-Guard® (Biometer International A/S).[5,6] Commercially available today are TOF-Watch®, TOF-Watch® S, TOF-Watch® SX (Biometer International A/S), and Infinity® Trident NMT Pod (Dräger Medical AG & Co. KGaA, Lübeck, Germany).

The piezoelectric transducer element is identical in all acceleromyographs, but the electronics have been upgraded over the years. Therefore, the latest models (the TOF-Watch® series) are less sensitive to artifacts, *e.g.*, accidental movements of the thumb, and the stimulation current circuitry has been improved, allowing constant current stimulation at a higher skin resistance (increased from 3.5 to 5 kΩ). The upgrades do not exclude comparison of measurement obtained with various models, because the accelerometric measurements are performed in an identical manner, and constant current stimulation including stimulation current monitoring has been present in all models. However, the TOF-Watch® and TOF-Watch® S are not intended for use in research. They automatically change the way the train-of-four (TOF) ratio is calculated, ensuring that a TOF value greater than 100% is never displayed.[7] The TOF-Watch®

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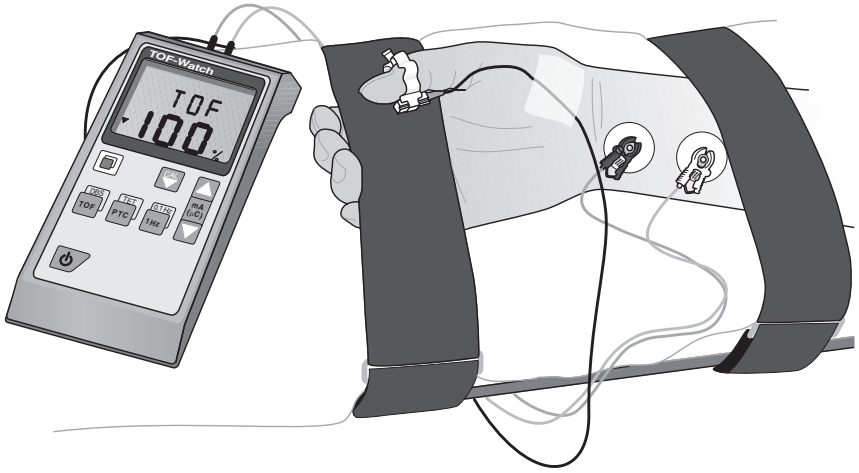

Fig. 1. The setup of acceleromyography. Two electrodes are placed above the ulnar nerve, and the response to nerve stimulation is measured using a small piezoelectrode acceleration transducer distally placed on the volar site of the thumb.

SX displays the unmodified TOF value and has an optional computer interface for recording stimulus parameters, evoked response data, and other relevant information.

Current Status

Ideally, neuromuscular function during anesthesia should be monitored objectively, *i.e.*, using a device that can measure and display the TOF fade ratio in real time.[8,9] However, there are clinicians who question the necessity and benefits of this practice.[10–13]

Furthermore, to our knowledge, in many countries there are no official guidelines recommending routine neuromuscular monitoring.

Neuromuscular function may also be evaluated using subjective clinical tests such as head lift and grip strength, but these tests are often unreliable, require patient cooperation, and may not rule out clinically significant residual curarization.[3,14–17] Visual or tactile evaluation of the response to nerve stimulation is often used in daily clinical practice, but these tests are relatively insensitive. Even if no fade is felt or seen in response to TOF, double-burst, or 50-Hz tetanic stimulation, residual neuromuscular blockade cannot be excluded.[18–20]

Available methods for objective neuromuscular monitoring are mechanomyography, electromyography, kinemyography,[21] phonomyography,[22] and acceleromyography. Although all five methods have advantages and disadvantages, acceleromyography is probably the most widely distributed method for objective monitoring of neuromuscular function during clinical anesthesia. In addition, acceleromyography is increasingly being used for research purposes.[23–29] Acceleromyography has, however, never been evaluated systematically for this purpose[30]—neither have electromyography and mechanomyography—and it is uncertain to what extent results obtained using acceleromyography can be used interchangeably with results obtained using these two more established methods.

Objective

The main purpose of this systematic review is to evaluate the current evidence of the relation between results obtained using acceleromyography and more established methods (mechanomyography and electromyography), and to evaluate whether acceleromyography can be used to exclude clinically significant residual neuromuscular block. Specifically, we aimed at answering the following key questions:

1. Does the use of acceleromyography produce results that differ significantly from those obtained using mechanomyography and electromyography for establishing dose–response relations and for evaluation of neuromuscular block during clinical anesthesia as well as in research?
2. What is the relation between the acceleromyographic TOF response and signs, symptoms, and clinical tests of residual neuromuscular block?

To answer these two questions, we also evaluated methodologic issues connected with the use of acceleromyography.

Materials and Methods

Search Strategy and Grouping of Articles

A comprehensive literature search was performed without time limits until November 2007 in the Cochrane Library, PubMed, BIOSIS, and Embase. We set our searching strategy deliberately broad without language restrictions using the combined search of: #1 (Neuromuscular) AND #2 (Acceleromyographically OR Acceleration transducer OR Acceleromyograph OR Accelerograph OR TOF-Guard OR TOF-Watch OR Mini-Accelograph OR Infinity Trident OR Acceleromyography OR Accelography OR Acceleromyographic monitor OR Accelerometry OR Accelerography). In addition, we studied the reference lists of all articles retrieved in the search and of other relevant articles known to the authors.

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The inclusion criterion was acceleromyography used for neuromuscular monitoring. Abstracts of all relevant articles were examined, and articles that were clearly not relevant to the key questions and did not evaluate acceleromyography were excluded. Animal studies were also excluded.

To answer the key questions, the remaining articles were divided into five groups: In group 1, we included studies comparing acceleromyography with mechanomyography or electromyography for construction of dose–response curves. Groups 2 and 3 included pharmacodynamic studies in which acceleromyography was compared with mechanomyography or electromyography, respectively. Group 4 included clinical studies where acceleromyography was compared with signs, symptoms, and tests of PORC (with or without a comparison with mechanomyography or electromyography). Finally, in group 5 were studies primarily dealing with basic methodologic problems comparing acceleromyography with mechanomyography and electromyography, such as preload, normalization (*i.e.*, referring TOF values during recovery to the baseline value) precision, baseline drift, and stability of the response.

Evaluation of Articles

We evaluated the quality of the scientific evidence using the Method for Evaluating Research Guideline Evidence developed by New South Wales Department of Health[31] and the Scottish Intercollegiate Guidelines Network (SIGN)[32,33] (appendix 1). However, because the actual influence of potential sources of bias may differ between types of studies, we sought to critically appraise bias control in the individual studies.[31,34] Accordingly, the quality of each article was evaluated independently by the authors using a checklist (appendix 2),[31–33] including salient methodologic issues relative to the outcome measures in question.[35–37]

When quality rating the *dose–response studies* comparing the use of acceleromyography with mechanomyography or electromyography (group 1), the method used for this comparison was carefully evaluated. Preferably, the cumulative method should only be used for long-acting drugs, and when using the single-bolus method, the patients should be randomly assigned to at least three different doses, which again should surround the anticipated ED values. Finally, handling of 0% and 100% responses should be described in detail.[37]

In *pharmacodynamic studies* comparing acceleromyography with mechanomyography or electromyography (groups 2 and 3), ideally, the two methods compared should be randomly allocated to the dominant and nondominant arm. For comparison of the results obtained using the different recording methods (mechanomyography, electromyography, and acceleromyography), researchers often use correlation or regression analysis or differences in means. However, as pointed out by Bland and Altman, none of these methods of analysis are suitable for such a comparison.[38,39] Instead, Bland and Altman have suggested that the precision of the new method, as well as the bias and limits of agreement in relation to the gold standard, should be established. For studies comparing acceleromyography with mechanomyography or electromyography, we therefore evaluated the method(s) used for the comparison. When the Bland–Altman method was used, we sought to establish whether it was used correctly.[38,39] If the precision (within-subject repeatability) for one of the methods is poor, the agreement between the methods will be poor as well. We therefore sought articles evaluating the within-subject repeatability, including an evaluation of whether or not the repeatability was dependent on the degree of block. According to Bland and Altman, in studies comparing two methods, the data should be plotted as differences between measurements against means of measurements with the two comparison methods.[38] The mean of these differences is the relative bias, and the hypothesis of zero bias can be examined by a paired *t* test. However, the bias may change with the values, *i.e.*, increase during recovery. Therefore, we examined whether investigators had taken this into account. Although the bias may be insignificant, there may be a clinically significant lack of agreement between individual measurements. For this reason, Bland and Altman suggest studying the limits of agreement (± 2 SDs) between the measurements. The confidence intervals for bias as well as for limits of agreement should be given. Finally, if repeated observations are made on each subject, the interdependence between these should be taken into account when constructing limits of agreement.[38,39]

In *studies comparing signs, symptoms, and tests of PORC with the acceleromyographic response* (group 4), emphasis was put on an evaluation of whether the evaluator was blind as to the acceleromyographic response.

In *studies evaluating the effect of applying a preload to acceleromyography* (group 5), we considered it important that the characteristics of the preload arrangement were clearly reported, making the setup reproducible for other investigators.

Level of Evidence Tables

Based on the type of study and the quality assessment (appendix 3), each article was allocated a level of evidence (appendix 4),[31] and levels of evidence tables were created for each key question, including data for the different outcome measures defining the key question (tables 1–7).[33]

Considered Judgment

For each outcome measure, the total body of evidence was summarized, and the key questions were answered using the best evidence available. In this process, the

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Table 1. Evidence Table for Studies Comparing AMG with MMG or EMG for Construction of Dose–Response Curves

Authors	Study Type	Subjects Included, n	NMBA	Setting	AMG Setup	Comparison Method	Methods/Setup	Outcome Measures	Results	Authors' Conclusion	Level of Evidence
McCluskey *et al.*,[40] 1997	CCT	15	Rocuronium	Pediatric surgery	AMG contralaterally without preload	MMG	Single dose–response technique	ED_{50} ED_{95} Slope (probit/log)	ED_{50} 36% higher with AMG No differences in ED_{95} Significant difference in slopes	AMG and MMG cannot be used interchangeably	III+
Comments: Sample size relatively small. Randomization to left and right hand and randomization to different doses of rocuronium not described. Results applicable to adults?											
Meretoja *et al.*,[41] 1989	CCT	14	Alcuronium	Pediatric surgery	AMG contralaterally without preload	EMG	Cumulative dose–response technique	ED_{50} ED_{95}	ED_{50} and ED_{95} 20% lower with AMG No significant differences in slope	AMG and EMG cannot be used interchangeably	III−
Comments: Sample size relatively small. Unclear whether Bland–Altman method was used correctly. Results applicable to adults?											
Kopman *et al.*,[42] 2005	CCT	30	Rocuronium	Adult surgery	AMG ipsilaterally with preload	EMG	Modified single dose–response technique based on Hill equation	ED_{50} ED_{95} Max block	No significant differences in ED_{50}, ED_{95}, or max block	AMG and EMG cannot be used interchangeably, but AMG is a valid method for determining drug potency	III+
Comments: Sample size analysis performed *post hoc*. Supramaximal stimulation not ensured (35 mA). The characteristics of the preload (a rubber band) not described and setup probably not reproducible. The method used to construct the dose–response curve (Hill equation) has not been validated—and so far only used by the senior author. A prerequisite for the method is that the slopes of all dose–response relations are the same.											

All three studies were nonrandomized and did not include a sample size analysis, and only Meretoja *et al.*,[41] 1989, described dropouts. In none of the studies was the stimulation pattern synchronized or used with the same frequency.

AMG = acceleromyography; CCT = controlled clinical trial; ED_{50} and ED_{95} = doses giving 50% and 95% twitch depression, respectively; EMG = electromyography; MMG = mechanomyography; NMBA = neuromuscular blocking agent.

generalizability (*i.e.*, the effectiveness as well as the efficacy) and the applicability (*i.e.*, influence of, for example, age, study setting, and population investigated) of the findings were also evaluated. The summarized evidence was then used to grade the strength of evidence according to a four-category grading system (appendix 5),[32,33] unless evidence was lacking or insufficient (table 8).

Results

Most of the studies found in our comprehensive literature search did not evaluate the use of acceleromyography. In these studies, acceleromyography was used for different purposes: in pharmacodynamic studies of neuromuscular blocking agents, to describe the frequency of PORC, or to monitor specific groups of patients (*e.g.*, children, elderly, patients with specific illness). In the majority of articles, acceleromyography was used without a comparison with mechanomyography or electromyography. Some articles described the use of acceleromyography monitoring sites other than the ulnar nerve/adductor pollicis muscle, *i.e.*, at the abductor hallucis muscle, the orbicularis oculi, or corrugator supercilii muscles. Only studies using ulnar nerve stimulation were evaluated. When the sites of neuromuscular monitoring differed (*i.e.*, mechanomyography monitoring of the adductor pollicis and acceleromyography monitoring of the orbicularis oculi), it was not possible to decide whether the reported differences in results were due to the different monitoring techniques or to the different monitoring sites. Therefore, these studies were also excluded. Accordingly, 55 articles evaluating the use of acceleromyography were left for further analysis.

Group 1: Use of Acceleromyography for Establishing Dose–Response Relations

We found three articles comparing acceleromyography to mechanomyography[40] or electromyography[41,42] for construction of dose–response curves (table 1). The study by McCluskey *et al.*[40] was stated to be randomized, but the concealed allocation was not described. It was therefore rated as a nonrandomized study, as were the other two. The study by Meretoja *et al.*[41] was judged to be methodologically somewhat weak (table 1), and a significant bias could not be excluded. It was therefore classified as level III− (appendix 4). The two other studies were classified as level III+. The study of McCluskey *et al.*[40] indicated ED_{50} to be 36% higher when measured using acceleromyography than with mechanomyography, and a significant difference in slope was found. However, there was no difference in ED_{95}. In contrast, Kopman *et al.*[42] found no differences in ED_{50},

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Table 2. Evidence Table for Pharmacodynamic Studies in which AMG was Compared with MMG

Authors	Subjects Included, n	NMBA	AMG Setup	Outcome Measures	Results	Authors' Conclusion	Level of Evidence
Viby-Mogensen *et al.*,[1] 1988	35	Vecuronium (30) No NMBA (5)	AMG contralaterally without preload	Control TOF	AMG TOF consistently higher than MMG and nearly always above 1.0	The higher control AMG TOF may impede comparisons between studies of subtle changes in neuromuscular function	III++
				TOF during recovery	Above MMG TOF 0.7, the mean AMG TOF deviated more and more from the line of identity, with higher AMG than MMG values	AMG fulfils basic requirements for clinical monitoring but should be used with caution in scientific studies	III+
Comments: Comparison using only regression analysis							
Itagaki *et al.*,[48] 1988	5	Vecuronium	AMG contralaterally with preload (light band between thumb and index finger)	Onset and recovery using 0.1-Hz stimulation	No significant difference between AMG and MMG	AMG may be a reliable device for monitoring NMB	III−
Comments: Insufficient sample size. Stabilization period and temperature not documented. Comparison using only regression analysis. T1 not referred to "final value."							
Werner *et al.*,[52] 1988	33 (1 dropout)	Atracurium or atracurium + succinylcholine	AMG contralaterally with preload (light band between thumb and index finger)	Control TOF	AMG TOF (0.95–1.15) nearly always exceeded MMG by 5–15%	The setup of AMG was easier and less time-consuming than MMG. AMG fairly accurate as compared with MMG. However, further research is needed	III+
				T1 (1 Hz) and PTC during recovery	No difference in twitch detection and PTC		III−
				TOF during recovery	Above TOF 0.7, the mean AMG TOF deviated more and more from the line of identity, with higher AMG than MMG values		III+
Comments: Temperature insufficiently reported. Comparison using only regression analysis. Different number of data points depending on the type of stimulation. Not clear how the data points were selected to be representative and when the stimulation pattern was changed.							
Ueda *et al.*,[51] 1989	15	Pancuronium	AMG contralaterally without preload	TOF, T1 (in TOF), and PTC during recovery	No differences in T1, TOF, and PTC	AMG gives identical information as MMG, but is easier to use	III−
Comments: Sample size relatively small. Stabilization period and temperature insufficiently documented. Comparison using only regression analysis. T1 not referred to the "final value."							
Harper *et al.*,[4] 1994	13	Atracurium	AMG contralaterally without preload	Control TOF	Control AMG TOF significantly higher than MMG		III++
				Onset and recovery using TOF stimulation	Onset time (T1) longer with AMG. Magnitude of drift (T1) greater with AMG. No systematic bias in TOF during recovery, but limits of agreement unacceptably wide	AMG easier to use than MMG. However, AMG and MMG cannot be used interchangeably	III+
Comments: Sample size relatively small. Randomization to dominant and nondominant hand; stabilization period and temperature insufficiently documented. T1 not referred to the "final value." Not possible to decide whether the Bland–Altman analysis was performed correctly. Relation not investigated beyond TOF ratio 0.7 during recovery.							
Ueda *et al.*,[5] 1994	12	Vecuronium	AMG contralaterally without preload (6 pts to the left arm, 6 pts to the right arm)	Control TOF	Control AMG TOF between 1.05 and 1.10 and always higher than MMG TOF		III+
				PTC TOF incl. T1 during recovery	PTC values higher with AMG, but same level at PTC = 0–1. AMG TOF higher than MMG TOF. T1 did not differ significantly	AMG's low cost, easiness of handling, simplicity, and compactness make AMG valuable for neuromuscular monitoring	III−
Comments: Sample size relatively small. Stabilization period not documented. Unclear how the data points were selected to be representative and whether TOF were referred to a control value (normalization). Comparison using regression analysis. T1 not referred to the "final value."							
Loan *et al.*,[6] 1995	28	Unknown	AMG contralaterally without preload	Control TOF	In the "majority of patients," AMG TOF was above 1.0		III−
				Onset and recovery using TOF stimulation	No significant difference in onset time. No systematic bias in TOF during recovery, but limits of agreement unacceptably wide	AMG and MMG cannot be used interchangeably	III−
Comments: Bland–Altman analysis used, but not possible to decide whether it was performed correctly. The bias seems to change with longer mean duration TOF 0.7. This is not taken into account. Less than 28 data points for many of the outcome measures without any explanation for the missing values.							

(continued)

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Table 2. Continued

Authors	Subjects Included, n	NMBA	AMG Setup	Outcome Measures	Results	Authors' Conclusion	Level of Evidence
Kirkegaard-Nielsen *et al.*,[49] 1998	32	Atracurium	AMG contralaterally without preload; 50% dominant, 50% nondominant arm	Control TOF	Control AMG TOF significantly higher than MMG		III++
				Onset	Onset time longer with AMG		III+
				TOF during recovery	Above MMG TOF 0.60, the mean AMG TOF deviated more and more from the line of identity, with higher AMG than MMG values	AMG and MMG cannot be used interchangeably for research, but is acceptable for clinical use	III+
Comments: Data points were excluded if two consecutive values deviated more than 5%. For some outcome measures, this meant a significant number of data dropouts. Not possible to decide whether the Bland–Altman analysis was performed correctly. Relation not investigated beyond TOF ratio 0.7 during recovery.							
Eikermann *et al.*,[47] 2004	12	Rocuronium (infusion)	AMG contralaterally without preload	TOF during recovery	No systematic bias between AMG and MMG TOF ratio during recovery, but limits of agreement wide	AMG and MMG cannot be used interchangeably	III−
Comments: (This article is also included in tables 4 and 7. Therefore, only points relevant for the comparison to MMG are summarized in this table.) Sample size relatively small. Randomization to left and right hand insufficiently described. Temperature not documented. Bland–Altman analysis seems to have been used, but incorrectly.							
Capron *et al.*,[53] 2004	30	Atracurium	AMG with preload calibrated incl. supramaximal stimulation	Control TOF	AMG TOF 0.97–1.02 (no comparison with MMG)	AMG and MMG cannot be used interchangeably, but AMG TOF 1.0 with calibration are accurate enough to detect low degrees of PORC in the clinical setting	III−
				Negative predictive value of AMG TOF 0.9, 0.95, and 1.0 to detect MMG TOF 0.9	Higher AMG TOF increased negative predictive value from 37% to 97%		III+
				Intraclass correlation coefficient for agreement during recovery	Intraclass coefficient was 0.71		III+
	30		AMG with preload uncalibrated +50-mA current	Control TOF	AMG TOF 1.00 to 1.17 (no comparison with MMG)		III+
				Negative predictive value of AMG TOF 0.9, 0.95, and 1.0 to detect MMG TOF 0.9	Higher AMG TOF increased the negative predictive value from 40% to 77%		III+
				Intraclass correlation coefficient for agreement during recovery	Intraclass coefficient was 0.73		III+
Comments: (This study is also presented in table 6, because the data were normalized in the "uncalibrated" group.) The authors stress that the study was performed under clinical conditions (not research conditions). The randomization to dominant and nondominant hand insufficiently described. Hand Adapter used as a preload for AMG. Stabilization period 3 min for MMG and only 45 s for AMG. It was not ensured that the stimulation current was supramaximal in the "uncalibrated" group. Peripheral temperature not reported. TOF-Watch® S was used. However, control TOF above 1.0 cannot be displayed with TOF-Watch® S. One wonders whether TOF-Watch® SX was used (*e.g.*, for the majority of patients in the uncalibrated group). Otherwise the data do not make sense.							
Dubois *et al.*,[46] 2005	20	Rocuronium	AMG contralaterally without and with preload (TOF tube or Hand Adapter)	TOF during recovery	If the fingers were fixed or a preload was applied, AMG TOF was higher than MMG TOF	None given in the article regarding the comparison of TOF	III−
Comments: (This study is also presented in tables 5 and 7.) Sample size relatively small. Randomization to the two arms and the setup of AMG insufficiently described. The AMG setup was changed four times during the study. The initial calibration was therefore lost. Stabilization period and temperature not documented. Supramaximal stimulation not ensured. Comparison using only regression analysis.							
Samet *et al.*,[50] 2005	40	Cisatracurium	AMG contralaterally with preload (Hand Adapter)	Sensitivity, specificity, and predictive values of a single uncalibrated AMG TOF to diagnose PORC (*i.e.*, MMG TOF <0.9)	Sensitivity 70%, specificity 88%, positive predictive value 95%, and negative predictive value 47%	A single AMG TOF cannot detect shallow degrees of residual block	III++

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Table 2. Continued

Authors	Subjects Included, n	NMBA	AMG Setup	Outcome Measures	Results	Authors' Conclusion	Level of Evidence
	25			Prediction of MMG TOF 0.9 from uncalibrated AMG TOF	An AMG TOF ratio reliably predicts the time interval until MMG TOF 0.9	Uncalibrated AMG TOF may be a valuable tool to predict the time to MMG TOF 0.9	III++
Comments: (This article is also included in table 4. Therefore, only points relevant for the comparison to MMG are summarized in this table.) Primary aim of study was to compare the performance of AMG TOF as a test for PORC (*i.e.*, MMG TOF <0.9) compared with DBS and 100-Hz, 5-s tetanic stimulation. Supramaximal current, stabilization, and calibration ensured for MMG, but not for AMG. Peripheral temperature not reported. Randomization to right or left arm insufficiently described.							
Capron *et al.*,[45] 2006	32	Rocuronium	AMG contralaterally without preload	AMG TOF during recovery	Good correlation between AMG TOF and MMG TOF, but AMG TOF was 5.3% higher than simultaneously measured MMG TOF, with wide limits of agreement. When AMG TOF ratio was 1.0, MMG TOF was 0.89	AMG and MMG cannot be used interchangeably, but AMG TOF 1.0, even uncalibrated, remains the most accurate test to exclude residual paralysis (*i.e.*, MMG TOF <0.9)	III+
Comments: (This article is also in table 4. Therefore, only points relevant for the comparison to MMG are summarized in this table.) The primary aim was to evaluate and compare all currently available tests: AMG TOF, MMG TOF, DBS, 50-Hz and 100-Hz tetanic fade, and the significance of applying the electrodes above the ulnar nerve *vs.* on both sides of the hand. Randomization to dominant or nondominant arm and randomization of stimulation site to ulnar nerve or hand insufficiently described. Supramaximal current ensured for MMG; current was 60 mA for AMG. Stabilization and calibration not described for MMG and not performed for AMG. Regression analysis used. Bland–Altman analysis used incorrectly.							

None of the studies included a sample size analysis or described concealed randomization. Only Kirkegaard-Nielsen *et al.*,[49] 1998, defined acceptable limits of agreement between the two methods taking into account possible variation between the two arms. Only Werner *et al.*,[52] 1988, Samet *et al.*,[50] 2005, Capron *et al.*,[53] 2004, and Capron *et al.*,[45] 2006, described possible dropouts.

AMG = acceleromyography; DBS = double-burst stimulation; MMG = mechanomyography; NMB = neuromuscular block; NMBA = neuromuscular blocking agent; PORC = postoperative residual curarization; PTC = posttetanic count; pts = patients; TOF = train-of-four.

ED_{95}, or maximum block between acceleromyography and electromyography.

Although two studies were assigned level III+ evidence, the external validity[35,36] (generalizability) was low. The study of McCluskey *et al.*[40] was performed in pediatric patients, and although the study was otherwise methodologically sound, it was performed in only 15 patients (without a power analysis). The study of Kopman *et al.* [42] was performed in adults with acceleromyography and electromyography ipsilaterally and with a preload applied. However, a novel nonvalidated method was used to construct the dose–response curve (Hill equation). A prerequisite for the validity of this method is that the slope of the dose–response relation is the same for acceleromyography and electromyography, and this has not convincingly been documented to be the case.

Summary of Evidence. There is insufficient evidence to confirm or deny that acceleromyography can be used interchangeably with mechanomyography and electromyography for construction of dose–response relations and for establishing the potency of neuromuscular blocking agents.

Group 2: Acceleromyography Compared with Mechanomyography in Pharmacodynamic Studies

In 15 articles, acceleromyography was compared with mechanomyography with respect to different pharmacodynamic variables (table 2). Two of the 15 studies were excluded; in one, the great toe was used for monitoring,[43] and in the other, a prototype of a mechanomyograph was sought validated using acceleromyography as the gold standard.[44]

The remaining 13 studies were all performed in adults (table 2).[1,4–6,45–53] In 11 of these, the primary aim was to compare acceleromyography with mechanomyography,[1,4–6,46–49,51–53] and in 2, it was to compare the performance of acceleromyographic TOF with other tests for PORC.[45,50] In one of the studies, a few intensive care patients were included,[52] and one study was performed in volunteers.[47] Otherwise, all studies included patients undergoing surgical procedures.

In none of the studies was a sample size analysis or a concealed randomization to dominant and nondominant arm performed as prescribed in the Consolidated Standards of Reporting Trials (CONSORT) Statement.[35,36] Only three studies described whether there were any dropouts.[45,50,53] All studies compared acceleromyography with mechanomyography in the contralateral arm, but only two studies took into account possible differences in response between the two arms.[49,52]

In five studies, a Bland–Altman analysis was used to compare the two methods.[4,6,45,47,49] In none of these studies was it possible to decide whether the analysis was performed correctly, and it often seemed that it was performed incorrectly. In only one study were acceptable limits of agreement between the two methods defined.[49]

Four studies compared the onset time found with acceleromyography and mechanomyography.[4,6,48,49]

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Table 3. Evidence Table for Pharmacodynamic Studies in which AMG was Compared with EMG

Authors	Subjects Included, n	NMBA	AMG Setup	Outcome Measures	Results	Authors' Conclusion	Level of Evidence
Ansermino *et al.*,[55] 1996	29 (7 dropouts)	Vecuronium	AMG contralaterally without preload	TOF incl. T1 during recovery	EMG T1 usually reappeared before AMG T1. AMG TOF higher than EMG TOF (bias 0.03; limits of agreement wide [−0.26 to 0.32]). At EMG TOF > 0.7, mean AMG TOF was 0.72 (range, 0.39–0.93). Duration TOF 0.7 was not significantly different	AMG is superior to clinical assessment, is easy to use, and provides assessment of TOF ratio which is as useful as EMG monitoring	III+
Comments: (This article is also in table 4.) Primary purpose of the study was to compare the use of AMG with visual evaluation of the TOF response. Randomization to left or right hand insufficiently described. Seven patients excluded (three because of unsatisfactory EMG recording, four because of end of surgery). TOF stimulation every 15 s for AMG and every 20 s for EMG. Bland–Altman used incorrectly. It is not taken into account that bias may change with level of block. Relation not investigated beyond TOF 0.7 during recovery. Study performed in pediatric patients; results may vary in adults.							
Dahaba *et al.*,[56] 1997	41	Vecuronium	AMG contralaterally without preload	Control TOF	Control AMG TOF significantly higher than EMG		III++
				Onset and recovery using TOF	No difference in onset (90% T1 depression). AMG TOF >EMG TOF up to TOF 0.45. Above this, no bias but wide limits of agreement	AMG and EMG cannot be used interchangeably. However, AMG is a reliable monitor in clinical practice	III+
Comments: Randomization procedure to left or right hand insufficient. TOF stimulation every 15 s for AMG and every 20 s for EMG. Stabilization period not described. Bland–Altman used incorrectly. Relation not investigated beyond TOF 0.8 during recovery.							
Nakata *et al.*,[60] 1998	28	Vecuronium	AMG contralaterally without preload	T1 (in TOF) during recovery	AMG T1 consistently lower than EMG T1. Wide limits of agreement	AMG and EMG cannot be used interchangeably. AMG T1 overestimates the extent of block as compared with EMG	III−
Comments: Computer-generated randomization to sevoflurane or xenon anesthesia. However, randomization to dominant or nondominant hand insufficiently described. Therefore, the study is recorded as being an N-RCT. TOF stimulation every 15 s for AMG and every 20 s for EMG. Different pulse width: AMG 0.2 ms, EMG 0.1 ms. Maximal stimulation current obtained but later changed to 60 mA for AMG and 70 mA for EMG. Stabilization period not described. Relation not investigated beyond T1 25%, and T1 not referred to the final value. Not possible to decide whether Bland–Altman analysis was performed correctly.							
Hemmerling *et al.*,[58] 2000	90	Rocuronium Suxamethonium	AMG contralaterally without preload	Onset and max block using T1 (0.1 Hz)	No significant difference in lag time, onset time, or max block between AMG and EMG	None given in article because the purpose was not to compare AMG and EMG	III+
Comments: Primary aim was to compare onset of 0.6 mg/kg rocuronium, 0.9 mg/kg rocuronium, and 1 mg/kg succinylcholine at the laryngeal and adductor pollicis muscles. Temperature not described. Only mean values were compared.							
Kopman *et al.*,[59] 2005	50	Atracurium	AMG ipsilaterally without or with preload (rubber band)	Control TOF	Control AMG TOF significantly higher than EMG		III++
				TOF included T1 during recovery	AMG TOF was significantly higher than EMG TOF (5–10%, with wide confidence intervals). Addition of an elastic preload decreased control TOF variability without affecting the relation between twitch height and TOF ratio	AMG and EMG cannot be used interchangeably. AMG overestimates the extent of EMG recovery by 5–15%, depending on the degree of recovery	III++
Comments: (This article is also in table 5.) TOF stimulation every 15 s for AMG and every 20 s for EMG. Supramaximal stimulation ensured with EMG but not with AMG. T1 referred to the final value. Relation between AMG and EMG TOF only examined at TOF 0.7 and TOF 0.9. Only mean values were compared.							
Hanzi *et al.*,[57] 2007	17 (3 dropouts)	Mivacurium	AMG ipsilaterally without preload	Changes in T1 during manipulations	AMG was more affected by external disturbances than EMG and less sensitive at deep block	EMG, as a more accurate method, is preferable for research and in situations where reliable monitoring is essential. AMG, as a simpler and stable method, is preferable for routine practice	III+
Comments: Relatively small sample size. Central temperature insufficiently documented. The same electrodes were used for stimulation of AMG and EMG, but with a time difference of 30 s. Supramaximal stimulation was found significantly higher with AMG(?). Differences found in T1 values caused by turn of hand may not apply to TOF values.							

All studies were nonrandomized. Only Kopman *et al.*,[59] 2005, included a sample size analysis. Only Ansermino *et al.*,[55] 1996, and Hanzi *et al.*,[57] 2007, described dropouts.

AMG = acceleromyography; EMG = electromyography; NMBA = neuromuscular blocking agent; N-RCT = nonrandomized clinical trial; TOF = train-of-four.

Two of these studies[6,48] found no difference in onset time, but the studies were assigned level III− evidence (table 2). In the two other studies, the onset time was found to be slightly longer when measured using acceleromyography.[4,49] It is uncertain whether this difference was statistically significant in one study, assigned level III+ evidence.[4] However, the last study, also assigned level III+, found the mean onset time of atracurium to be 23% longer with acceleromyography (160 *vs.* 130 s).[49]

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Table 4. Evidence Table for Studies Comparing AMG with Signs, Symptoms, and Tests of Residual Neuromuscular Block

Authors	Design	Subjects Included, n	Blind	Description of Dropouts	NMBA	Outcome Measures*/AMG TOF Compared with	Setup	Results	Authors' Conclusion/Most Important Findings	Level of Evidence
Mortensen *et al.*,[68] 1995	RCT	40 (19 monitored with AMG)	Yes	Yes (4 dropouts)	Pancuronium	MMG TOF Clinical tests	Randomization to ± perioperative monitoring with AMG. After tracheal extubation: MMG and clinical signs	All patients with AMG TOF ≥0.7 had a MMG TOF ratio ≥0.7 and could lift arm to opposite shoulder and protrude the tongue. All but one patient with AMG TOF ≥0.7 could sustain head lift for 5 s	Perioperative monitoring using AMG prevents PORC after pancuronium and is superior to clinical tests	II+
Comments: Primary aim was to evaluate whether perioperative use of AMG would decrease the intensity and severity of PORC (*i.e.*, MMG TOF <0.7). MMG was recorded immediately after tracheal extubation, but setup of MMG is insufficiently described (*i.e.*, supramaximal stimulation, calibration, stabilization), and it is not clear whether the recording was repeated to ensure reliable results.										
Ansermino *et al.*,[55] 1996	N-RCT	29	Yes	Yes (7 dropouts)	Vecuronium	Visual TOF fade	EMG on one hand, AMG and visual fade contralaterally	AMG superior to visual evaluation of TOF response. When fade was no more visible, TOF was ≥0.4 with both AMG and EMG	AMG is as useful as EMG for excluding PORC	III+
Comments: Primary aim was to compare the use of AMG with visual evaluation of the TOF response, but also a comparison between AMG and EMG was performed (article is also included in table 3). It is not clear whether it was the same anesthetist who was blinded in all cases. Repeated visual assessment by the same observer may have introduced bias. The EMG TOF could be from 0 to 80% when no fade was visible. The explanation might be that visual fade was evaluated contralaterally to EMG. Study performed in pediatric patients; results may vary in adults.										
Bissinger *et al.*,[61] 2000	N-RCT	83	Yes (double)	Yes (7 dropouts)	Pancuronium (49) Vecuronium (27)	Clinical tests	1.5 mg neostigmine to all pts at end of operation Extubation according to clinical criteria AMG, signs and tests in PACU	All patients unable to sustain head lift for 5 s had an AMG TOF ratio <0.7, but only 4 of 12 patients with an AMG TOF ratio <0.7 had an impaired head-lift test	Assessment of neuromuscular function via clinical criteria alone is often unreliable. An AMG TOF ratio <0.7 is a better indicator of PORC than the head-lift test	III++
Comments: Primary aim was to compare the incidence of postoperative pulmonary impairment (*i.e.*, hypoxemia and hypercapnia) after pancuronium and vecuronium. Secondary aim was to correlate these incidences with signs of PORC and an AMG TOF <0.7. PORC was defined as the mean of three consecutive AMG TOF ratios <0.7 obtained (with supramaximal stimulation). Stabilization period not described.										
Gätke *et al.*,[69] 2002	RCT	120 + 20	Yes	Yes (20 dropouts)	Rocuronium	MMG TOF	Randomization to ± perioperative monitoring with AMG. MMG TOF after tracheal extubation	All patients with AMG TOF ratio ≥0.8 also had an MMG TOF ratio ≥0.8	Perioperative monitoring using AMG prevents PORC. Clinical criteria with reversal of all patients did not prevent PORC	II++
Comments: Primary aim was to evaluate whether perioperative use of AMG would decrease the incidence and severity of PORC (*i.e.*, MMG TOF <0.8). Sufficient recovery defined as AMG TOF 0.85 (*i.e.*, no need for reversal). Twenty extra patients were included because of major protocol violations. MMG measurements were performed immediately after arrival to PACU, but it is not clear whether the measurement was repeated to ensure reliable recordings.										
Kim *et al.*,[64] 2002	OBS	602	No	No	Vecuronium (364) Rocuronium (238)	Clinical tests	Clinical evaluation perioperatively, reversal at the discretion of the anesthetist. AMG and clinical tests in PACU	A relation was found between AMG TOF recovery, and head lift and tongue depressor tests. At an AMG TOF ratio of ≤0.5, no patient could sustain a 5-s head-lift test or successfully perform the tongue depressor test	The use of clinical criteria with reversal but without neuromuscular monitoring did not prevent PORC	IV
Comments: Primary aim was to compare the incidence and severity of PORC after vecuronium and rocuronium. PORC defined as AMG TOF <0.7. AMG TOF was recorded immediately after arrival in PACU. It is not clear whether the recording was repeated to ensure reliable results. The ulnar nerve was stimulated with 50 mA and reduced if required to reduce pain (*i.e.*, supramaximal stimulation not ensured).										

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Table 4. Continued

Authors	Design	Subjects Included, n	Blind	Description of Dropouts	NMBA	Outcome Measures*/AMG TOF Compared with	Setup	Results	Authors' Conclusion/Most Important Findings	Level of Evidence
Kopman *et al.*,[65] 2003	CR	1	NA	NA	Mivacurium	Tactile TOF fade	AMG used to quantify neuromuscular block in a patient with prolonged duration of action of mivacurium	When no tactile fade was present, AMG TOF was only 0.36	AMG TOF is more sensitive in diagnosing PORC than visual or tactile evaluation of the TOF response	IV
Comments: AMG monitoring was initiated when it was clear that recovery was delayed (tactile count of 4 with fade after reversal). The setup of the AMG is insufficiently described (*i.e.*, stimulation current, fixation, preload, *etc.*).										
Eikermann *et al.*,[62] 2003	N-RCT	12	NA	No	Rocuronium	Respiratory function Muscle function Visual TOF fade	Recording of respiratory and muscle function between TOF 0.5 and 1.0 in nonanesthetized volunteers	Visual TOF fade in only 1 of 12 volunteers, when AMG TOF ratio was around 0.5. To exclude swallowing and drinking difficulties and to have an acceptable recovery of respiratory function, the AMG TOF ratio has to be 1.0. Even then, however, respiratory function may still be impaired	Visual TOF fade or head lift test cannot detect PORC with certainty. AMG TOF 1.0 predicts high probability of adequate recovery	III+
Comments: Primary aim was to test whether AMG predicts effects on respiratory function of residual paralysis. Adequate recovery of the respiratory function was observed in all patients some minutes after TOF 1.0. TOF-Watch® used (calculates the TOF ratio differently; see Historical Background). This may have introduced some bias.										
Debaene *et al.*,[17] 2003	OBS	526	Yes	No	Rocuronium (402) Atracurium (77) Vecuronium (47)	Visual or tactile TOF fade Visual DBS fade Clinical tests	A single ($2 \times ED_{95}$) dose of NMBA. Neuromuscular transmission monitoring was left to the discretion of the anesthesiologist unaware that the neuromuscular function was evaluated in PACU	AMG TOF ratios (0.7 or 0.9) are more sensitive in excluding PORC than tactile evaluation of TOF and DBS responses and clinical tests. However, 10–13% of patients with an AMG TOF ratio >0.9 could not sustain head lift and/or hold a tongue depressor	The use of clinical tests and tactile evaluation of TOF fade do not exclude PORC. AMG is the best method to detect PORC, but even AMG TOF >0.9 does not exclude subtle PORC	IV
Comments: Primary outcome measure was the incidence of PORC after a single $2 \times ED_{95}$ dose of the NMBA. The ulnar nerve was stimulated with 40 mA and reduced if required to reduce pain (*i.e.*, supramaximal stimulation not ensured). TOF-Watch® used (calculates the TOF ratio differently; see Historical Background). This may have introduced some bias.										
Cammu *et al.*,[70] 2003	N-RCT	20	Yes	Yes (4 dropouts)	Rocuronium (infusion)	Clinical criteria	Two groups: blinded or nonblinded AMG monitoring	High incidence of TOF <0.9 at end of surgery. Clinical criteria for extubation were misleading, and one patient was extubated at TOF 0.55	A necessity to use objective neuromuscular monitoring for reasons of safety	III+
Comments: The study was powered to detect a difference in extubation time of 15 min when AMG was used. However, the sample size is probably too small for comparison of the other outcome measures (*e.g.*, TOF at time of extubation, need for reversal, duration from end of surgery to TOF 0.9). Randomization to blinded or not blinded neuromuscular monitoring insufficiently described.										
Eikermann *et al.*,[47] 2004	12	N-RCT	NA	No	Rocuronium (infusion)	MMG TOF Respiratory function	Rocuronium infusion to MMG TOF 0.5–0.8. Respiratory function before NMBA, at TOF 0.5–0.8, and during recovery	AMG TOF ratio predicts effect on respiratory function as valid as MMG TOF ratio. With both methods, a TOF ratio of 0.9–1.0 is associated with adequate recovery of pulmonary function in the vast majority of measurements	An AMG TOF ratio of 0.9–1.0 predicts sufficient recovery as valid as MMG TOF ratio	III++
Comments: (Article is also in tables 2 and 7.) Primary aim was to test which of MMG TOF or AMG TOF allows the most accurate estimation of pulmonary function. Only points relevant for the prediction of sufficient recovery are summarized in this table. Methodologically well performed study. However, sample size was relatively small.										

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Table 4. Continued

Authors	Design	Subjects Included, n	Blind	Description of Dropouts	NMBA	Outcome Measures*/AMG TOF Compared with	Setup	Results	Authors' Conclusion/Most Important Findings	Level of Evidence
Murphy *et al.*,[66] 2004	N-RCT	70	No	Yes (1 dropout)	Pancuronium (35) Rocuronium (34)	Visual symptoms Facial, oral, pharyngeal and general weakness Clinical tests Arterial oxygen saturation	NMBA at induction and for maintenance at T1–T2. AMG TOF before extubation and in PACU × 2. Clinical tests in PACU × 2	Though there was no association between AMG TOF and symptoms of muscle weakness, significant more patients with AMG TOF <0.9 had hypoxemia in PACU	The association between PORC (TOF <0.9) and postoperative hypoxemia indicates that neuromuscular block should be monitored objectively	III−
Comments: Primary aim was to compare the incidence and degree of PORC in patients randomly assigned to receive pancuronium or vecuronium. The use of AMG was not randomized. Therefore, the design is recorded as an N-RCT. The assessors of signs and symptoms of muscle weakness also did the AMG measurement. PORC was defined as the mean of two consecutive, postoperative AMG TOF ratios, without calibration or signal stabilization. Supramaximal stimulation not ensured. All patients were reversed, and AMG TOF was >0.64 in all patients at arrival in the PACU, which might explain why there was no relation between AMG TOF and muscle weakness.										
Samet *et al.*,[50] 2005	N-RCT	40	Yes	Yes (no dropouts)	Cisatracurium	MMG TOF Tactile DBS fade 100-Hz tetanic fade	Calculation of sensitivity, specificity, negative predictive value, and positive predictive value of DBS, AMG TOF, and 100-Hz tetanic fade to detect PORC (*i.e.*, MMG TOF <0.9)	Even a single AMG TOF ratio, without calibration or signal stabilization, performs better than subjective evaluation of DBS and 100-Hz tetanic fade. However, it does not reliably detect shallow degrees of block	AMG TOF is more sensitive in diagnosing PORC than subjective evaluation of DBS and 100-Hz tetanic fade. It is possible from the AMG TOF to reliably predict the time interval until MMG TOF 0.9	III++
Comments: Primary aim was to compare the performance of AMG TOF with DBS and 100-Hz tetanic fade for excluding PORC (*i.e.*, MMG TOF <0.9). (For comparison of AMG with MMG [study 2, n = 25], see table 2). Hand Adapter used as preload. Only one single, postoperative AMG TOF ratio without calibration or signal stabilization was obtained.										
Murphy *et al.*,[67] 2005	N-RCT	120	Yes	No	Rocuronium	Clinical tests TOF fade TET fade	Rocuronium at induction and for maintenance at T1–T2. Reversal. Clinical criteria (including absence of fade to TOF or TET stimulation) for extubation followed by AMG TOF	Despite the use of an intermediate-acting NMBA, visual evaluation of the TOF response, reversal, no fade in TOF or tetanic responses, and the use of relevant clinical tests, 105 of 120 patients had a AMG TOF ratio <0.9 at scheduled time for tracheal extubation	Even careful clinical examinations, no TOF or TET fade, and reversal do not exclude AMG TOF <0.9. To exclude PORC (*i.e.*, AMG TOF <0.9), quantitative monitoring is required	III++
Comments: Primary aim of study was to access the AMG TOF ratios, when full recovery had occurred judged from clinical criteria and peripheral nerve stimulation. Two to four consecutive postoperative AMG TOF ratios, without calibration or signal stabilization, were obtained. Supramaximal stimulation not ensured.										
Capron *et al.*,[45] 2006	N-RCT	32	Yes	Yes (no dropouts)	Rocuronium	Tactile TOF fade DBS fade 50-Hz and 100-Hz tetanic fade MMG TOF	MMG at one hand; AMG or tactile evaluation of TOF, DBS, or tetanic fade at the other hand	To exclude PORC (*i.e.*, MMG TOF <0.9), TOF fade, DBS fade, and TET fade are inadequate. AMG is most reliable to exclude PORC	AMG TOF 1.0 is the best test in excluding PORC	III++
Comments: Primary aim was to compare the performance of AMG TOF with all currently available tests to exclude PORC (*i.e.*, MMG TOF <0.9). (For comparison with MMG, see table 2.) Only points relevant for the comparison to other tests than MMG TOF are summarized in this table. AMG measurements without calibration or signal stabilization were obtained. Supramaximal stimulation not ensured.										
Eikermann *et al.*,[63] 2006	CT	142	NA	Yes (12 dropouts)	Rocuronium Cisatracurium	Inability to swallow Respiratory function	Spirometry before anesthesia, just after tracheal extubation, and 30 min later. Three doses of NMBA. Tracheal extubation at AMG TOF >0.9. Frequency of inability to swallow normally and FVC fade >10%	With a TOF ratio of 0.9, only 2 of 70 pts with UAO had PORC (FVC fade >10%). The negative predictive value of a TOF ratio of 0.9 for absence of PORC-induced UAO was 97%. Four of 70 pts with UAO were unable to swallow normally	AMG TOF 0.9 can be used in clinical practice as an indicator of sufficient neuromuscular recovery. However, persistent effects on upper airway integrity may still occur in some patients	III+
Comments: Primary aim was to determine the frequency of upper airway obstruction after obtaining an AMG TOF ratio of 0.9. Secondary endpoint was to determine how many pts with UAO had PORC. PORC was defined as a decrease in FVC by ≥10% between two spirometric maneuvers. This definition, which is based on another study by the authors, is not generally accepted. Baseline spirometric maneuver was performed after patients received 3.75–7.5 mg midazolam. Many patients (n = 48) were too sedated to perform spirometry after anaesthesia. Setup of AMG is insufficiently described (*i.e.*, calibration, stabilization, supramaximal stimulation).										

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Table 4. Continued

Authors	Design	Subjects Included, n	Blind	Description of Dropouts	NMBA	Outcome Measures*/AMG TOF Compared with	Setup	Results	Authors' Conclusion/Most Important Findings	Level of Evidence
Eikermann *et al.*,[71] 2007	CT	10	No	Yes	Rocuronium	Upper airway function	MRI analysis, force and EMG activity, magnetometers, and pneumotachograph before NMB, at AMG TOF 0.5, 0.8, and 1.0 and 15 min after TOF 1.0	At AMG TOF 1.0, the upper airway function did not differ significantly from baseline. However, 2–4 patients still had impaired upper airway function	AMG TOF 1.0 does not guarantee full recovery of all upper airway muscles. However, all patients had recovered 15 min after TOF 1.0 was reached	III++

Comments: Randomization to left or right hand and randomization of the sequence of MR images insufficiently described. All patients were fully recovered 15 min after AMG TOF 1.0 (*i.e.*, no impaired upper airway function). However, the value of AMG TOF at this time point is not documented.

Samet *et al.*,[50] 2005, applied a preload to AMG. Gätke *et al.*,[69] 2002, Debaene *et al.*,[17] 2003, Cammu *et al.*,[70] 2003, Murphy *et al.*,[66] 2004, Eikermann *et al.*, 2006,[63] and Eikermann *et al.*,[71] 2007, were the only researchers to include a sample size analysis.

* Clinical tests are, for example, sustained head lift for 5 s, sustained hand grip for 5 s, sustained leg lift for 5 s, tongue depressor test, protrusion of tongue, arm lift to opposite shoulder, eye opening.

AMG = acceleromyography; CR = case report; CT = clinical trial; DBS = double-burst stimulation; EMG = electromyography; FVC = forced vital capacity; MMG = mechanomyography; MR = magnetic resonance; MRI = magnetic resonance imaging; NA = not applicable; NMB = neuromuscular block; NMBA = neuromuscular blocking agent; N-RCT = nonrandomized controlled study; OBS = observational study; PACU = postanesthesia care unit; PORC = postoperative residual curarization; pts = patients; RCT = randomized controlled trial; TET = tetanic; TOF = train-of-four; UAO = upper airway obstruction.

Three studies compared posttetanic count values obtained with acceleromyography to those obtained with mechanomyography during deep/intense neuromuscular block.[5,51,52] In all three studies, regression analysis was used and a high correlation was found. However, this analysis is inadequate for this purpose,[5,51] and all three studies were classified as level III−.

Ten studies compared acceleromyography and mechanomyography obtained TOF values during recovery.[1,4–6,45–47,49,51,52] Five of these studies were methodologically sound (level III+), and all concluded that acceleromyography and mechanomyography cannot be used interchangeably.[1,4,45,49,52] Three studies[1,49,52] showed that the bias between the two methods increases during recovery and that it becomes significant at a mechanomyographic TOF ratio of 0.6–0.7 or greater. The limits of agreement between the two methods during recovery are wide, being up to ±0.3 at a mechanomyographic TOF ratio of 0.7.[4,45,49]

Summary Statement. There is fair evidence (grade C) that acceleromyography and mechanomyography cannot be used interchangeably in pharmacodynamic studies measuring onset time or recovery using TOF stimulation. However, there is insufficient evidence to confirm or deny that the two methods can be used interchangeably for monitoring deep/intense neuromuscular block with posttetanic count stimulation.

Group 3: Acceleromyography Compared with Electromyography in Pharmacodynamic Studies

In seven studies, acceleromyography was compared with electromyography for recording pharmacodynamic variables during a surgical procedure.[54–60] We excluded one study because the great toe was used for monitoring.[54] Accordingly, six studies[55–60] were analyzed (table 3).

The primary aim of the studies varied. In three studies,[56,59,60] it was to compare acceleromyography with electromyography; in one,[55] it was to compare the use of acceleromyography with clinical evaluation of recovery; and in one,[58] it was to compare onset times at the laryngeal and adductor pollicis muscles using electromyography with those of the adductor pollicis muscle using acceleromyography. In the last study,[57] the primary aim was to compare the sensitivity of acceleromyography and electromyography with changes in the degree of neuromuscular block and with manipulations of the hand (see Group 5: Methodologic Issues Using Acceleromyography, Stability [Influence of External Disturbances]). Five of the six studies were performed in adults,[42,56–58,60] and one was performed in pediatric patients.[55] Four studies compared acceleromyography and electromyography contralaterally,[55,56,58,60] and two compared the two methods at the same arm.[57,59]

In only one of the six studies was a sample size analysis performed,[59] and in only two were possible dropouts described.[55,57] In the four studies, where the two methods were used contralaterally, possible differences between the arms were not taken into account, and the two methods were not randomized to dominant and nondominant hand.[55,56,58,60] In none of the six studies was the nerve stimulations synchronized. Although a Bland–Altman analysis was performed in four studies, acceptable limits of agreement were not defined, and it was not possible to decide whether the analyses were performed correctly.[55,56,59,60]

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Table 5. Evidence Table for Applying a Preload Installation to AMG

Authors	Subjects Included, n	NMBA	Setup	Outcome Measures	Results	Authors' Conclusion	Level of Evidence
Pelgrims and Vanacker,[72] 2001	13	Rocuronium	No preload *vs.* a preload of 0.5 N contralaterally	T1 20% Max block TOF during recovery	No difference in any recovery parameter when a preload was applied to AMG	Results repeated in the conclusion section	III−
Comments: Sample size relatively small. The preload of 0.5 N and the randomization procedure to the two arms insufficiently described. No stabilization period. Only mean values are compared, and there is no discussion of the results. The conclusion is simply a repetition of the results section.							
Kopman *et al.*,[74] 2002	16	Mivacurium	No preload (n = 8) Rubber band (n = 8)	Control TOF Relation between T1 and TOF during recovery	Control TOF significantly lower with preload (1.10 *vs.* 1.20) No difference in relation between T1 and TOF	None in relation to the use of a preload	III−
Comments: Sample size relatively small (eight patients in each group). No randomization of the preload. Only the size of the rubber band is described, not the elasticity. It is insufficiently documented that the preload did not affect the relation between T1 and TOF. The fact that the control TOF differed in the two groups is not discussed.							
Dubois *et al.*,[46] 2005	20	Rocuronium	No fixation Taping of ulnar fingers Hand Adapter TOF tube (ipsilaterally)	Variability (*i.e.*, SD)	Less variability with TOF tube compared with no fixation or only tape. No difference from Hand Adapter	TOF tube and Hand Adapter reduces variability	III−
				Accuracy (difference from MMG)	TOF tube, Hand Adapter, and tape fixation overestimated the TOF ratio compared with MMG	Highest accuracy without fixation, but the high variability reduces this advantage in clinical practice. TOF tube and to a lesser extent Hand Adapter improved the feasibility	III−
Comments: (This article is also in tables 2 and 7.) Sample size relatively small. Randomization to the two arms and the setup of AMG insufficiently described. Further the AMG setup was changed four times during the study. The initial calibration was therefore lost. For each AMG installation, only four successive TOF measurements were used to estimate "variability" and "accuracy" and compared with simultaneously obtained MMG values from the contralateral arm. "TOF tube" developed by the authors and so far used only by them. A rubber band is used with the TOF tube for reposition of the thumb. However, the characteristics of the rubber band and the TOF tube are insufficiently described. Stabilization period and temperature not documented. Supramaximal stimulation not ensured. The authors' conclusion is not supported by the results.							
Kopman *et al.*,[59] 2005	50	Atracurium	No preload *vs.* preload with rubber band (different patients)	Control TOF	No difference in control TOF with or without a rubber band	Elastic preload does not affect control TOF	III−
				Variability (*i.e.*, SD)	Less variability in control TOF with a rubber band	Elastic preload decreases TOF variability	III−
Comments: (This article is also included in table 3.) TOF stimulation every 15 s for AMG and every 20 s for EMG, ipsilaterally. Supramaximal stimulation ensured with EMG not for AMG. The characteristics of the rubber band insufficiently described. Uncertain how preload affected variability of TOF values in consecutive measurements during recovery.							

AMG = acceleromyography; EMG = electromyography; MMG = mechanomyography; NMBA = neuromuscular blocking agent; TOF = train-of-four.

Two studies[56,58] (both classified as level III+ evidence) stated that onset time does not differ between acceleromyography or electromyography (table 3).

We found no studies comparing acceleromyography with electromyography to monitor deep/intense neuromuscular block.

Three methodologically sound studies compared the TOF during recovery.[55,56,59] In one study[55] (level III+), bias between the two methods did not change during recovery; in two studies,[56,59] the bias did change, but in different directions. Dahaba *et al.*[56] (level III+) found the mean acceleromyographic TOF ratio to be approximately 0.05 higher than the corresponding electromyographic TOF ratio. However, at an electromyographic TOF ratio of 0.5 or greater, the bias was not significant. In contrast, Kopman *et al.*[59] (level III++) found the electromyographic TOF ratio to be 0.6 and 0.85 when the acceleromyographic TOF was 0.7 and 0.9, respectively. All three studies[55,56,59] found wide limits of agreement (*i.e.*, 0.15–0.30) between the two methods during recovery and concluded that the methods cannot be used interchangeably.

Summary Statement. There is fair evidence (grade C) that acceleromyography and electromyography can be used interchangeably for measuring onset times, but also fair evidence (grade C) that the two methods cannot be used interchangeably in pharmacodynamic studies using TOF stimulation. However, there is no evidence to confirm or deny that acceleromyography and electromyography can be used interchangeably to monitor deep or intense block with posttetanic count stimulation.

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Table 6. Evidence Table for Using "Normalizing" (*i.e.*, Refer to Control TOF) TOF Values during Recovery

Authors	Subjects Included, n	NMBA	Setup	Outcome Measures	Results	Authors' Conclusion	Level of Evidence
Capron *et al.*,[53] 2004	30	Atracurium	AMG with preload MMG contralaterally	Negative predictive value of AMG TOF 0.9, 0.95, and 1.0 to detect MMG TOF 0.9	The negative predictive values increased from 40–77% to 89–96% when TOF was referred to control value (normalization)	Normalization improved the detection of PORC (*i.e.*, MMG TOF >0.9)	III+
				Intraclass correlation coefficient for agreement during recovery	Intraclass coefficient increased from 0.73 to 0.84 when TOF was referred to control value (normalization)		
Comments: (Part of the study is also presented in table 2.) Supramaximal stimulation not ensured and peripheral temperature not reported. Hand Adapter used as a preload for AMG. TOF-Watch® S was used. However, the TOF-Watch® S does not display a control TOF above 1.0, as given in this article! One wonders whether TOF-Watch SX was used (for the majority of patients in the uncalibrated group). Otherwise the data do not make sense.							
Kopman *et al.*,[76] 2005 (letter to the editor)	50	Atracurium	AMG with or without preload EMG ipsilaterally	TOF > 0.6 during recovery	Normalization of AMG TOF ratios improved the agreement with EMG but did not eliminate considerable individual differences	Average normalized AMG TOF ratios are not significantly different from average EMG TOF ratios	III+
Comments: (This is a letter to the editor following an article[58] included in table 3.) Normalization of the data was not an original aim of the study. TOF stimulation every 15 s for AMG and every 20 s for EMG, ipsilaterally. Supramaximal stimulation ensured with EMG but not for AMG. The characteristics of the rubber band insufficiently described. Uncertain how the preload affected variability of TOF values in consecutive measurements during recovery. In this letter, the data (with or without preload) are pooled.							
Suzuki *et al.*,[75] 2007	120 (8 dropouts)	Vecuronium	AMG without preload	Time to TOF 0.9	Time to TOF 0.9 significantly longer with normalization (mean, 10.0 min; range, 3.0–26.8 min)	The non-normalized TOF ratio necessary to exclude PORC depends on the control TOF ratio, but most often it exceeds 1.0	III++
Comments: No comparison method. Data compared as "raw data" with "normalized data." Eight dropouts because of "baseline drift." Unclear why this should exclude the patients.							

AMG = acceleromyography; EMG = electromyography; MMG = mechanomyography; NMBA = neuromuscular blocking agent; PORC = postoperative residual curarization; TOF = train-of-four.

Group 4: Clinical Studies Where Acceleromyography Was Compared with Signs, Symptoms, and Tests of PORC

In 16 articles, clinical signs and symptoms of residual block, different lung function tests, or visual or tactile evaluation of the response to nerve stimulation were compared with acceleromyographic TOF response (table 4).[17,45,47,50,55,61–71] In 6 of these 16 studies, either the mechanomyographic or the electromyographic TOF response was used for comparison with the acceleromyographic TOF response or for defining a threshold value (*e.g.*, mechanomyographic TOF ratio ≥0.9) for excluding PORC.[45,47,50,55,68,69] In 9 studies, the primary aim was to compare the acceleromyographic TOF response with other tests, including tests of respiratory function,[45,47,50,55,62,63,65,67,71] and in 4, it was to determine the incidence of PORC after routine use of different neuromuscular blocking agents.[17,61,64,66] The last 3 studies evaluated the significance of perioperative use of acceleromyography for PORC.[68–70] All but 1 study[55] were performed in adults. Except for 3 studies performed in volunteers,[47,62,71] all were performed in surgical patients.[17,45,50,55,61,63–70]

In two studies (level II+), the patients were randomly assigned to be monitored with or without acceleromyography perioperatively.[68,69] Both studies concluded that perioperative use of acceleromyography prevents PORC (*i.e.*, mechanomyographic TOF ratio ≥0.7) and is superior to clinical tests. Seven studies compared visual or tactile fade in response to TOF, double-burst, and tetanic stimulation with acceleromyographic TOF monitoring.[17,45,50,55,62,65,67] All seven studies (level III++ to IV) showed that acceleromyographic TOF was superior to visual and tactile evaluation of fade in excluding PORC. Visual and tactile fade were absent at TOF ratios as low as less than 0.4.[17,45,50,55,65] Even if the block was reversed, acceleromyography was superior to clinical tests and tactile fade in excluding PORC.[61,65] Seven studies (level II+ to IV) consistently found acceleromyography to be superior to the "reliable" clinical tests[8] (*e.g.*, 5-s head lift).[17,61,62,64,67,68,70] Four studies examined the relation between acceleromyography and respiratory function, swallowing, and upper airway function.[47,62,63,71] Three studies (level III+ to III++) indicated that an acceleromyographic TOF ratio of 0.9–1.0 could be used in clinical practice to exclude PORC.[47,62,63] One study[47] (level III++) found acceleromyography to be as valid as mechanomyography to predict PORC (*i.e.*, recovery of pulmonary function). However, a recent, very well-performed and well-documented study (level III++) indicated that full recovery (after rocuronium) is only guaranteed 15 min after acceleromyographic TOF 1.0 is reached.[71]

Summary Statement. There is good evidence (grade A) that acceleromyography is more sensitive in diagnosing PORC than both of the usually applied clinical tests, and good evidence (grade B) that acceleromyography is more sensitive than subjective (visual or tactile) evaluation of the evoked response to TOF, double-burst, or 50-Hz tetanic stimulation. Also, there is good evidence

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Table 7. Evidence Table for Evaluating the Precision of AMG

Authors	Subjects Included, n	NMBA	Setup	Precision Defined as	Results	Authors' Conclusion	Level of Evidence
May *et al.*,[77] 1988	6	Atracurium	AMG without preload MMG contralaterally	Analysis of variance applied to the regressions on time during recovery in respect of both T1 and TOF readings	AMG did not differ from MMG with respect to precision	AMG is equal to MMG with regard to precision	III−
Comments: Insufficient sample size. Stabilization period and temperature not documented. In the figures, only few data points are presented, and it is not explained how these data points were selected.							
Eikermann *et al.*,[47] 2004	12	Rocuronium (infusion)	AMG without preload MMG contralaterally	Variability in 20 consecutive TOF measurements	Variability of AMG TOF exceeds that of MMG TOF	Reliability of AMG was less compared with MMG	III+
Comments: (This article is also included in tables 2 and 4. Therefore, only points relevant for the precision are summarized in this table.) Sample size relatively small. Randomization to left and right hand insufficiently described. Temperature not documented. Precision measured during 5 min of TOF stimulation in nonanesthetized volunteers.							
Dubois *et al.*,[46] 2005	20	Rocuronium	AMG without and with preload (TOF tube or Hand Adapter) MMG contralaterally	Variability in 4 consecutive TOF measurements	Significantly higher variability with AMG than with MMG	AMG without preload has a wide variability and also numerous failed measurements. Use of a preload reduces variability	III−
Comments: (This study is also included in tables 2 and 5.) Sample size relatively small. Randomization to the two arms and the setup of AMG insufficiently described. The AMG setup was changed four times during the study. The initial calibration was therefore lost. Stabilization period and temperature not documented. Supramaximal stimulation not ensured. Only four successive measurements in every patient for estimation of the variability.							
Baillard *et al.*,[78] 2004	253	Rocuronium Vecuronium Atracurium	AMG TOF in PACU	Absolute average difference in 2 consecutive TOF measurements	The precision was only 15 ± 17%	AMG as used in this study does not always provide precise TOF measurements	III+
Comments: Supramaximal stimulation not ensured. Only two consecutive TOF measurements in awake patients. TOF-Watch® used, which cannot display TOF above 100% (see Historical Background). However, TOF values above 100% are given: One wonders whether TOF-Watch® SX was used in all patients or in some.							
Dubois *et al.*,[79] 2005	20	Rocuronium	AMG without preload	Absolute average difference in 2 consecutive TOF measurements	The precision was 2.1 ± 2.5%	Less variability of AMG when used before emergence from anesthesia	III+
Comments: This study was reported as a letter to the editor in response to the study by Baillard *et al.*,[77] 2004. Sample size relatively small. Supramaximal stimulation not ensured. Only two consecutive TOF measurements in anesthetized patients. TOF ranging from 0.6 to 1.0, but it is not documented how many of the patients were relaxed at the time of measurements or whether the neuromuscular block was reversed in some patients.							

AMG = acceleromyography; EMG = electromyography; MMG = mechanomyography; NMBA = neuromuscular blocking agent; PACU = postanesthesia care unit; TOF = train-of-four.

(grade A) that perioperative monitoring with acceleromyography improves detection of PORC, and that acceleromyography is as useful as mechanomyography in this respect (grade B). However, the evidence is insufficient to decide whether the uncorrected (not normalized) acceleromyographic TOF ratio should be 0.9, 1.0, or even higher to exclude clinically significant PORC.

Group 5: Methodologic Issues Using Acceleromyography

Preload. We found five studies (table 5) evaluating the effect of using a preload.[46,59,72–74] One of the studies[73] was excluded, because acceleromyography with a prototype of a preload (TOF tube) was validated using acceleromyography with TOF-Watch® arm board with an insufficiently described rubber band as the comparison method (gold standard). The four other studies[46,59,72,74] tested different preloads in a research setting. However, the characteristics of the preloads were insufficiently described, and all four studies were assigned level III− (table 6).

Summary Statement. There is insufficient evidence to confirm or deny the benefit of using a preload when acceleromyography is used.

Control TOF Ratio. Most studies (level III− to III++) have found that the control TOF ratio typically is higher than unity when acceleromyography is used,[1,4–6,40,41,49,52,53,56,59,73–75] but with large individual differences (0.92 to 1.47). Six studies, each including a control group monitored with either mechanomyography or electromyography (level III++), have documented that the control acceleromyographic TOF ratio is higher than unity when a preload is not used (mean values 1.08–1.16),[1,4,41,49,56,59] and significantly higher than both control mechanomyography TOF ratio (0.98–1.01)[1,4,49] and control electromyographic TOF ratio (1.01)[41,56,59] (tables 2 and 3).

It is uncertain how a preload will affect the control TOF (table 5). Probably because of different preload installations, the same research group found conflicting results in two studies: In one[59] (level III−), there was no significant difference in control acceleromyo-

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Table 8. Summary of Evidence for Using AMG for Monitoring Neuromuscular Block

	Statement	Strength of Evidence
Pharmacodynamics		
Dose–response relation	There is insufficient evidence that AMG can be used interchangeably with MMG or EMG for establishing dose–response relation	
Control TOF	AMG control TOF is most often higher than unity and significantly higher than MMG and EMG control TOF	B
Onset time	AMG cannot be used interchangeably with MMG for recording onset times	C
	AMG can be used interchangeably with EMG for recording onset times	C
Intense/deep block	There is insufficient evidence that AMG can be used interchangeably with MMG or EMG for evaluating deep and intense block	
Recovery	AMG cannot be used interchangeably with MMG or EMG for recording of recovery using TOF stimulation	C
PORC	AMG is more sensitive in diagnosing PORC than	
	• usually applied clinically tests	A
	• visual or tactile fade, independent of stimulation pattern	B
	AMG used perioperatively improves detection of PORC	A
	AMG is as effective as MMG in excluding PORC*	B
Methodologic issues		
Stability	AMG T1 is more sensitive to external disturbances than EMG T1	C
Baseline drift	AMG is more prone to baseline drift than MMG	C
Precision	There is insufficient evidence that the precision of AMG differs from that of MMG or EMG	
Preload	There is insufficient evidence that applying a preload to AMG will	
	• influence TOF ratio	
	• change the precision	
Normalization	AMG TOF values approach MMG TOF values when AMG TOF is "normalized"	C

* The evidence is insufficient to decide whether the uncorrected (not normalized) acceleromyography (AMG) train-of-four (TOF) ratio should be 0.9, 1.0, or even higher to exclude postoperative residual curarization (PORC).

EMG = electromyography; MMG = mechanomyography.

graphic TOF ratio when using a preload; in another[74] (level III−), preload decreased the control TOF significantly.

Summary Statement. There is good evidence that the control acceleromyographic TOF ratio without a preload most often is higher than unity (grade B) and significantly higher than both control mechanomyographic and electromyographic TOF ratios (grade B). However, there is also evidence that the control acceleromyographic TOF does not always exceed unity (grade B). There is insufficient evidence to confirm or deny that the use of a preload will influence the control acceleromyographic TOF ratio.

Normalization. Three studies[53,75,76] examined the effect of normalizing TOF values (table 6). The two studies (level III+) comparing acceleromyography with mechanomyography[53] or electromyography[76] showed an improved agreement between acceleromyography and the comparison method when the acceleromyographic TOF response was normalized. However, there were still wide individual differences. In the third study[75] (level III++), recovery to TOF 0.9 was compared for normalized and raw TOF values, without a comparison method. The time to TOF 0.9 after 0.1 mg/kg vecuronium was significantly longer when acceleromyographic TOF response was normalized as compared with the raw values (mean, 10.0 min; range, 3.0–26.8 min).

Summary Statement. There is fair evidence (grade C) that it is beneficial to normalize acceleromyographic TOF values if the aim is to ensure a mechanomyographic TOF ratio of 0.90, but consequently, the duration of time to TOF 0.9 will be prolonged (grade B).

However, there is also fair evidence that because of wide individual differences even when acceleromyographic TOF values are normalized, acceleromyography cannot be used interchangeably with mechanomyography and electromyography (grade C).

Precision. Five studies[46,47,77–79] dealt with the precision (the repeatability or variability) of acceleromyography (table 7), and in only three[46,47,77] was a control group (*i.e.*, mechanomyography) included. Two of these[46,77] were assigned level III−. In the study by Eikermann *et al.* [47] (level III+), the precision was defined as the variance in 20 consecutive TOF measurements, and the variability of acceleromyographic TOF exceeded mechanomyographic TOF. However, the study was performed in awake, partially paralyzed (TOF 0.5–0.8) volunteers, and it is uncertain whether the variability would be the same at all levels of block and in anesthetized patients. In the two studies[78,79] (level III+) without a control group, the repeatability between two succeeding acceleromyographic TOF responses was evaluated. The study by Baillard *et al.*[78] was performed in awake patients in the postoperative care unit stimulated sub-

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maximally, known to decrease the precision.[80,81] The study by Dubois *et al.*[79] was reported as a letter to the editor in response to the study by Baillard *et al.*[78] Dubois *et al.*[79] measured the response to nerve stimulation (supramaximal stimulation not ensured) in patients before emergence from anesthesia. Not surprisingly, Dubois *et al.*[79] found a somewhat better precision compared with the study by Baillard *et al.*[78] when the assessment was performed during anesthesia. However, it is not possible to draw any conclusions regarding the precision of acceleromyography in general from only two consecutive measurements.

Summary Statement. There is insufficient evidence to confirm or deny that the precision of acceleromyography differs from that of mechanomyography and electromyography, or whether the application of a preload will increase the precision of acceleromyography.

Baseline Drift. In only one study[4] (classified as level III+) was the magnitude of drift in T1 compared when using mechanomyography and acceleromyography (table 2). The drift was significantly more pronounced with acceleromyography than with mechanomyography: The mean final acceleromyographic T1 was 20.6% lower than control acceleromyographic T1 (range, −54% to 0), as opposed to only 5.7% (range, −37% to +12.5%) with mechanomyography. In another study,[82] the magnitude of drift in acceleromyography was only −7% (range, −18% to +8%), but the study did not compare acceleromyography with mechanomyography.

Summary Statement. There is fair evidence (grade C) that baseline drift in twitch height is more pronounced with acceleromyography than with mechanomyography, the final value often being lower than the control value.

Stability (Influence of External Disturbances). We found only one study[57] (level III+) comparing the stability of acceleromyographic twitch height (without a preload) and electromyography when the infusion rate of the neuromuscular blocking agent was changed and the hand turned 90° (table 3). The study showed that acceleromyography was significantly more sensitive to hand movements than electromyography. The mean acceleromyographic T1 decreased 10.01% as compared with only 0.26% with electromyographic T1. However, the results may not apply to monitoring using TOF stimulation.

Summary Statement. There is fair evidence that acceleromyographic twitch height without preload is more sensitive to external disturbances than electromyography (grade C).

Strength of Evidence

The current evidence for using acceleromyography for monitoring neuromuscular block and to exclude PORC is summarized in table 8.

Discussion

The three main findings of this systematic review are as follows: First, there is insufficient evidence to confirm or deny that acceleromyography can be used interchangeably with mechanomyography or electromyography for constructing dose–response relation. Second, there is good evidence that acceleromyography cannot be used interchangeably with mechanomyography or electromyography in pharmacodynamic studies. Third, there is good evidence that perioperative monitoring with acceleromyography improves detection of PORC and in this respect is more sensitive than any of the usually applied clinical tests and than subjective visual or tactile evaluation of the response to nerve stimulation.

We have strived to find and evaluate available evidence about the use of acceleromyography for monitoring neuromuscular block. To achieve this goal, two key questions were formulated: Does the use of acceleromyography produce results that differ from those obtained using mechanomyography and electromyography, and what is the relation between the acceleromyographic TOF response and signs, symptoms, and tests of residual block? However, we soon realized that we were facing problems in evaluating relevant studies with respect to these questions. Not only were the studies extremely heterogeneous with respect to aims, methods, and quality, but also we could not rely solely on known quality rating systems designed to evaluate randomized controlled trials, such as Jadad *et al.*[83] The Jadad scale is one of the most cited and validated scales to access the quality of randomized controlled trials. However, the scale consists of only three items directly related to control the bias: randomization, blinding, and withdrawals and dropouts. Obviously, the scale gives more weight to the reporting than the methodologic quality. Actually, the scale does not allow division of trials into "high"- and "low"-quality studies.[84] The methodologic problems connected with the use of the three different recording systems (acceleromyography, mechanomyography, and electromyography) and not least with comparisons of the systems are quite extensive, and handled differently and often apparently incorrectly in the studies. Based on and inspired by MERGE,[31] SIGN 50,[32,33] Good Clinical Research Practice in pharmacodynamic studies of neuromuscular blocking agents,[37] the CONSORT Statement,[35,36] and our own experiences, we therefore designed checklists for evaluation of the quality of the studies (appendix 2). We then used these checklists to quality rate each article and summarize the evidence for the use of acceleromyography. We recognize that these checklists have not been validated. However, we constructed them using both the CONSORT Statement,[35,36] which is an evidence-based but more comprehensive approach of reporting randomized controlled studies than the Jadad scale,[83] and Good Clinical Research Prac-

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tice in pharmacodynamic studies of neuromuscular blocking agents,[37] which consists of guidelines made to improve the methodologic quality in neuromuscular research. Our assessment approach involves a degree of subjective judgment, and although we based our quality rating on MERGE and SIGN 50, these methods are more comprehensive than used in this study, including a multidisciplinary guideline development group of 15–25 members. These limitations may have introduced bias and influenced our conclusions. Nevertheless, it is our hope that the checklists and the level of evidence tables makes it clear for the reader how we reached our conclusions. Because we were familiar with most of the articles before starting the systematic review, it was not possible to blind the evaluation of the studies.

To minimize bias, we made a comprehensive search strategy not limited to English-language articles. From the title and abstract, we discovered nine articles[85–93] not written in English (*i.e.*, seven other languages) that seemed to evaluate acceleromyography. Although these nine articles were not translated, we found nothing in the abstracts indicating that the results would change our conclusions of this review. We therefore decided not to have them translated and further evaluated. Of course, theoretically, this could lead to a language bias. On the other hand, lower quality of trials not published in English may also introduce bias.[94]

At first glance, our finding that acceleromyography cannot be used interchangeably with mechanomyography or electromyography in pharmacodynamic studies may seem surprising. According to Newton's second law of motion, stating that force equals mass times acceleration, acceleromyography should be interchangeable with mechanomyography if the mass (in this case the mass of the thumb) is constant. In theory, electromyography should also be in agreement with acceleromyography, because it measures the compound action potential from many motor units.[56] However, in contrast to mechanomyography and electromyography, the isotonic contractions during acceleromyography monitoring involve a three-dimensional movement involving three joints, frictional forces, and deformation of tissues, which may at least in part explain the differences.[52]

Of the 19 studies comparing acceleromyography with mechanomyography (table 2) or electromyography (table 3), 11 used the method described by Bland and Altman.[4,6,40–42,45,47,49,55,56,60] However, in none of these studies was the method used according to the original suggestions of Bland and Altman.[38,39] This is not only a problem when comparing acceleromyography with mechanomyography or electromyography. It is also commonly seen when other measurement methods are compared.[95] Therefore, the latest version of Good Clinical Research Practice in pharmacodynamic studies of neuromuscular blocking agents now includes suggestions for statistical evaluation when comparing different measurement techinques.[37]

It is a prerequisite for acceleromyography that the thumb is allowed to move and for isometric mechanomyography that a preload of 200–300 g is applied.[37] It is therefore not possible to compare acceleromyography with isometric mechanomyography at the same arm. Accordingly, in all studies, acceleromyography and mechanomyography were tested on contralateral arms. Also, in the majority of studies comparing acceleromyography with electromyography, the two techniques were tested on contralateral arms. Surprisingly, only two studies[49,52] took into account possible differences between the two arms. Furthermore, the stimulation frequency, the stabilization period, the electrical charge delivered (*i.e.*, supramaximal stimulation), and the peripheral temperatures were often insufficiently documented, or performed differently on the two arms.

When acceleromyography was first introduced, it was considered a prerequisite that the thumb could move freely.[1] However, it is not always possible to avoid the thumb touching the palm of the hand or the drapes during monitoring, and the thumb may be displaced to a new position during the stimulation.[96] It was therefore suggested to use a preload, and in two of the early articles on acceleromyography, an elastic band between the thumb and the index finger was used.[48,52] Since then, five other studies[46,47,77–79] have evaluated the use of a preload. However, different preloads were used in the different studies, and the characteristics of the preload were most often insufficiently described, making it difficult to generalize the findings. The manufacturer of the commercially available TOF-Watch®, Organon, also produces a commercially available and simple preload (Hand Adapter), which is now being used also in research.[50,53,97–99] However, it should be kept in mind that the Hand Adapter has never been sufficiently validated, and as shown in this review, there is insufficient evidence that a preload applied to acceleromyography will improve agreement with mechanomyography (or electromyography) or increase the precision.

Evaluation of precision of acceleromyography was performed differently in the five studies[46,47,77–79] dealing with precision (table 7). Because the degree of neuromuscular block changes during recovery (even in two consecutive measurements), it is a challenge to establish the precision of the measurements. This is most probably the reason why different approaches for evaluating the precision were chosen in the studies and why there is insufficient evidence to state which method (acceleromyography, electromyography, or mechanomyography) is the most precise method.

The control acceleromyographic TOF value, in contrast to mechanomyographic and electromyographic TOF, is most often higher than unity. To reduce the bias between the TOF ratios measured using acceleromyogra-

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phy, mechanomyography, or electromyography, it has therefore been suggested to refer all acceleromyographic TOF values to the baseline control value. If, for example, the acceleromyographic TOF ratio is 1.20 before injection of a neuromuscular blocking agent, a displayed TOF value of 0.90 during recovery corresponds to a "normalized" TOF of only 0.75 (90/120).[74,100] When normalized in this way, the mean acceleromyographic TOF values are comparable to those obtained using mechanomyography or electromyography. Therefore, if at the end of a study using acceleromyography the aim is to ensure a mechanomyographic TOF ratio of 0.9, it seems reasonable to "normalize" the acceleromyographic TOF to exclude PORC (using the aforementioned example, acceleromyographic TOF should be 90% of 1.20 = 1.08). Because the acceleromyographic control TOF is most often higher than unity, the time to TOF 0.9 will of course be longer,[75] and even with normalization the individual differences between acceleromyography and mechanomyography/electromyography are large.[53,76] So far, there is no consensus on whether to normalize acceleromyographic TOF values,[37] but studies with only normalized TOF data have been published.[101]

The majority of articles where acceleromyography was compared with signs, symptoms, and tests of PORC (table 4) were judged to have a low or very low risk of bias (appendix 3). Accordingly, the evidence was comparatively strong (grade A or B) for the statements regarding this part of our review (table 8). However, at least one of our statements is at variance with the finding of a recent meta-analysis of the effect of perioperative monitoring of neuromuscular function on the incidence of PORC.[13] We found strong evidence (grade A) that acceleromyography improves detection of PORC (table 8). In contrast, the authors of the meta-analysis "could not demonstrate that the use of an intraoperative neuromuscular function monitor decreased the incidence of PORC."[13] This apparent discrepancy between the findings of our broad systematic review of acceleromyography for use in scientific and clinical practice and the more focused meta-analysis of the significance of neuromuscular monitoring for PORC may be explained by the differences in methodologies. The meta-analysis by Naguib *et al.*[13] included both comparative and noncomparative studies and did not—at least in the original publication—distinguish between objective and subjective monitoring. It is to be expected, however, that the incidence of PORC will depend on whether the monitoring is objective or subjective,[102] and our review is only concerned with the effect of using acceleromyography. Accordingly, we included and meticulously evaluated the quality of only prospective comparative studies, where acceleromyography was used for this purpose. Of note, of 24 studies included in the meta-analysis of Naguib *et al.*, only five used objective monitoring, and all five concluded that objective monitoring improves the detection of PORC.[68,69,103–105]

Significance of Findings

Where do the findings of this review leave us with respect to the use of acceleromyography in research and in daily practice?

First, it is important to realize that absence of evidence or insufficient evidence for a given claim does not necessarily indicate that the claim is not true. Evidence may lack because of lack of studies or because of insufficient design of studies actually performed.

Second, we have sought rigorously and systematically to evaluate acceleromyography for use in research as well as in the clinical setting, when possible based on studies comparing acceleromyography with the more established methods, mechanomyography and electromyography. However, neither mechanomyography nor electromyography has been validated systematically in the same way, nor has the precision of the two methods been established with certainty. And as stressed by Bland and Altman,[39] if the precision of a comparison method (*e.g.*, mechanomyography) is poor, the agreement between the two methods will be poor as well.

Acceleromyography for Use in Research. The most important consequence of finding insufficient or no evidence for use of acceleromyography interchangeably with mechanomyography or electromyography for measuring a given variable is of course that results obtained using acceleromyography cannot directly be compared with those obtained using one of the other methods. This implies that practically all results obtained so far using acceleromyography in dose-finding studies and pharmacodynamic studies measuring onset times, duration of action, recovery times, *etc.* cannot and should not be compared directly with previous studies performed using mechanomyography or electromyography (with the exception of onset times measured using electromyography, where the evidence is fair for using the methods interchangeably). It is not possible to make any general statement about the significance of these differences in results obtained using acceleromyography, mechanomyography, and electromyography. The magnitude of differences—and thus the clinical significance—depends on several factors, *e.g.*, the neuromuscular blocking agent and the outcome measurements in question. When investigating a long-acting neuromuscular blocking agent, the difference in time to TOF 0.9 most probably will be both statistically and clinically highly significant. In contrast, when measuring, for example, onset time or time to

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reappearance of the first twitch when using a rapid-onset and ultrashort-acting agent, the differences between the methods are less pronounced and therefore of less clinical significance.

The new reversal agent sugammadex has gone through phase 1 and 2 studies using acceleromyography to evaluate the dose–response relation.[27–29] Apparently, acceleromyography was chosen because electromyography and mechanomyography monitors were no longer manufactured, and the simpler method of acceleromyography was widely used in the clinical setting.[27,28] Therefore, acceleromyography could be used in a large number of test sites with little previous neuromuscular expertise. Another argument was that the slope of the recovery curve after sugammadex reversal is very steep, and accordingly, the differences between the various techniques would be a matter of seconds rather than minutes.[28] Though not based on evidence, the new Good Clinical Research Practice in pharmacodynamic studies of neuromuscular blocking agents guidelines[37] do allow acceleromyography to be used in phase 1 and 2 studies. However, again it should be remembered that results obtained using acceleromyography varies from those obtained using mechanomyography or electromyography.

Acceleromyography for Use in Daily Practice. Judging from the increasing number of publications in recent years, acceleromyography is increasingly being used in the clinical setting for titrating muscle relaxants and their antagonists. This review documents that the evidence for this is good. There is good evidence that acceleromyography is better than usually applied clinical tests and subjective evaluation of evoked responses in preventing PORC.

An important question remains: What acceleromyography TOF ratio is necessary to exclude clinically significant PORC? Though with insufficient evidence, three studies[1,49,52] convincingly indicate that the bias between acceleromyography and mechanomyography increases during recovery and that it becomes significant at a mechanomyographic TOF ratio of 0.70 or greater. The current generally accepted threshold for exclusion of PORC is a mechanomyographic TOF 0.9.[8] Samet *et al.*[50] showed that the mean time interval from an acceleromyographic TOF 0.9 to a mechanomyographic TOF 0.9 was 4 min during recovery from cisatracurium, but two studies indicate insufficient recovery with an acceleromyographic TOF ratio of 0.9–1.0.[17,62] However, when acceleromyographic and mechanomyographic responses are related to pulmonary function, both methods predict sufficient recovery equally at TOF 0.9–1.0,[47] and the negative predictive value of one acceleromyographic TOF ratio of 0.9 for absence of PORC-induced upper airway obstruction is 97%.[63] Under the assumption that acceleromyographic TOF is approximately 10% higher than mechanomyography, an acceleromyographic TOF value of 1.0 should be aimed at. However, one study[71] indicated that sufficient recovery after rocuronium is only guaranteed approximately 15 min after acceleromyographic TOF 1.0 is reached. The problem is probably that there is a great individual variation in control acceleromyographic TOF. In accord with other investigators, Suzuki *et al.*[75] found control TOF to be 0.95–1.47. If baseline control TOF is below 1.0, it may be impossible to reach 1.0 during recovery. Furthermore, sufficient recovery may not be reached even 15 min after TOF 1.0 if the control TOF was approximately 1.4. Normalization of TOF values may be the solution to improve the detection of PORC. However, clinicians may not always know the baseline control TOF. In addition, the simplicity of the automatic calculated TOF ratio is lost, and the applicability of the method is more difficult.

An alternative approach is used in two acceleromyograph models (TOF-Watch® and TOF-Watch® S) intended for use in the daily clinic.[7] These monitors automatically change the way the TOF ratio is calculated, ensuring that the displayed TOF value never exceeds 100%. By definition, the TOF ratio is the height of the fourth twitch divided by the height of the first twitch in the TOF response. However, when neuromuscular recovery is nearly complete, the second and often subsequent acceleromyographic responses may exceed the first (T1). When this occurs, the TOF-Watch® (S) monitors display the T4/T2 rather than the T4/T1 ratio. Further, if this ratio is above 1.0, the monitor will limit the display to 100%.[7] Because T2 rarely exceeds T1 until the uncorrected TOF ratio is 0.90 or greater, these units will most likely not suggest adequate recovery more falsely than TOF Watch® SX.[7] Although this algorithm has not been validated for use in the research setting, it seems to be a sensible approach in the clinical setting.

Conclusion

This systematic review documents that the evidence for clinical use of acceleromyography is good, because acceleromyography is better in detecting PORC than usually applied clinical tests and subjective evaluation of evoked responses. Acceleromyography is now also being used not only in phase 3 and 4 studies but also in early phase 1 and 2 studies, and for constructing dose–response relation.[23,28] However, the current evidence is insufficient to support the use of acceleromyography interchangeably with mechanomyography or electromyography for these purposes.

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Although the evidence is insufficient, studies do indicate that it may be beneficial to use a preload to increase the precision of acceleromyography. However, there is currently insufficient evidence to support routine use of a preload and only fair evidence for the use of normalization of the TOF ratio whenever acceleromyography is used.

Finally, it seems from this systematic review that there is a need for well-designed, sufficiently powered, randomized controlled trials comparing acceleromyography with mechanomyography and electromyography with respect to applicability, precision, and accuracy (bias and limits of agreement), and for studies evaluating which of the methods is more applicable, precise, and accurate to predict clinically relevant endpoints.

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Appendix 1: Sequence of Events in Evaluating the Evidence

Step 1: Formulation of key questions
Step 2: Search Strategy to identify possible relevant studies
Step 3: Inclusion and exclusion criteria to select studies to be included
Step 4: Dividing of the studies into five groups, according to relevance for the key questions
Step 5: Criteria used to assess the quality of the included studies (appendices 2 and 3)
Step 6: Evidence tables based on study type and quality assessment (tables 1–7)
Step 7: Considered judgment/summary statement about level of evidence (appendix 4)
Step 8: Strength of evidence (appendix 5; table 8)

Appendix 2: Checklist Used for Evaluation of Individual Articles

Section 1: Quality Parameters Used in Evaluation of All Articles

1.1. Does the study address an appropriate and clearly focused question (*i.e.*, hypothesis, primary and secondary aims)?
1.2. Are relevant outcome measures collected in a standardized, valid, and reliable way?
1.3. Is the only relevant difference between groups the recording method (acceleromyography, electromyography, or mechanomyography)?
1.4. Are the statistical methods used for the data analyses appropriate and correctly and sufficiently reported?
1.5. Is the number of patients included sufficient? (Ideally, was the necessary sample size estimated beforehand, or was a power analysis performed *post hoc*?)
1.6. Are numbers and reasons for dropouts and/or missing data described?
1.7. When relevant:
  1.7.1. Is the method for randomization adequate (adequate allocation concealment)?
  1.7.2. Is the method of data collection blind?

Section 2: Quality Parameters Used in Evaluation of the Recording Methods (Acceleromyography, Electromyography, or Mechanomyography)

2.1. Were the electrodes used and the setup procedure appropriate and sufficiently reported?
2.2. Was supramaximal stimulation ensured and sufficiently reported?
2.3. Was the initial signal stabilization sufficient?
2.4. Was the twitch height (T1) referred to a final value at the end of the procedure?
2.5. Were the stimulations applied simultaneously and with the same frequency with the two methods?
2.6. Were the peripheral and central temperature kept constant and above 32° and 36°C, respectively?

Appendix 3: Quality Rating for Individual Studies[32,33]

Risk of Bias	Rating	Overall Assessment
Very low risk of bias	++	Applies if all or most criteria from the checklist are fulfilled; where criteria are not fulfilled, the conclusions of the study or review are thought very unlikely to alter.
Low risk of bias	+	Applies if some of the criteria from the checklist are fulfilled; where criteria are not fulfilled or are not adequately described, the conclusions of the study or review are thought unlikely to alter.
High risk of bias	−	Applies if few or no criteria from the checklist are fulfilled; where criteria are not fulfilled or are not adequately described, the conclusions of the study or review are thought likely or very likely to alter.

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Appendix 4: Levels of Evidence of Individual Studies According to Source of Evidence and Quality Rating[31]

Source of Evidence	Level of Evidence	Quality Rating	Risk of Bias
Systematic reviews of all relevant randomized controlled trials; large multicentre randomized controlled trials	I	++ +	Very low Low
Randomized controlled trials	II	++ +	Very low Low
Controlled trials without randomization; cohorts; case–control analytic studies	III	++ +	Very low Low
Other observational studies	IV		
Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	V		

Appendix 5: Grades of Recommendation[31–33]

A	At least one meta-analysis, systematic review, or RCT rated as I++ or II++, and directly applicable in the perioperative setting; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as I+ or II+, directly applicable in the perioperative setting, and demonstrating overall consistency of results
B	A body of evidence including studies rated as III++ directly applicable in the perioperative setting and demonstrating overall consistency of results; or extrapolated evidence from studies rated as I++, I+, II++, or II+
C	A body of evidence including studies rated as III+ directly applicable in the perioperative setting and demonstrating overall consistency of results; or extrapolated evidence from studies rated as III++
D	Evidence level IV or V; or extrapolated evidence from studies rated as III+

If the evidence is insufficient or lacking, no recommendation is made.

RCT = randomized controlled trial.

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