

Can Acceleromyography Detect Low Levels of Residual Paralysis?

A Probability Approach to Detect a Mechanomyographic Train-of-four Ratio of 0.9

Florent Capron, M.D.,* Francois Alla, M.D.,† Claire Hottier, M.D.,* Claude Meistelman, M.D.,‡ Thomas Fuchs-Buder, M.D.§

Background: The incidence of residual paralysis, *i.e.*, a mechanomyographic train-of-four (TOF) ratio (T4/T1) less than 0.9, remains frequent. Routine acceleromyography has been proposed to detect residual paralysis in clinical practice. Although acceleromyographic data are easy to obtain, they differ from mechanomyographic data, with which they are not interchangeable. The current study aimed to determine (1) the acceleromyographic TOF ratio that detects residual paralysis with a 95% probability, and (2) the impact of calibration and normalization on this predictive acceleromyographic value.

Methods: In 60 patients, recovery from neuromuscular block was assessed simultaneously with mechanomyography and acceleromyography. To obtain calibrated acceleromyographic TOF ratios in group A, the implemented calibration modulus 2 was activated in the TOF-Watch S®; to obtain uncalibrated acceleromyographic TOF ratios in group B, the current was manually set at 50 mA ($n = 30$ for each). In addition, data in group B were normalized (*i.e.*, dividing the final TOF ratio by the baseline value). The agreement between mechanomyography and acceleromyography was assessed by calculating the intraclass correlation coefficient. Negative predictive values were calculated for detecting residual paralysis from acceleromyographic TOFs of 0.9, 0.95, and 1.0.

Results: *Group A:* For a mechanomyographic TOF of 0.9 or greater, the corresponding acceleromyographic TOF was 0.95 (range, 0.86–1.0), and the negative predictive values for acceleromyographic TOFs of 0.9, 0.95, and 1.0 were 37% (95% CI, 20–56%), 70% (95% CI, 51–85%), and 97% (95% CI, 83–100%), respectively. *Group B:* Without normalization, an acceleromyographic TOF of 0.97 (range, 0.68–1.18) corresponded to a mechanomyographic TOF of 0.9 or greater, with negative predictive values for acceleromyographic TOFs of 0.9, 0.95, and 1.0 being 40% (95% CI, 23–59%), 60% (95% CI, 41–77%), and 77% (95% CI, 58–90%), respectively. After normalization, an acceleromyographic TOF of 0.89 (range, 0.63–1.06) corresponded to a mechanomyographic TOF of 0.9 or greater, and the negative predictive values of acceleromyographic TOFs of 0.9, 0.95, and 1.0 were 89% (95% CI, 70–98%), 92% (95% CI, 75–99%), and 96% (95% CI, 80–100%), respectively.

Conclusion: To exclude residual paralysis reliably when using acceleromyography, TOF recovery to 1.0 is mandatory.

FOR many years, a train-of-four (TOF) ratio greater than 0.7, when measured by mechanomyography at the ad-

ductor pollicis, was considered synonymous with adequate neuromuscular recovery.¹ However, recent studies on the consequences of residual neuromuscular blockade have suggested that more rigorous criteria are needed for determining the adequacy of neuromuscular recovery. A large outcome study from Scandinavia demonstrated that a TOF ratio of 0.7 or less is a risk factor for development of postoperative pulmonary complications.² Recently, Kopman *et al.*³ showed in healthy volunteers that visual disturbance persists until a TOF ratio recovery greater than 0.9 is attained. Moreover, when a mechanomyographic TOF is less than 0.9, there is a significant decrease in carotid body chemosensitivity to hypoxia,^{4,5} as well as pharyngeal dysfunction with an increased risk for aspiration.^{6,7} Therefore, return to normal muscle function, including normal pharyngeal function, requires a mechanomyographic adductor pollicis TOF ratio of 0.9 or greater. Combining the results of these investigations and considering the poor performances of subjective monitoring in the assessment of residual paralysis,^{8,9} there is currently sufficient evidence to support a general change in the attitude toward routine quantitative monitoring of neuromuscular recovery.^{10–12} Indeed, with the introduction of acceleromyographic monitors in the mid-1990s, the ability to objectively quantify the TOF ratio in daily clinical practice is currently possible.¹³ However, the limits of agreement between this first generation of portable acceleromyographs (TOF-Guard®; Organon, Oss, The Netherlands) and mechanomyographically measured recovery data are relatively wide. Harper *et al.*¹⁴ reported that when the mechanomyographic TOF was 0.7, the corresponding acceleromyographic TOF varied between 0.4 and 1.0. Similar results were also reported by others.^{15–19} The existing data therefore suggest that the two methods cannot be used interchangeably. A TOF of 0.9 measured by acceleromyography does not necessarily indicate a mechanomyographic TOF of 0.9, the current benchmark for the adequacy of neuromuscular recovery. The current study aimed to determine (1) the acceleromyographic TOF ratio—measured under routine clinical conditions—that detects with a 95% probability a mechanomyographic TOF ratio of 0.9 and (2) the impact of calibration and normalization on this predictive acceleromyographic TOF.

Materials and Methods

Patients

The research protocol was approved by the institutional review committee (Centre Hospitalier Universita-

* Staff Member, ‡ Professor and Chairman, § Associate Professor, Department of Anesthesia and Critical Care, † Staff Member, Department of Epidemiology.

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Address reprint requests to Prof. Meistelman: Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire, Nancy/Brabois; 4 Rue du Morvan, F-54511 Vandœuvre-Les-Nancy, France. Address electronic mail to: c.meistelman@chu-nancy.fr. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

ire, Nancy/Brabois, France). Sixty adult patients with American Society of Anesthesiologists physical status class I-III were studied after giving their written informed consent. Patient selection was random from those scheduled for elective surgical procedures under general anesthesia with tracheal intubation. Exclusion criteria included neuromuscular, hepatic, or renal disease; abnormal airway anatomy (Mallampati score of 3 or 4); deviation from ideal body mass of 25% or greater; pregnancy; receiving medication that influences neuromuscular blockade; or having a history of allergic reaction to drugs used in the study. One hour before arrival on the operating room, all patients were premedicated with 1 mg/kg oral hydroxyzine.

According to calibration modus of the TOF-Watch S[®] (Organon), the 60 patients were randomly divided (number draws) into two groups of 30 patients: group A, in which the implemented calibration algorithm of the TOF-Watch S[®] was activated (*i.e.*, calibration mode two), and group B, in which this algorithm was not applied.

Induction and Maintenance of Anesthesia

Monitoring, established on arrival on the operating room, included electrocardiography, noninvasive arterial pressure monitoring, pulse oximetry, and capnography. Anesthesia was induced in all patients with 2.5–3.5 mg/kg propofol and 0.2–0.3 μ g/kg sufentanil. Propofol ($8\text{--}12\text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$), intermittent bolus doses of sufentanil ($0.1\text{--}0.2\text{ }\mu\text{g/kg}$), and oxygen–nitrous oxide (50%–50%) *via* facemask maintained anesthesia until tracheal intubation. The central temperature was maintained over 35°C using a warming blanket covering the upper body and both arms (Bair Hugger; Arizant Healthcare, Eden Prairie, MN); end-tidal partial pressure of carbon-dioxide (Pco_2) was maintained between 32 and 36 mmHg.

Neuromuscular Monitoring

Both arms were placed in the abducted position on padded arm boards, and each patient was monitored on one arm with the mechanomyograph (Adductor Pollicis Monitoring[®]; Gould Instruments, Valley View, OH) and on the other arm with the acceleromyograph (TOF-Watch S[®]). The force-displacement transducer of the mechanomyograph was fixed to the thumb, and a 300-g preload was applied. The acceleration transducer of the acceleromyograph was fixed to the volar side of the distal phalanx of the contralateral thumb on a small elastic hand adapter applying a constant 75-g preload (TOF-Watch Handadapter[®]; Organon). The transducers of the mechanomyograph and the acceleromyograph were allocated randomly to the patient's dominant hand and nondominant hand. Surface electrodes were placed on the cleaned skin over the ulnar nerves of both wrists, and two TOF-Watch S[®] nerve stimulators were used for supramaximal TOF stimulation (four pulses of 0.2 ms in duration, at a frequency of 2 Hz, every 15 s). The mecha-

nomyograph was calibrated as follows. After stable baseline of the mechanomyographic response was obtained, *i.e.*, variation of no more than $\pm 2\%$ of the first response in TOF for at least 3 min, the current supplied was recalibrated and adjusted to produce supramaximal stimulation. Thereafter, the acceleromyograph was calibrated in group A using the implemented TOF-Watch S[®] calibration mode 2. Applying this algorithm, the stimulation current was set automatically by the device to 60 mA, and the gain was then automatically adjusted so that the response of the single twitch was set to a 100% value. Then, the current was decreased in steps of 5 mA until the response screen value decreased below 90% (*e.g.*, at 35 mA), and 10% was added to the value before the decrease of this value (*e.g.*, 40 mA). The current is then, in this example, set by the device to $40\text{ mA} + 10\% = 44\text{ mA}$ (supramaximal stimulation). As a last step, the response screen value setting was repeated, but with a stimulus current of 44 mA, and the TOF ratio before injection of the neuromuscular blocking agent was noted as a control value, which could be greater than 1.0. In group B, the acceleromyograph was set up manually to deliver supramaximal TOF stimulation (50 mA), and the TOF ratio before injection of the neuromuscular blocking agent was noted as a control value, which could be greater than 1.0. Data in group B were presented as both raw data (uncalibrated TOF) and normalized data (normalized TOF). Normalized TOFs were calculated by dividing the TOF noted on the acceleromyographic monitor display screen by the control value, as suggested.¹¹ For example, for a control TOF of 1.1, a TOF recovery of 0.85 corresponds to 0.77 of control value. When the acceleromyographic TOF was constant for three consecutive measurements (*i.e.*, variation of the TOF of no more than $\pm 2\%$), the stimulations of the mechanomyographic and acceleromyographic devices were synchronized, permitting simultaneous measurement of the force of contraction of the adductor pollicis on one hand and the acceleration of the thumb of the contralateral hand. Thereafter, 0.5 mg/kg atracurium ($2 \times \text{ED}_{95}$) was given as a bolus, and orotracheal intubation was performed. During surgery, bolus doses of 0.1 mg/kg atracurium were reinjected as clinically needed. Simultaneous monitoring with the mechanomyograph and the acceleromyograph was continued until complete recovery of the acceleromyographic and mechanomyographic TOF ratios (baseline values $\pm 5\%$).

Statistical Analysis

Patient characteristics were compared using the Mann-Whitney U test and were expressed as mean \pm SD and range; a *P* value of less than 0.05 was considered statistically significant. To investigate the agreement between mechanomyography and acceleromyography in the assessment of neuromuscular recovery, the intraclass cor-

Table 1. Demographic Data and Duration of Surgery

	Group A	Group B
Age, yr	56 ± 15	62 ± 14
Weight, kg	70 ± 14	72 ± 12
Sex (M/F)	18/12	14/16
ASA (I/II/III)	8/17/5	9/10/11
Duration, min	79 ± 52	97 ± 68
Start temperature, °C	36.0 ± 0.4	36.1 ± 0.4
End temperature, °C	36.1 ± 0.5	36.1 ± 0.5

Values are presented as mean ± SD.

ASA = American Society of Anesthesiologists (physical status); group A = calibrated acceleromyography; group B = uncalibrated acceleromyography.

relation coefficients were calculated.^{20,21} In addition, the negative predictive values of acceleromyographic TOFs of 0.9, 0.95, and 1.0 to detect a mechanomyographic TOF of 0.9 were calculated (*i.e.*, absence of residual paralysis at the respective acceleromyographic recovery) according to standard formulae; values were expressed as percentage and 95% CI.²²

Results

Data from all 60 patients could be analyzed without dropout. There were no significant differences among the two groups with respect to age, weight, height, sex distribution, temperature, and duration of surgery (table 1).

Group A

The baseline acceleromyographic TOF was 0.99 (range, 0.97–1.02). At the first recovery of the mechanomyographic TOF to 0.9 or greater, the corresponding acceleromyographic TOF was 0.95 (range, 0.86–1.0); at the first recovery of the acceleromyographic TOF to 0.9 or greater, the respective mechanomyographic TOF was 0.83 (range, 0.64–0.93) (tables 2 and 3). The negative predictive values of acceleromyographic TOFs of 0.9,

Table 4. Negative Predictive Values of Different Acceleromyographic TOF Ratios

Acceleromyographic TOF ratio	Negative Predictive Value		
	Group A	Group B	
		Data not normalized	Data normalized
0.9	37 (20–56)	40 (23–59)	89 (70–98)
0.95	70 (51–85)	60 (41–77)	92 (75–99)
1.0	97 (83–100)	77 (58–90)	96 (80–100)

Values are presented as percent and 95% confidence interval.

Negative predictive value = percent of patients without residual paralysis at acceleromyographic train-of-four ratios of 0.9, 0.95, and 1.0; TOF = train-of-four.

0.95, and 1.0 to detect residual paralysis were 37% (95% CI, 20–56%), 70% (95% CI, 51–85%), and 97% (95% CI, 83–100%), respectively (table 4). The intraclass correlation coefficient was 0.71 (95% CI, 0.67–0.75).

Group B

The baseline acceleromyographic TOF was 1.11 (range, 1.00–1.17). Without normalization of the final acceleromyographic TOF response, the first recovery of mechanomyographic TOF to 0.9 or greater corresponded to an acceleromyographic TOF of 0.97 (range, 0.68–1.18), and the first acceleromyographic TOF of 0.9 or greater corresponded to a mechanomyographic TOF of 0.83 (range, 0.65–1.0), (tables 2 and 3). The negative predictive values of acceleromyographic TOFs of 0.9, 0.95, and 1.0 to detect residual paralysis were 40% (95% CI, 23–59%), 60% (95% CI, 41–77%), and 77% (95% CI, 58–90%), respectively (table 4). The intraclass correlation coefficient was 0.73 (95% CI, 0.69–0.77). The first recovery of the mechanomyographic TOF to 0.9 or greater corresponded to a normalized acceleromyographic TOF of 0.89 (range, 0.63–1.06), and the first normalized acceleromyographic TOF of 0.9 or greater

Table 2. Acceleromyographic TOF Recovery at Mechanomyographic TOF Ratio ≥ 0.9

	Group A	Group B
Mechanomyographic TOF ratio recovery	0.9 (0.9–0.91)	0.91 (0.9–0.93)
Acceleromyographic TOF ratio	0.95 (0.86–1)	0.97 (0.68–1.18), data not normalized 0.89 (0.63–1.06), data normalized

Values are presented as mean and range.

TOF = train-of-four.

Table 3. Mechanomyographic TOF Recovery at Acceleromyographic TOF Ratio ≥ 0.9

	Group A	Group B
Acceleromyographic TOF ratio recovery	0.9 (0.9–0.94)	0.92 (0.9–0.95)
Mechanomyographic TOF ratio	0.83 (0.64–0.93)	0.83 (0.65–1), data not normalized 0.9 (0.75–0.97), data normalized

Values are presented as mean and range.

TOF = train-of-four.

corresponded to a mechanomyographic TOF of 0.9 (range, 0.75–0.97) (tables 2 and 3). The negative predictive values of acceleromyographic TOFs of 0.9, 0.95, and 1.0 to detect residual paralysis were 89% (95% CI, 70–98%), 92% (95% CI, 75–99%), and 96% (95% CI, 80–100%), respectively (table 4). The intraclass correlation coefficient was 0.84 (95% CI, 0.81–0.86).

Discussion

This study examined the performance of acceleromyography to detect residual paralysis, *i.e.*, an adductor pollicis mechanomyographic TOF of less than 0.9, under routine clinical conditions. The most important result was that to detect residual paralysis reliably with acceleromyography, recovery of the TOF to 0.9 was insufficient, but recovery to unity was mandatory to confirm complete recovery from neuromuscular block.

Debaene *et al.*²³ recently reported that after a single intubating dose of intermediate-duration relaxant, with no further doses administered during surgery, 45% of the patients arrived in the postanesthetic care unit with a residual neuromuscular block (TOF < 0.9). Several similar studies confirmed this alarmingly high incidence of residual paralysis despite the use of intermediate-acting neuromuscular blocking agents.^{24–28} Moreover, Debaene *et al.*²³ found that neither clinical tests (5-s head lift, tongue depressor test) nor visual estimation of TOF or double burst stimulation were accurate enough to detect residual paralysis. In their study, residual paralysis (TOF ratio < 0.9) was present in greater than 90% of patients who demonstrated fade in response to TOF or double burst stimulation. However, complete recovery was seen in only half of the patients with no fade. Thus, complete recovery could not be confirmed with qualitative instrumental tests or clinical tests.

This highlights the need for quantitative TOF measurement each time a muscle relaxant is given.¹² However, no mechanomyographic or electromyographic monitors that meet the single criteria of usability in the clinical setting are commercially available. Therefore, acceleromyography has been proposed as the only satisfactory alternative.¹¹ Indeed, the latest generation of such monitors is simple to use, and the setup time is close to that required when using conventional, qualitative peripheral nerve stimulators.¹¹ However, the data of the current study revealed that at the first recovery to a TOF of greater than 0.9 measured with a TOF-Watch S® device, the mean mechanomyographic TOF was 0.83. In group A, 19 of the 30 patients still had a mechanomyographic TOF of less than 0.9; two of them even had a TOF of less than 0.7. Similar results were observed in group B. This is in accord with previous studies reporting an overestimation of the acceleromyographic TOF recovery when compared with mechanomyography.²⁹ Therefore, slight

levels of residual paralysis were not always detected by acceleromyography. Nevertheless, as recently demonstrated by Eikermann *et al.*,³⁰ even such a slight degree of residual paralysis may have significant clinical consequences. They demonstrated that, in healthy volunteers, an acceleromyographic TOF of 0.8 was still associated with impaired forced inspiratory volume, increased upper airway obstruction, and impaired ability to swallow. These pathophysiologic consequences of slight residual paralysis may even be aggravated in patients in the immediate postoperative period by the residual effects of volatile anesthetics or opioids. To give clinically useful information and thus contribute to adequate decision making, neuromuscular monitoring must also detect such slight levels of residual paralysis.

Ideally, the acceleromyographic and mechanomyographic recordings should have been obtained simultaneously in the same arm. However, it is not possible to measure an acceleration and an isometric muscle contraction in the same arm at the same time; we therefore used a two-arm technique. Kirkegaard-Nielsen *et al.*³¹ demonstrated substantial variation between simultaneous mechanomyographic recordings of neuromuscular transmission obtained in contralateral arms. According to the authors, this factor should be taken into account when studying neuromuscular monitoring methods using the two-arm technique. The reason for these differences is not obvious, but real differences between the two arms may contribute. To control this factor in the current study, acceleromyographic and mechanomyographic transducers were randomly allocated to the patient's dominant hand and nondominant hand. Whether other factors contribute to the phenomenon observed by Kirkegaard-Nielsen *et al.* cannot yet be excluded with certainty. As a consequence, the agreement between both measurement methods may be even better than indicated by the current study.

However, both monitors cannot be used interchangeably. At the first acceleromyographic TOF ratio of 0.9 or greater, complete recovery was seen in only one third of the patients (negative predictive value, 37%) in group A. Normalization, *i.e.*, dividing the final TOF recovery value noted at the acceleromyographic monitor screen by the control value taken before injection of the neuromuscular blocking agent, improved the detection of residual paralysis in group B, but a negative predictive value of 89% still did not allow reliable detection of residual paralysis. Certainly, acceleromyography performs better for detection of residual paralysis than visual or tactile evaluation of fade using TOF or even double burst stimulation. However, slight levels of residual paralysis (mechanomyographic TOF, 0.7–0.9) were not reliably detected by acceleromyography. By consequence, quantitative neuromuscular monitoring with acceleromyography is unlikely to significantly improve detection of residual paralysis, at least when taking an acceleromyo-

graphic TOF of 0.9 as the benchmark. Therefore, we speculated that a higher degree of acceleromyographic recovery might allow a more reliable detection of residual paralysis. To test this hypothesis, the negative predictive values of acceleromyographic TOF ratios of 0.95 and 1.0 to detect residual paralysis were calculated. Increasing acceleromyographic TOF recovery to 0.95 and 1.0 increased the negative predictive values in group A to 70% and 97%, respectively. To achieve a similar performance in group B, normalization was mandatory (table 4).

The current study may have clinical implications: Acceleromyography is accurate enough to detect residual paralysis reliably, but an acceleromyographic recovery to 0.9 was insufficient in this context. Recovery of the acceleromyographic TOF ratio to unity and calibration or normalization further improves the performance of acceleromyography. However, calibration and normalization require setup of the acceleromyograph before the injection of the neuromuscular blocking agent. Without calibration or normalization, the performance of acceleromyography is less convincing; the negative predictive values of acceleromyographic TOFs of 0.9, 0.95, and 1.0 are 40, 60, and 77%, respectively. For comparison, the negative predictive value of the most performing qualitative test, *i.e.*, double burst stimulation, has recently been estimated to be 57%.²³ Therefore, in situations where setup before injection of the myorelaxant is not possible, as, for example, to selectively assess neuromuscular recovery at the end of surgery, quantitative neuromuscular monitoring using acceleromyography does not seem to be precise enough to reliably confirm complete recovery.

The latest generation of commercially available acceleromyographs, *i.e.*, TOF-Watch S[®], and a recently introduced hand adapter, both primarily designed for clinical use, were used. We used the hand adapter because it is easy to apply and allows the thumb to return to the same resting position as the original baseline before the first stimulation; this should make acceleromyographic monitoring less vulnerable to changes of the patients position and thus lead to more reliable results when using acceleromyography in daily clinical practice.³² However, first evidence suggests that the acceleromyographic recovery data were not influenced by preload.²⁹ Whether similar results would have been obtained without the hand adapter, therefore, remains speculative. For calibration, the setup algorithm implemented in the TOF-Watch S[®] was activated in group A; in group B, the stimulation current was set up manually, as currently practiced in clinical routine.^{29,33,34} There was a difference in the baseline TOF ratios between group A and group B (0.99 [range, 0.97–1.02] *vs.* 1.11 [range, 1.00–1.17], respectively). This is unexpected because calibration involves the twitch height and not the TOF ratio; application of TOF-Watch S[®] calibration mode 2 sets the twitch height

at 100% and not the TOF ratio. One possible explication for this difference may be the different stimulation currents in both groups. In group A, the stimulation current was automatically set and was allowed to reach 60 mA, whereas the stimulation current in group B was manually set at 50 mA. Therefore, one may speculate that more patients might be stimulated supramaximally in group A, and this could explain the differences observed between the two groups. However, according to the findings of Helbo-Hansen *et al.*,³⁵ a stimulation current of at least 45 mA is required for adequate accuracy and precision of TOF monitoring. Therefore, the stimulation current chosen in group B (*i.e.*, 50 mA) should be sufficient. We suppose that another mechanism may contribute to the differences observed between calibrated and uncalibrated baseline TOF ratios. Calibration mode 2 of the TOF-Watch S[®] sets the stimulation current and gain so that the control single twitch equals 100%. It does not directly set the TOF ratio at 100%, but, as confirmed by the manufacturer of the TOF-Watch S[®] (Organon), the first of the four twitches of the TOF stimulations after the calibration maneuver approaches 100%, too. The TOF ratio, however, is the quotient of the fourth and the first twitch (T₄/T₁), and thus, influencing the denominator obviously influences the whole quotient (here the TOF ratio). Without calibration, as in group B, the denominator is not automatically controlled near 100%, which may explain the differences observed between both groups. However, the aim of this study was not the validation of the TOF-Watch S[®] for research purpose, but to examine the performance of acceleromyography in the detection of residual paralysis during routine clinical conditions. Thus, we did not apply any of the calibration protocols proposed when using acceleromyography as a research tool.^{29,30,36,37} Therefore, these acceleromyographic recovery data probably do not reflect the best performance possible with this measurement technique; however, they reflect precisely the performance of acceleromyography to detect residual paralysis in the clinical setting, the primary aim of this study. Moreover, the current study does not evaluate the repeatability of the TOF-Watch S[®], which is best determining during stable neuromuscular blockade.³¹ However, an earlier study demonstrated that the acceleromyographic transducer was comparable in precision with the myograph transducer.¹⁷ In contrast, Harper *et al.*¹⁴ have reported that with acceleromyography, twitch height may be prone to excessive drift as compared with mechanomyography, thus indicating diminished drift with the latter device. However, such a drift affects only twitch height and not TOF ratio.³¹ The current study, however, focused on TOF ratio.

In conclusion, the current study demonstrates that recovery of the acceleromyographic TOF ratio to unity is accurate enough to detect low degrees of residual paralysis in the clinical setting.

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