

Is the Performance of Acceleromyography Improved with Preload and Normalization?

A Comparison with Mechanomyography

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Background: Many studies have indicated that acceleromyography and mechanomyography cannot be used interchangeably. To improve the agreement between the two methods, it has been suggested to use a preload and to refer all train-of-four (TOF) ratios to the control TOF (normalization) when using acceleromyography. The first purpose of this study was to test whether a preload applied to acceleromyography would increase the precision and the agreement with mechanomyography. The second purpose was to evaluate whether normalization would improve the agreement with mechanomyography.

Methods: Sixty patients were randomized to acceleromyography with or without a preload (Hand Adapter; Organon, Oss, the Netherlands). On the contralateral arm, mechanomyography was used. Anesthesia was induced with propofol and an opioid, and neuromuscular block with 0.6 mg/kg rocuronium. The precision and the bias and limits of agreement (with or without normalization) between the methods were evaluated using TOF stimulation.

Results: Preload improved the precision of acceleromyography by 21%, but it also increased the mean control TOF ratio from 1.07 to 1.13. Normalization of the acceleromyographic TOF ratios diminished the bias to mechanomyography during recovery (e.g., from 0.15 to 0.05 at TOF 0.90); when the mechanomyographic TOF values were normalized as well, the bias was eliminated. However, normalization did not exclude wide individual differences between acceleromyography and mechanomyography (± 0.10 – 0.20 at TOF 0.90).

Conclusion: Preload increases the precision of acceleromyography, and normalization of the TOF ratios decreases bias in relation to mechanomyography. When both acceleromyography and mechanomyography are normalized, there is no significant bias between the two methods.

ACCELEROMYOGRAPHY was introduced for use in daily clinical practice in 1988,¹ as a simple, reliable, and easily applicable monitor for objective neuromuscular monitoring to replace the more cumbersome setup of mecha-

nomyography.² Mechanomyography is considered the standard for objective neuromuscular monitoring.³ Mechanomyography, which measures the isometric force of contraction of a muscle or digit (e.g., the thumb) in response to nerve stimulation, requires a time-consuming stringent setup with a tight fixation and a nonelastic preload of the thumb.³ This makes the method unsuitable for daily clinical practice. Furthermore, monitors based on mechanomyography are no longer commercially available, and acceleromyography has increasingly replaced this method in clinical practice and research.

Acceleromyography measures the acceleration (isotonic contraction) of a muscle or digit. The method is based on Newton's second law of motion, which states that force equals acceleration times mass.¹ If the mass (e.g., the thumb) is constant, the acceleration is directly proportional to the force. However, in contrast to mechanomyography, acceleromyography in principle measures the unrestricted movement of the muscle in question. When acceleromyography was introduced, this was considered an advantage because the setup was much simpler.^{1,4} It is now apparent that the freely moving thumb may cause artifacts and unstable recordings because the thumb often touches the palm of the hand or the sterile cover. Furthermore, the setup is very sensitive to external disturbances.⁵

Many studies have documented that acceleromyography cannot be used interchangeably with mechanomyography probably as a result of differences in setup and muscle contraction.^{6–12} This is a problem when one wants to compare pharmacodynamic data from different studies using the two recording methods. However, it has been suggested that an elastic preload applied to acceleromyography may increase the precision and agreement with mechanomyography,¹³ and the manufacturer of the commercially available acceleromyography monitors (TOF-Watch® series; Organon, Oss, The Netherlands) has made an elastic preload commercially available (the Hand Adapter; Organon).³ This device is applied to the palm of the hand, and with a stretching wing it assures that the thumb does not touch the palm during nerve stimulation and returns to its original position between the nerve stimulations. The Hand Adapter is now increasingly being used in daily clinical practice as well as in research.^{10,14} However, the device has not been sufficiently validated.¹²

A consistent finding in previous studies is that the control baseline train-of-four (TOF) ratio of acceleromyo-

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graphy is higher than that of mechanomyography.^{1,6,8,12} The control acceleromyographic TOF ratio is often 1.10–1.15,^{1,6,8,15} or even as high as 1.47.¹⁶ In contrast, the control mechanomyographic TOF ratio most often ranges between 0.93 and 1.02.^{1,6,8,12} Intuitively, a higher control baseline value would influence TOF ratios during recovery. For instance, in a patient with a high control baseline value (e.g., TOF 1.20), a higher TOF ratio during recovery is probably necessary to exclude residual block compared to a patient with a low control baseline value (e.g., TOF 0.95). It is generally accepted that the TOF ratio should be at least 0.90^{12,17,18} to exclude clinically significant residual paralysis; using the above example, a TOF ratio of 1.08 (90% of 1.20) would represent safe recovery in the first patient, whereas a TOF ratio of 0.86 (90% of 0.95) would suffice in the other patient. To overcome such problems, it has been suggested to refer the actually obtained TOF ratios during recovery to the baseline control TOF ratio (normalization).^{16–18}

In accordance with this, the primary objective of this study was to test the hypothesis that the use of the Hand Adapter would improve the precision (*i.e.*, variance during recovery) and the agreement of acceleromyography with mechanomyography. Our secondary objective was to test the hypothesis that normalization of the actually obtained TOF ratios during recovery would improve the agreement between acceleromyography and mechanomyography.

Materials and Methods

Patients

After obtaining approval by the local Ethics Committee (Copenhagen County, Denmark) and written informed consent, we enrolled 60 patients (American Society of Anesthesiologists class I–III; age 18–65 yr) who were scheduled to undergo surgery in supine position with both arms available for neuromuscular monitoring and with an anticipated surgery duration greater than 1 h. Pregnant and breast-feeding women, patients with known illness or use of medications known to influence the neuromuscular transmission, known significant renal or hepatic dysfunction or allergy to medications used in the study were excluded. Only patients within 20% of the ideal body weight (men: weight in kg = height in cm – 102; women: weight in kg = height in cm – 106) were included.

Anesthesia

The patients were monitored with electrocardiography, noninvasive blood pressure, pulse oximetry, and capnography. Anesthesia was induced and maintained with propofol and opioid at the discretion of the anesthesiologist. Peripheral temperatures were measured over the thenar eminence of both arms and kept above 32°C. The

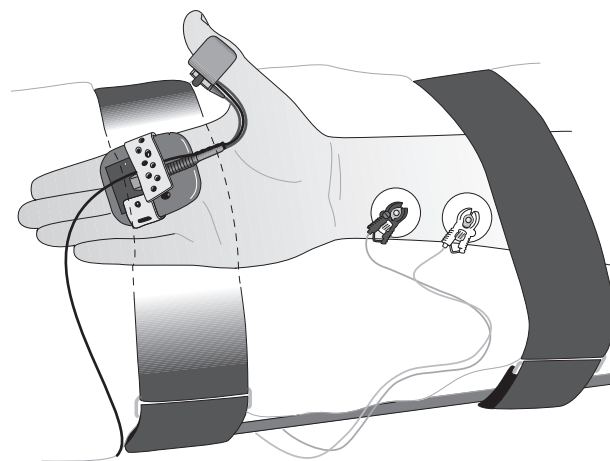


Fig. 1. The setup of acceleromyography with preload (Hand Adapter; Organon, Oss, the Netherlands). Two electrodes are placed above the ulnar nerve and, the response to nerve stimulation is measured using a small piezoelectric acceleration transducer placed in the Hand Adapter. The stretching wing ensures that the thumb does not touch the palm of the hand.

central temperature was monitored in esophagus and kept above 35°C.³ All patients were placed under an upper body forced air warming blanket. The trachea was intubated without the use of muscle relaxant. Ventilation was adjusted to maintain normocapnia (end tidal CO₂ 4.5–5.6 kPa).

Neuromuscular Monitoring

Neuromuscular monitoring followed the Good Clinical Research Practice guidelines in pharmacodynamic studies of neuromuscular blocking agents.³ After carefully cleaning of the skin, two pediatric surface electrodes (Neotrode®; ConMed Corporation, NY) were placed on both arms over the ulnar nerve near the wrist with a distance of 3–6 cm. Using a computer-generated number system and serially numbered, sealed, and opaque envelopes, the patients were randomized to acceleromyography (TOF-Watch® SX; Organon) on the dominant or nondominant hand, with (n = 30) or without (n = 30) a preload of 75–150 g (Hand Adapter, Organon). According to the randomization, the acceleration transducer was placed in the Hand Adapter (fig. 1) or distal to the interphalangeal joint of the thumb (fig. 2), and the fingers were fixed to the arm board. Contralaterally, mechanomyography (Myograph 2000; Biometer Int., Odense, Denmark)² was applied (fig. 3). The arm with mechanomyography (n = 60) was fixed to an armboard and the thumb to a force transducer (TD100; Biometer) with a preload of 200–300 g. The ulnar nerves were stimulated simultaneously by using a trigger cable from the TOF-Watch® SX to the stimulation unit of the Myograph 2000. To decrease the stabilization period, a 50-Hz tetanic stimulation was applied for 5 s^{3,19} and followed after 1 min by TOF stimulation every 15 s. When the response to TOF was stable, calibration and supramaximal stimulation was ensured by the built-in calibration

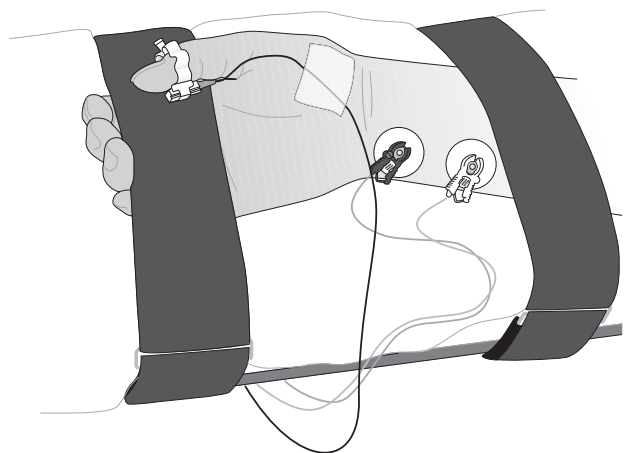


Fig. 2. The setup of acceleromyography without preload. Two electrodes are placed above the ulnar nerve, and the response to nerve stimulation is measured using a small piezoelectric acceleration transducer placed distally on the volar site of the thumb.

function (CAL 2) of the TOF-Watch[®] SX and manually at the Myograph 2000. Stable baseline was documented in at least 2–5 min (less than 5% variation in the first twitch [T1] and TOF) before the neuromuscular blocking agent was administered. Rocuronium 0.6 mg/kg was administered in a fast-running saline infusion within 5 s. Acceleromyography data were collected on a laptop using the TOF-Watch[®] SX monitor program (version 2.1). Mechanomyography data (*i.e.*, the first response to TOF [T1] and TOF) were collected on a laptop using an analog-to-digital converter and a specifically developed software program. The neuromuscular transmission was moni-

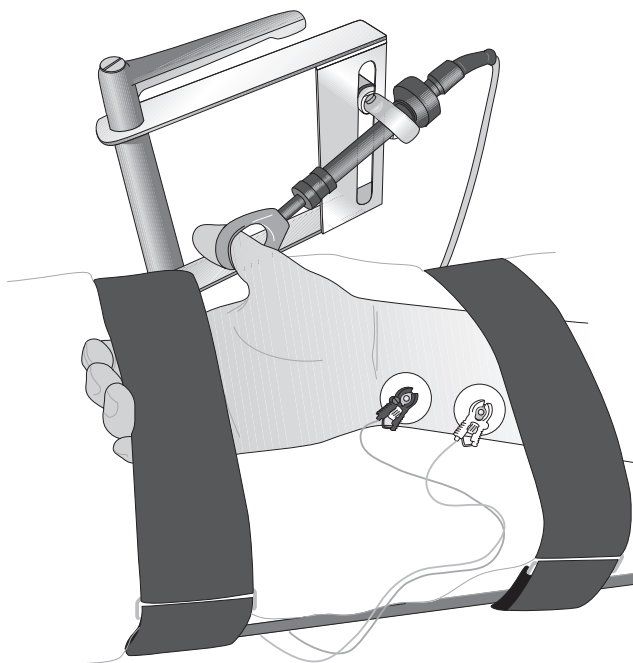


Fig. 3. The setup of mechanomyography. Two electrodes are placed above the ulnar nerve, and the response to nerve stimulation is measured using a forced transducer placed at the proximal phalanx of the thumb.

tored to the end of surgery and until a mechanomyographic TOF of at least 0.90 was achieved. If necessary, the neuromuscular block was reversed with neostigmine and glycopyrrolate.

Statistical Analysis

The precision (or repeatability) was evaluated during recovery to at least a mechanomyographic TOF 0.90. Ideally, it would be defined from repeated observations of TOF ratios during constant block; however, the block was at no time constant during recovery, so we used the variance around a local linear regression line, involving nine consecutive TOF measurements over time and allowing for elimination of a possible trend. The variance was divided by the local squared average, yielding a squared coefficient of variation, which was then averaged over time to give a single coefficient of variation for each individual patient. These coefficients of variation were then compared using *t* tests (on a logarithmic scale to achieve normal distributions). A paired *t* test was used when comparing acceleromyography and mechanomyography, whereas an unpaired *t* test was used when assessing the impact of a preload on acceleromyography.²⁰

The following pharmacodynamic data obtained with mechanomyography and acceleromyography (with or without preload) were compared: onset time (time to $\geq 95\%$ twitch depression of T1 in TOF), time to reappearance of the first to fourth twitch in TOF (T1–T4), time to T1 25% (of the final T1), interval 25–75%, time to TOF 0.90 (with and without normalization), and the differences in level of block during recovery at TOF 0.20–1.00 (with and without normalization). Graphical illustrations of the difference between the two methods against the average (Bland-Altman plots)^{3,21,22} showed often wider scatter at higher values, but differences were constant on a log-scale. As the bias increased with increasing time to TOF 0.90, all data were logarithmically transformed, and the antilog on bias and limits of agreement were calculated to give bias and limits of agreement on a ratio scale.³ This allowed us to give the relative bias (*i.e.*, proportional agreement) between the methods.

The agreement between acceleromyography and mechanomyography was assessed by the method described by Bland and Altman.^{3,21,22} The bias is defined as the mean difference of simultaneously obtained measurements of the two methods used, and the limits of agreement define the limits within 95% of the differences (bias ± 2 SD) will lie. The bias and the limits of agreement surrounding the bias were calculated with 95% confidence intervals.

The time of a certain level of block was defined as the first occurrence of three consecutive values above the given block. If the TOF ratios in four consecutive measurements were 0.85, 0.91, 0.92, and 0.94, the time to TOF 0.90 corresponds to the time when TOF 0.91 was measured. To decrease the effect of random fluctuation

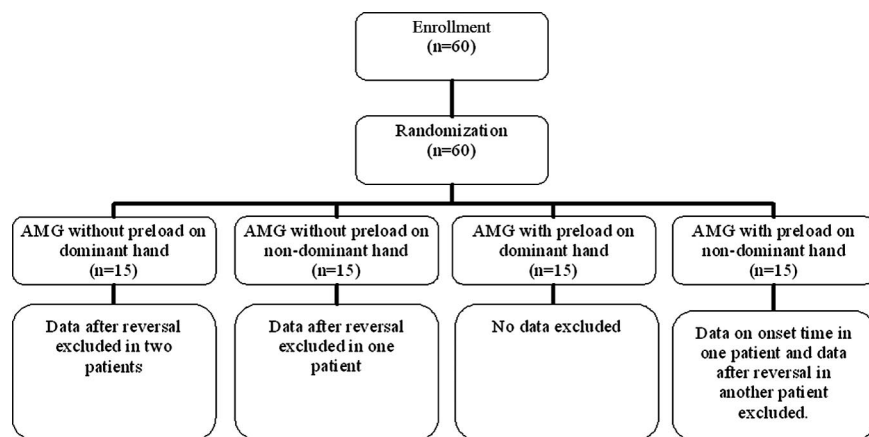


Fig. 4. The flow diagram shows the enrollment and allocation to the four groups. No patients were lost to follow up, but a few data were excluded from the main analysis (see Results section further explanation). AMG = acceleromyography.

(at first crossing, the value will typically be larger than expected), the level of block (TOF 0.20–1.00) at this time was defined as the mean of the three values around the given block; using the above example, the TOF ratio at “level of block 0.90” was the mean of 0.85, 0.91, and 0.92, *i.e.*, 0.89. The TOF-Watch® SX does not calculate the TOF if T1 is below 20%. One of the three TOF ratios surrounding the “level of block TOF 0.10” could therefore include zero, which made a significant bias. “Level of block TOF 0.10” is therefore not presented.

When the TOF ratios were normalized, all TOF data were referred to the mean control TOF ratio during stable baseline (less than 5% variation in at least 2 min) just before the neuromuscular block was induced. If, for instance, the mean TOF ratio before the neuromuscular block was 1.20, all TOF ratios during recovery referred to this ratio. Accordingly, a recorded TOF ratio of 0.60 was “normalized” to only 0.50 (0.60/1.20).

In the light of the multitude of statistical comparisons and quantifications stated in this paper, there is an obvious risk of mass significance. A concise correction for this is not possible, but it should be born in mind in connection with moderate *P* values, *e.g.*, in the range 0.001 to 0.05.

The sample size was determined using the following criteria: a significance level of 5% and a power of 80% to detect a reduction in SD of at least 20% when a preload was used. We allowed for individual variations in the SD of 50% (meaning that the standard deviations for two randomly chosen patients would typically have a ratio below 1.5). When standard deviations are estimated with

seven degrees of freedom (corresponding to nine consecutive measurements with elimination of trend), this demands a total of 54 patients. We included 60 patients both because the variation in standard deviations was only an estimate and to take possible dropouts into account.

Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

Results

All 60 patients (American Society of Anesthesiologists I/II: 50/10; age 28–64 yr; ideal weight: –16% to +18%; male/female: 1/59) completed the study. The neuromuscular block had to be reversed in three patients without a preload (one at reappearance of T3, two at mechanomyographic TOF ratios of 0.70 and 0.85) and in one patient with preload at a mechanomyographic TOF ratio of 0.60. In all four patients, the data obtained after reversal were excluded because the pronounced shift in the rate of recovery made analysis of precision impossible. In one patient (with preload), rocuronium was infused very slowly by mistake. Accordingly, the onset was significantly delayed and the data on onset were therefore excluded. Figure 4 shows the flow of participants through the study.

Effect of Preload

Table 1 shows the effect of preload on *control TOF*. The acceleromyographic control TOF ratio was statistically significantly higher than the control mechanomyo-

Table 1. Effect of Preload on Control AMG TOF Ratio and on Bias and Limits of Agreement (95% CI) between AMG and MMG Control Ratios

	AMG		MMG		Bias	Limits of Agreement
	Mean	Range	Mean	Range		
Without preload	1.07	0.92 to 1.24	0.96	0.90 to 1.00	0.11 (0.08 to 0.14)†	–0.05 to 0.27 (–0.10 to 0.32)
With preload	1.13*	1.01 to 1.23	0.96	0.92 to 0.99	0.17 (0.15 to 0.19)†	0.06 to 0.28 (0.02 to 0.32)

* Control AMG TOF statistically significant higher with preload ($P = 0.008$); † Statistically significant bias between control AMG TOF and MMG TOF ($P < 0.0001$). AMG = acceleromyography; CI = confidence interval; MMG = mechanomyography; TOF = train-of-four.

Table 2. Effect of Preload on Precision of AMG TOF and MMG TOF during Recovery

	AMG	MMG at Contralateral Arm
Without preload	2.21 (1.89 to 2.59)	1.84 (1.57 to 2.15)
With preload	1.74 (1.59 to 1.90)*	1.98 (1.74 to 2.26)

Precision is expressed as the geometric mean of the percentual coefficient of variation, meaning that the discrepancy between repeated observations of TOF is typically within ± 2 times this number (e.g., for AMG with preload, the observations typically vary with $\pm 3.5\%$). Hence, the lower the geometric mean, the higher the precision.

* Statistically significant difference ($P = 0.008$) between AMG with and without preload.

AMG = acceleromyography; MMG = mechanomyography; TOF = train-of-four.

graphic TOF ($P < 0.0001$), independent of whether a preload was applied to the thumb. However, application of the preload increased the mean control acceleromyographic TOF ratio from 1.07 to 1.13 ($P = 0.008$), and the bias between the acceleromyograph and the mechanomyograph from 0.11 to 0.17 ($P < 0.0001$).

Table 2 shows the effect of preload on precision during recovery. There was no statistically significant difference in precision between acceleromyography and mechanomyography independently of whether a preload was applied. However, application of the preload significantly improved the precision of acceleromyography, the average coefficients of variation being 21% (95%

confidence interval, 6–34%) less with a preload than without ($P = 0.008$).

Tables 3 and 4 show the effect of applying a preload to the thumb on bias and limits of agreement between acceleromyography and mechanomyography during onset and recovery. The onset time recorded with acceleromyography without a preload was 19.3% longer than when recorded using mechanomyography ($P < 0.001$) (table 3). However, when measured with acceleromyography with a preload, there was no statistically significant difference compared to mechanomyography (table 3).

During recovery, acceleromyographic T1–T4 in general reappeared a little, but most often statistically significantly, earlier than the mechanomyographic T1–T4 independently of whether a preload was used. The time to T1 = 25% was not significantly different between the two methods when a preload was not used (table 3). In contrast, when a preload was applied, the time to T1 = 25% was 7.0% longer with acceleromyography ($P < 0.001$) (table 3). The interval 25–75% did not differ between the two methods of whether a preload was applied. The time to TOF 0.90 was 11.5 and 17.8% shorter with acceleromyography without and with preload (table 3), respectively, than with mechanomyography ($P < 0.0001$).

Table 4 illustrates that the bias between the acceleromyographic and mechanomyographic TOF ratios in-

Table 3. Effect of Preload on Bias and Limits of Agreement (95% Confidence Intervals) between Different Parameters Recorded with AMG and MMG during Onset and Recovery

	N*	Relative Bias (%) AMG-MMG	Limits of Agreement	P Value
AMG without preload				
Onset†				
Time to 95% twitch depression	30	19.3 (8.5 to 31.2)	–29.0 to 100.4 (–36.1 to 107.6)	< 0.001
Recovery				
Time to				
Reappearance of T1	30	–0.5 (–5.4 to 4.7)	–24.6 to 31.3 (–28.4 to 35.1)	0.84
Reappearance of T2	30	–4.6 (–7.1 to –2.1)	–17.3 to 10.0 (–19.3 to 12.0)	< 0.001
Reappearance of T3	30	–4.5 (–6.9 to –2.0)	–17.2 to 10.1 (–19.1 to 12.1)	0.001
Reappearance of T4	29	–4.1 (–6.8 to –1.3)	–17.7 to 11.8 (–19.9 to 14.0)	0.006
T1 = 25%	30	1.5 (–1.1 to 4.2)	–12.1 to 17.1 (–14.0 to 19.1)	0.26
Interval 25–75%	29	4.3 (–3.2 to 12.4)	–30.2 to 55.9 (–45.8 to 61.5)	0.26
Time to TOF 0.90	27	–11.5 (–14.4 to –8.4)	–25.6 to 5.4 (–29.9 to 11.8)	< 0.0001
AMG with preload				
Onset				
Time to 95% twitch depression	29‡	–1.4 (–7.3 to 5.0)	–29.5 to 38.0 (–34.2 to 42.7)	0.66
Recovery				
Time to				
Reappearance of T1	30	6.6 (2.8 to 10.6)	–12.8 to 30.4 (–15.5 to 33.1)	0.001
Reappearance of T2	30	–2.3 (–5.2 to 0.7)	–17.2 to 15.2 (–19.5 to 17.5)	0.12
Reappearance of T3	30	–3.6 (–6.1 to –1.0)	–16.7 to 11.6 (–18.7 to 13.6)	0.009
Reappearance of T4	30	–4.0 (–6.5 to –1.4)	–16.9 to 11.1 (–18.9 to 13.1)	0.004
T1 = 25%	30	7.0 (4.1 to 9.9)	–7.8 to 24.2 (–9.8 to 26.2)	< 0.001
Interval 25–75%	29	–7.5 (–14.9 to 0.5)	–40.8 to 44.6 (–47.1 to 50.8)	0.06
Time to TOF 0.90	29	–17.8 (–21.2 to –14.2)	–34.3 to 3.0 (–39.0 to 10.9)	< 0.0001

Bias is given as the relative bias (%). When time to T1 = 25%, e.g., 25 minutes measured with MMG in a patient, a 7.0% longer duration corresponds to 26.75 minutes if AMG with a preload had been used. See Statistical Analysis section.

* Data following reversal is excluded; † an example of a Bland-Altman plot is presented for the onset times in figure 5; ‡ One drop-out; rocuronium given in > 5 s.

AMG = acceleromyography; MMG = mechanomyography; TOF = train-of-four.

Table 4. Bias with Limits of Agreement (95% Confidence Intervals) between the Raw AMG without or with Preload and MMG TOF Ratios at Different Levels of Block as Defined by the Raw AMG TOF Ratios

AMG TOF Level	N*	Mean AMG TOF	Mean MMG TOF	Bias AMG-MMG	Limits of Agreement	P Value
AMG without preload						
0.20	29	0.20	0.18	0.03 (−0.02 to 0.07)	−0.22 to 0.27 (−0.30 to 0.35)	0.26
0.30	29	0.31	0.28	0.02 (−0.02 to 0.07)	−0.22 to 0.27 (−0.30 to 0.35)	0.33
0.40	29	0.40	0.36	0.05 (0.00 to 0.09)	−0.18 to 0.27 (−0.25 to 0.34)	0.035
0.50	29	0.50	0.43	0.07 (0.03 to 0.11)	−0.15 to 0.28 (−0.22 to 0.35)	0.002
0.60	28	0.60	0.53	0.08 (0.04 to 0.11)	−0.10 to 0.25 (−0.16 to 0.31)	< 0.0001
0.70	28	0.71	0.61	0.09 (0.06 to 0.12)	−0.07 to 0.25 (−0.12 to 0.30)	< 0.0001
0.80	28	0.81	0.71	0.09 (0.06 to 0.12)	−0.05 to 0.23 (−0.10 to 0.28)	< 0.0001
0.90	28	0.90	0.81	0.10 (0.07 to 0.12)	−0.04 to 0.23 (−0.09 to 0.28)	< 0.0001
1.00	25	1.00	0.88	0.12 (0.09 to 0.14)	−0.01 to 0.24 (−0.05 to 0.28)	< 0.0001
AMG with preload						
0.20	29	0.20	0.18	0.03 (−0.02 to 0.07)	−0.22 to 0.27 (−0.30 to 0.35)	0.27
0.30	30	0.30	0.28	0.02 (−0.03 to 0.07)	−0.23 to 0.28 (−0.31 to 0.36)	0.33
0.40	30	0.40	0.37	0.03 (−0.02 to 0.08)	−0.23 to 0.29 (−0.31 to 0.38)	0.18
0.50	30	0.50	0.46	0.04 (−0.01 to 0.09)	−0.22 to 0.30 (−0.30 to 0.39)	0.075
0.60	29	0.60	0.54	0.06 (0.02 to 0.11)	−0.16 to 0.29 (−0.24 to 0.37)	0.0062
0.70	29	0.70	0.62	0.09 (0.05 to 0.12)	−0.12 to 0.29 (−0.19 to 0.39)	0.00012
0.80	29	0.80	0.69	0.11 (0.07 to 0.15)	−0.08 to 0.30 (−0.14 to 0.37)	< 0.0001
0.90	29	0.90	0.75	0.15 (0.11 to 0.18)	−0.02 to 0.32 (−0.08 to 0.38)	< 0.0001
1.00	28	1.00	0.84	0.16 (0.14 to 0.18)	0.05 to 0.27 (0.01 to 0.31)	< 0.0001

$P < 0.05$, significant difference between AMG and MMG.

* If the first twitch was below 20%, the TOF was not calculated by the TOF-Watch® SX (Organon, Oss, The Netherlands). Furthermore, four patients were given neostigmine and data after reversal excluded.

AMG = acceleromyography; MMG = mechanomyography; TOF = train-of-four.

creased during recovery, becoming statistically significant at acceleromyographic TOF 0.40 without preload and TOF 0.60 with a preload, respectively.

Bland-Altman plots were made for all effect parameters. An example is shown in figure 5.

Effect of Normalization

When acceleromyographic TOF ratios obtained without preload were normalized (table 5), there was no statistically significant difference between the acceleromyographic and mechanomyographic responses below a mean TOF ratio of 0.70. However, at this ratio and above, the mean acceleromyographic TOF response was statistically significantly higher than the mean mechanomyographic TOF response (0.04–0.06).

When acceleromyographic TOF ratios obtained with preload were normalized (table 5), there was no statistically significant difference between the acceleromyographic and mechanomyographic responses below a mean TOF ratio of 0.80. At this ratio and above, the mean acceleromyographic TOF response was statistically significantly higher (0.04–0.06) than the mean mechanomyographic response.

Finally, when both acceleromyography and mechanomyography were normalized, there were no statistically significant differences between TOF ratios obtained with the two methods of whether a preload was used (table 6), except for a normalized acceleromyographic TOF ratio of 1.00 when measured without a preload (table 6). At this TOF ratio, the acceleromyographic TOF was an average of 0.03 higher than the mechanomyographic

response ($P < 0.009$). However, at all levels of block, the limits of agreement were quite wide, *i.e.*, ± 0.20 –0.30.

When both the acceleromyographic and mechanomyographic responses were normalized, there were no statistically significant differences in times to TOF 0.90 obtained with the two methods, independent of whether a preload was used with acceleromyography (mean bias: 0.004 and −0.0011 with and without preload, respectively).

Discussion

With respect to application of a preload (*i.e.*, Hand Adapter) the major findings of our study are that: (1) it increases the precision of the acceleromyographic response, (2) it eliminates the bias in onset time between acceleromyography and mechanomyography, and (3) it increases the control TOF, thereby increasing the bias in relation to mechanomyography during late recovery (TOF 0.90–1.00).

With respect to the effect of normalization, the major findings are: (1) normalization of the acceleromyographic TOF ratios significantly decreases the bias between acceleromyography and mechanomyography, independent of whether a preload is being applied, and (2) when both the acceleromyographically and mechanomyographically obtained TOF ratios are normalized, there is no statistically significant difference between the two methods, except for TOF of 1.00 or more measured with acceleromyography without a preload.

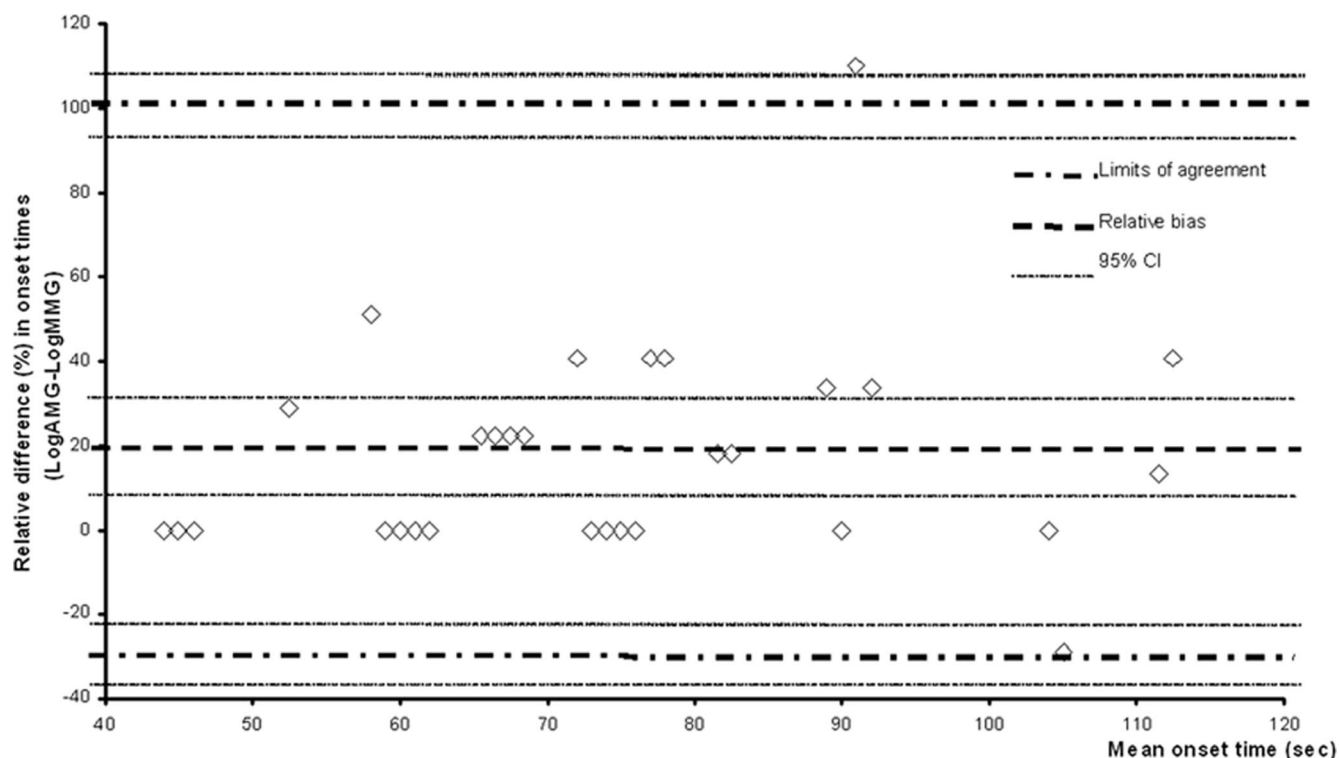


Fig. 5. Bland-Altman scatter plot of relative bias in percent against the mean onset times for patients without a preload applied to acceleromyography (AMG) and mechanomyography (MMG) ($n = 30$). The bias increases as the mean onset time increases. Therefore, all data are logarithmically transformed, and the bias is presented as the relative bias (%). Data are also presented in table 3. LogAMG = logarithmically transformed AMG train-of-four ratios data; LogMMG = logarithmically transformed MMG train-of-four ratios data.

Effect of Preload

In contrast to the isometric contraction of mechanomyography, acceleromyographic measurements imply a movement. The swinging thumb might touch the sterile cover, a warming blanket, or the palm of the hand. This will cause artifacts, and the measurements become unreliable. Brull and Silverman¹³ videotaped the thumb movement in response to TOF stimulation and observed that the position between third and fourth response was displaced 5 ± 4 mm from the original resting position, most probably decreasing the precision.

Our study is the first randomized controlled study showing that the Hand Adapter increases the precision throughout the recovery period.¹² The Hand Adapter consists of a flexible preload, ensuring that the thumb does not touch the palm of the hand and that it returns to the original position after each stimulus in the TOF, thereby probably increasing the precision. Other preload applications have been tested. Kopman *et al.*^{15,17} used a rubber band as preload and found that the variability in control TOF decreased.¹⁵ Dubois *et al.*²³ compared the freely moving thumb, the Hand Adapter, and a prototype of a preload ("the TOF tube") with mechanomyography. In their study, the precision was defined as the variability in only four consecutive measurements in each of 20 subjects. Nevertheless, they also found that a preload reduces the variability.

We hypothesized that the Hand Adapter applied to acceleromyography would increase the agreement to mechanomyography. However, in contrast to our hypothesis, the acceleromyographic control TOF increased when a preload was applied, thereby increasing the bias to the mechanomyographic control TOF. Although the bias was not statistically significant during early recovery (*i.e.*, TOF 0.20–0.50), the bias increased during late recovery (*i.e.*, TOF 0.90–1.00) when a preload was applied. This is also reflected in the fact that the bias in "time to TOF 0.90" between acceleromyography and mechanomyography increased when a preload was applied. Dubois *et al.*²³ also found that TOF ratios increased with application of the Hand Adapter. In contrast, Kopman *et al.* found the control TOF to be decreased¹⁷ or unchanged¹⁵ with a rubber band. The differences might be explained by the characteristics of the elastic rubber band as compared to the Hand Adapter. We have no explanation as to why application of the Hand Adapter increased the TOF ratios, thereby increasing the bias in relation to mechanomyography.

Effect of Normalization

There is consensus that the TOF should be 0.90 to exclude clinically significant residual block. However, the first studies indicating that TOF should be 0.90 were done using mechanomyography.^{24–27} Later studies suggest that the TOF measured with acceleromyography

Table 5. Bias with Limits of Agreement (95% Confidence Intervals) between the Normalized AMG without or with Preload and the Recorded Raw MMG TOF Ratios at Different Levels of Block as Defined by the Normalized AMG TOF Ratios

Normalized AMG TOF Level	n*	Mean Normalized AMG TOF	Mean MMG TOF	Bias AMG-MMG	Limits of Agreement	P Value
AMG without preload						
0.20	29	0.21	0.19	0.01 (−0.03 to 0.06)	−0.22 to 0.25 (−0.30 to 0.33)	0.53
0.30	29	0.31	0.32	−0.01 (−0.05 to 0.04)	−0.24 to 0.23 (−0.31 to 0.30)	0.82
0.40	29	0.41	0.39	0.20 (−0.20 to 0.06)	−0.20 to 0.24 (−0.27 to 0.31)	0.34
0.50	29	0.51	0.47	0.03 (−0.007 to 0.07)	−0.17 to 0.24 (−0.24 to 0.30)	0.10
0.60	28	0.61	0.58	0.03 (−0.00 to 0.07)	−0.14 to 0.20 (−0.20 to 0.26)	0.051
0.70	28	0.71	0.67	0.04 (0.01 to 0.07)	−0.12 to 0.20 (−0.17 to 0.25)	0.012
0.80	28	0.80	0.76	0.04 (0.01 to 0.07)	−0.10 to 0.19 (−0.15 to 0.23)	0.004
0.90	26	0.91	0.86	0.05 (0.02 to 0.07)	−0.08 to 0.17 (−0.12 to 0.21)	0.0006
1.00	18	1.00	0.93	0.06 (0.04 to 0.08)	−0.02 to 0.15 (−0.06 to 0.19)	< 0.0001
AMG with preload						
0.20	30	0.21	0.21	−0.01 (−0.06 to 0.04)	−0.26 to 0.25 (−0.35 to 0.33)	0.80
0.30	30	0.31	0.33	−0.02 (−0.06 to 0.03)	−0.26 to 0.23 (−0.34 to 0.31)	0.51
0.40	30	0.41	0.42	−0.01 (−0.07 to 0.04)	−0.29 to 0.26 (−0.38 to 0.35)	0.57
0.50	30	0.51	0.52	−0.01 (−0.05 to 0.03)	−0.25 to 0.23 (−0.33 to 0.30)	0.61
0.60	29	0.61	0.60	0.00 (−0.04 to 0.05)	−0.21 to 0.22 (−0.28 to 0.29)	0.84
0.70	29	0.71	0.68	0.03 (−0.01 to 0.06)	−0.17 to 0.22 (−0.23 to 0.28)	0.17
0.80	29	0.80	0.76	0.04 (0.01 to 0.07)	−0.11 to 0.19 (−0.16 to 0.24)	0.007
0.90	28	0.91	0.86	0.05 (0.03 to 0.07)	−0.06 to 0.16 (−0.10 to 0.19)	< 0.001
1.00	13	1.00	0.95	0.06 (0.03 to 0.08)	−0.01 to 0.12 (−0.04 to 0.15)	0.0003

$P < 0.05$, significant difference between AMG and MMG.

* If the first twitch was below 20%, the TOF was not calculated by the TOF-Watch® SX (Organon, Oss, The Netherlands). Furthermore, four patients were given neostigmine, and data after reversal were excluded.

AMG = acceleromyography; MMG = mechanomyography; n = number of datasets; TOF = train-of-four.

should be higher than mechanomyographic TOF to predict sufficient recovery after neuromuscular block⁹ and that an acceleromyographic TOF of 0.90 or even 1.00 would not ensure sufficient recovery in all patients.^{28–30} In accordance with previous studies,^{1,8,12} we found the

control acceleromyographic TOF to be higher than the mechanomyographic TOF and most often higher than unity. Accordingly, it has been suggested to refer all acceleromyographic TOF ratios to the baseline control value.¹⁷ This approach seems rational to minimize the

Table 6. Bias with Limits of Agreement (95% Confidence Intervals) between the Normalized AMG without or with Preload and the Normalized MMG TOF Ratios at Different Levels of Block as Defined by the Normalized AMG TOF Ratios

Normalized AMG TOF Level	n*	Mean Normalized AMG TOF	Mean Normalized MMG TOF	Bias AMG-MMG	Limits of Agreement	P Value
AMG without preload						
0.20	29	0.21	0.20	0.005 (−0.04 to 0.05)	−0.24 to 0.25 (−0.32 to 0.33)	0.81
0.30	29	0.31	0.33	−0.02 (−0.07 to 0.03)	−0.26 to 0.22 (−0.34 to 0.30)	0.42
0.40	29	0.41	0.40	0.003 (−0.04 to 0.05)	−0.23 to 0.23 (−0.30 to 0.31)	0.89
0.50	29	0.51	0.49	0.01 (−0.03 to 0.05)	−0.20 to 0.23 (−0.28 to 0.30)	0.55
0.60	28	0.61	0.60	0.01 (−0.03 to 0.04)	−0.17 to 0.19 (−0.24 to 0.25)	0.61
0.70	28	0.71	0.70	0.01 (−0.02 to 0.04)	−0.16 to 0.18 (−0.22 to 0.24)	0.50
0.80	28	0.80	0.79	0.01 (−0.02 to 0.04)	−0.15 to 0.17 (−0.21 to 0.23)	0.50
0.90	26	0.91	0.89	0.01 (−0.01 to 0.04)	−0.12 to 0.15 (−0.17 to 0.20)	0.30
1.00	18	1.00	0.96	0.03 (0.01 to 0.06)	−0.07 to 0.13 (−0.11 to 0.17)	0.009
AMG with preload						
0.20	30	0.21	0.22	−0.02 (−0.07 to 0.04)	−0.28 to 0.25 (−0.37 to 0.34)	0.56
0.30	30	0.31	0.34	−0.03 (−0.08 to 0.02)	−0.29 to 0.23 (−0.37 to 0.32)	0.23
0.40	30	0.41	0.44	−0.03 (−0.09 to 0.02)	−0.32 to 0.25 (−0.41 to 0.35)	0.23
0.50	30	0.51	0.54	−0.03 (−0.08 to 0.01)	−0.28 to 0.22 (−0.36 to 0.29)	0.14
0.60	29	0.61	0.63	−0.02 (−0.06 to 0.02)	−0.24 to 0.20 (−0.32 to 0.27)	0.30
0.70	29	0.71	0.71	−0.004 (−0.04 to 0.03)	−0.20 to 0.19 (−0.27 to 0.26)	0.83
0.80	29	0.80	0.80	0.007 (−0.02 to 0.04)	−0.14 to 0.16 (−0.19 to 0.21)	0.61
0.90	28	0.91	0.89	0.01 (−0.01 to 0.03)	−0.09 to 0.12 (−0.13 to 0.16)	0.21
1.00	13	1.00	0.99	0.02 (−0.01 to 0.04)	−0.05 to 0.08 (−0.08 to 0.11)	0.12

$P < 0.05$, significant difference between AMG and MMG.

* If the first twitch was below 20%, the TOF was not calculated by the TOF-Watch® SX (Organon, Oss, The Netherlands). Furthermore, four patients were given neostigmine, and data after reversal were excluded.

AMG = acceleromyography; MMG = mechanomyography; n = number of datasets; TOF = train-of-four.

bias between TOF ratios obtained with mechanomyography and acceleromyography. Capron *et al.*¹⁰ showed that the probability of excluding residual block by the use of acceleromyography was significantly higher when based on normalized acceleromyographic TOF ratios compared to the nonnormalized TOF ratios. Thus, the probability of excluding residual block defined as a mechanomyographic TOF of 0.90 or more increased from 40% to 89% by using a normalized acceleromyographic TOF ratio of 0.90 or more. Similarly, Kopman *et al.*^{15,31} found that the bias between acceleromyographically and electromyographically obtained TOF ratios above 0.60 became insignificant when the acceleromyographic TOF ratios were normalized. We found that not only would normalization of the acceleromyographic TOF ratios decrease the bias to mechanomyography, but the bias became insignificant when the mechanomyographic TOF ratios were also normalized. The reason is that the control mechanomyographic TOF is most often below unity and occasionally as low as 0.90. In these patients, the time to TOF 0.90 during recovery is significantly prolonged, and sometimes a TOF 0.90 is not reached unless the TOF ratios are normalized. To date, no studies have compared the normalized TOF ratios of acceleromyography and mechanomyography to clinical signs and symptoms of residual paralysis.

Limitations of the Study

Our study has several limitations. The research setup of both the mechanomyograph³ and the acceleromyograph (with or without Hand Adapter) was more meticulous and stringent than in normal daily clinical practice. The forearms and hands were tightly fixed to the armboards, and the patients included were scheduled to operations in the supine position, where the risk of external disturbances by for instance the surgeons were expected to be low. For this reason, the majority of patients were women scheduled to undergo gynecological procedures. We did this to increase the precision of the neuromuscular monitoring, as it makes no sense to compare the precision of two methods if the setup is disturbed by the surgeon throughout the monitoring. Moreover, the agreement between two methods is bound to be poor if the precision of one or both methods are poor.^{3,22} We found acceleromyography with or without preload as well as mechanomyography to be very precise. In the daily clinical setting with more external disturbances, the Hand Adapter most probably will be of even greater benefit with respect to precision; it will diminish the effect of many artifacts caused by the freely moving thumb. However, this remains to be investigated.

It is not possible to apply the two methods on the same arm, as mechanomyography requires an isometric contraction and acceleromyography an isotonic contraction. However, possible differences between arms (arm-

to-arm variation) should be taken into account when comparing two methods on different arms. Kirkegaard-Nielsen *et al.*⁸ did not find any bias between contralateral arms monitored with mechanomyography, but they found wide limits of agreement. We have recently examined the arm-to-arm variation in patients monitored with acceleromyography and mechanomyography. We found no significant bias between arms, but the limits of agreement were quite wide, even when using the same method on both arms. Most of the individual differences between arms when comparing acceleromyography and mechanomyography on contralateral arms therefore might be explained by differences between arms.

In this study, the Hand Adapter was used because this device is simple and commercially available. However, further studies are needed to establish the optimal characteristics of a preload device (*e.g.*, load before and throughout the response to nerve stimulation, elasticity, length of contraction, etc.).³

We examined the effect of normalization because we thought this would be the best approach to handle the high TOF ratios measured with acceleromyography. However, it might be cumbersome when acceleromyography is used in the daily clinic. First, a prerequisite for normalization is obviously a reliable control TOF ratio, measured before administration of the neuromuscular blocking agent, and this is often difficult to achieve when busy with daily routine work. Second, the automatically calculated TOF ratio most often given by the monitoring units loses some of its usefulness in this way. Therefore, with the neuromuscular monitoring equipment currently commercially available, normalization is most often not an option in daily clinical practice. The manufacturer of the TOF-Watch[®] chose another method. In two of three TOF-Watch models (TOF-Watch[®] and TOF-Watch[®] S) intended for use in the daily clinic, the method of TOF ratio calculation is modified, ensuring that the displayed TOF ratio never exceeds 1.00. 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%.³² We believe a more appropriate and relatively straightforward solution could be to incorporate an algorithm taking into account the control TOF in new versions of neuromuscular monitoring units for use in research when calculating normalized TOF ratio during recovery.

Conclusion and Recommendations

Mechanomyography and acceleromyography (without preload and normalization) cannot be used interchange-

ably in pharmacodynamic studies because of a statistically significant and clinically relevant bias between the two methods, especially during late recovery.

Preload (the Hand Adapter) increases the precision of acceleromyography, and we therefore advocate its use by researchers and clinicians. However, application of the Hand Adapter also increases the bias in relation to mechanomyography during late recovery. Therefore, when the Hand Adapter is used in clinical practice, an acceleromyographic TOF ratio of 1.00 or greater should be the target during recovery provided that the monitor does not have another integrated algorithm.

Normalization of the acceleromyographic response decreases the bias in relation to mechanomyography. In research, therefore, the acceleromyographic response should be normalized whenever one wants to be able to compare pharmacodynamic data with data obtained using mechanomyography.

Normalization of both the acceleromyographic and mechanomyographic response eliminates the bias between the two methods. However, we do not currently recommend this procedure. To date, all studies comparing TOF ratios to residual effects of neuromuscular blocking agents have been based on nonnormalized TOF data, and there is a need for studies investigating the relationship between the normalized (acceleromyographic and mechanomyographic) TOF ratios and clinical signs and symptoms of residual paralysis.

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